Underactive Bladder Syndrome: An Often Overlooked Condition

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Abstract

Urinary bladder outlet obstruction can cause lower urinary tract symptoms in men and women, such as a weak or interrupted urine stream, straining to void, hesitancy, and the feeling of incomplete bladder emptying. These symptoms can also be associated with underactive bladder syndrome. This urological condition has a high prevalence in both genders, especially in older age groups. The most common risk factors that can contribute to the pathogenesis of underactive bladder syndrome are aging, detrusor myopathy, neuroinflammatory, neurodegenerative and other lesions of the central and peripheral nervous system, and diabetes mellitus. Reduced detrusor contractility, or detrusor underactivity, is the most common pathology of underactive bladder syndrome. Detrusor underactivity is a urodynamic definition provided by the International Continence Society. The urodynamic trace is characterised by a low urine flow rate accompanied by low detrusor pressure or brief detrusor muscle contraction. Underactive bladder syndrome is often recognised and treated poorly in clinical practice because the symptoms are not specific. Furthermore, underactive bladder can be asymptomatic or coexist with bladder outlet obstruction and overactive bladder syndrome.

The aim of this study was to review recent research concerning the aetiology, classification, diagnostic evaluation, and available treatment methods for patients with symptoms of underactive bladder syndrome. Making an accurate underactive bladder diagnosis is challenging because it is a multifactorial condition with various patterns of manifestation. Consequently, there is still no general agreement and standardisation regarding the most favourable diagnostic and therapeutical approach.

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Introduction
The storage and excretion of urine in women and men depend on the coordinated activity of the neural centres, smooth muscles of the bladder and urethra, and the urethral striated muscle (1). Various urological and neurological diseases can cause voiding dysfunction, which manifests with lower urinary tract symptoms (LUTS), clinical signs, and syndromes (2). Straining to void, a weak urine stream, hesitancy, and other LUTS during the voiding phase of micturition are prevailing symptoms that urologists encounter in an outpatient and clinical setting. These LUTS are more often present in men than in women and are commonly associated with bladder outlet obstruction (BOO) (3). Benign prostatic hyperplasia (BPH) and urethral stricture are the usual suspects in men, while in women, the most common causes of BOO are functional sphincteric obstruction, anti-incontinence surgery, urethral stricture and pelvic organ prolapse (4, 5). These symptoms may be a consequence of detrusor underactivity (DUA) (6). DUA is caused by reduced detrusor contractility, which can be idiopathic or result from various neurological, urological, autoimmune, muscular, and other diseases (7, 8). According to the International Continence Society (ICS) terminology, DUA is a diagnosis based on urodynamic investigations (9). DUA is characterised by a low urine flow rate accompanied by low detrusor pressure, brief detrusor contraction, or absent detrusor contraction (10). The result of this is prolonged micturition, failure to achieve complete bladder emptying in an expected time interval, and a high bladder post-void residual volume (PVR).

Underactive bladder syndrome (UAB) is a contemporary clinical term that describes symptomatic DUA as a cause of voiding dysfunction (11, 12). UAB is defined as a complex of voiding symptoms, such as a weak urine stream, straining to void, and hesitancy (13, 14). Storage and post-micturition symptoms, such as a reduced sensation of bladder filling, terminal dribbling, and a feeling of incomplete bladder emptying may also be present, with or without PVR (15). It can be challenging to distinguish if BOO or UAB is the problem because these conditions have similar symptoms and they can coexist and intertwine, especially in men with BPH (16). UAB is not so popular when compared with overactive bladder syndrome (OAB) and these two syndromes may be present at the same time (17).

Detrusor overactivity (DOA) is another urodynamic diagnosis and OAB represents symptomatic DOA (18). DOA is characterised by involuntary detrusor contractions during the filling phase, which can be spontaneous or provoked during a urodynamic study (9). OAB consists of storage LUTS and it is defined as urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or obvious pathology (19). We are better acquainted with the pathophysiology and diagnostic approach of OAB compared to UAB (20). Also, OAB treatment methods are more efficient and safer (21). Storage, voiding and post-micturition LUTS are associated with significant morbidity and mortality of men and women aged 65 and over. For example, nocturia associated with BPH and OAB can lead to a fall-related bone fracture, persistently high PVR associated with UAB can cause bilateral hydronephrosis, chronic cystitis, overflow incontinence, and formation of bladder stones, which can seriously affect the quality of life (QOL) (22-25).

Despite new research initiatives and the latest information about UAB and DUA, there is still no consensus on a diagnostic and therapeutical approach. Furthermore, assessment can be different in men and women. If we could reach a general agreement on diagnosing UAB and DUA, then we could establish the parameters of non-invasive assessment tools, for example, a combination of UAB symptom score questionnaire, ultrasound measurement of detrusor wall thickness, and uroflowmetry result (26). This could help us distinguish patients with UAB and DUA from those with BOO and BPH.

The aim of this review was to describe the clinical and urodynamic aspects of UAB and to emphasise the latest insights in the diagnostic
evaluation and available UAB treatment methods.

Prevalence of underactive bladder syndrome

The prevalence rates vary because UAB is often a poorly recognised condition in clinical practice, frequently mistaken for BOO, and usually not associated with a possible neurological condition. The reason for this is that there is no classification of UAB and a definitive diagnosis can be achieved only by conducting a urodynamic study. According to previous research, UAB has a high prevalence in both genders, especially in older age groups. UAB has the potential of being a serious public health problem in the future because it is expected that the percentage of people aged 65 and over will approach 20% of the total population by 2050 (13, 27). Also, neurodegenerative disorders and other neurologic conditions that can lead to LUTS and UAB increase in prevalence with age (28). The prevalence of UAB in men under the age of 50 ranges from 9% to 28% and increases with age, affecting 48% of men over the age of 70 (6). The prevalence of UAB is approximately 12% in younger women and 45% in older female patients (29). One epidemiological survey, which included a total of 633 participants aged 60 and over, showed that 23% of them had voiding and post-micturition LUTS, with no difference regarding gender or age; however, only 11% of the participants heard about UAB (30). In another original scientific study, urodynamic testing was performed on 1,179 patients with LUTS aged over 65. After the evaluation of the results, it was established that out of 40.2% of men and 13.3% of women who had DUA, 72.6% of the women with DUA had DOA or stress urinary incontinence (SUI) and 46.5% of men with DUA also had DOA or BOO (31).

Aetiology of underactive bladder syndrome

There are many diseases that alone or combined cause bladder innervation disorders and/or damage to the detrusor muscle. This can lead to the inability of the detrusor muscle to generate sufficient intravesical pressure to empty the urinary bladder. Therefore, the aetiology of UAB is multifactorial and the most important aetiological factors are age-related factors, neurological disorders, BOO, and diabetes mellitus (DM) (32). If there is no specific cause, UAB can be classified as idiopathic, which is more common in younger patients (33). Older people are more likely to develop UAB symptoms. The amount of acetylcholine esterase-positive nerves in the bladder decreases with age and a reduced response to bladder filling in the insular cortex occurs (34, 35). Also, the proportion of collagen fibres increases with age and the number of smooth muscle cells and muscarinic receptors decreases (34, 36). Neurological diseases account for the largest share of risk factors for lower urinary tract disorders such as OAB and UAB. Patients could have LUTS but no formally diagnosed neurological condition. LUTS could be an early symptom in the manifestation of an underlying neurological disease, which is referred to as “occult neurology” (37). If we fail to identify an undiagnosed neurological aetiology, we risk poor outcomes for LUTS treatment. OAB symptoms are more common in patients who have had an acute cerebrovascular accident (CVA) and in patients with multiple sclerosis (MS) and Parkinson’s disease, but UAB symptoms and high PVR have also been reported (38-40). Urinary retention and DUA can occur in early stages of Guillain-Barré syndrome, but long-term LUTS are not so common.

Traumatic, degenerative and other spinal cord injuries can also cause voiding dysfunction. Symptomatology depends on the spinal cord injury level. Spinal cord injuries below the sacral micturition centre (SMC), which is located in the intermediolateral grey of the sacral cord from S2-S4, are most often partial, resulting in weakened bladder contractility and UAB symptoms. Partial or complete injuries above the SMC and neuroinflammatory and neurodegenerative diseases of the central nervous system often result in the appearance of OAB symptoms. Infectious diseases, such as
neurosyphilis, herpes zoster, herpes simplex, and acquired immunodeficiency syndrome, are also associated with a neurological dysfunction that causes the symptoms of UAB and/or OAB (41-44). Radical prostatectomy, radical hysterectomy, and other pelvic surgical procedures, in which peripheral nerve damage may occur, are examples of an iatrogenic cause of UAB (35). Even OAB and BOO can cause structural changes of the urinary bladder over time, which include a reduction in detrusor blood flow, detrusor muscle deterioration, and proliferation of connective tissue, which can lead to DUA and UAB (45).

DM is one of the most common diseases in general population, which has recently reached epidemic proportions in many countries and is associated with numerous complications and organ damage (46). One of the more common complications of DM is diabetic cystopathy (DC) (47). The prevalence of DC ranges from 20 to 90% (48). As with UAB, we still lack a standardised diagnostic assessment of DC. The symptoms include an impaired sensation of bladder fullness, reduced bladder contractility, increased bladder capacity, and increased PVR. DC can be asymptomatic early in the course of DM (49). DC is a result of sensory and autonomic polyneuropathy, microvascular damage, dysfunction of detrusor smooth muscle cells, and dysfunction of urothelial cells (50). Urothelial cells were considered to be just a barrier between the urinary tract lumen and underlying tissues of the urinary tract wall, but they have a more active role in bladder physiology. These cells form a functional unit that responds to external events by releasing adenosine triphosphatase, nitric oxide, and prostaglandins (51, 52). These modulator agents regulate the activity of afferent nerves and the detrusor smooth muscle and process the information about the urinary tract chemical and physical status (e.g. luminal pressure, urine composition) (53). With all this said, it just goes to show that we still have a lot to learn about the function of the lower urinary tract and surrounding tissues.

**Diagnostic evaluation of underactive bladder syndrome**

The symptoms of UAB are not specific and they can overlap with other voiding dysfunctions, especially with BOO. The symptoms that may be suggestive of UAB include hesitancy or a delay in passing urine, weak or thin urine stream, interrupted urine flow, post-void dribbling of urine, feeling of having to go again after the stream has stopped, voiding a second or even multiple times after the initial voiding has completed, having to strain to facilitate voiding, and frequent urination day and night in small volumes (54). With history-taking and a physical examination in medical practice, we can only assume that an observed patient has UAB. It is especially important to consider neurological symptoms and diseases. During a physical examination, we palpate the suprapubic region to check the pain and fullness of the bladder. Also, we assess the tone of the anal sphincter, perianal sensation, bulbocavernosus reflex, and plantar reflex, which can be compromised, absent, or significantly diminished (55, 56). Some studies have examined the usefulness of non-invasive methods, such as flow pattern on uroflowmetry, intravesical prostatic protrusion (IPP), PVR volume, and bladder voiding efficiency (BVE) to distinguish between UAB and BOO (15, 57).

Non-invasive methods are very useful for the assessment of patients who cannot go through invasive urodynamic testing. Uroflowmetry is a simple and non-invasive urodynamic test of measuring and recording the voided volume, urinary flow rate, and wave shape throughout micturition (58). It is a screening procedure and its results may be indicative of BOO or UAB. IPP is measured during almost every examination of men with LUTS. It is measured using the transabdominal ultrasound in the sagittal view and defined as the vertical distance from the tip of the protrusion to the base of the prostate (59, 60). Regarding this distance, IPP can be quantified into three grades, which more or less correlate with the symptoms related to BOO: grade 1 (≤ 5 mm), grade 2 (5-10 mm), grade 3 (≥ 10 mm). PVR is measured immediately after...
voiding by ultrasound or by inserting a catheter into the bladder through the urethra. Using ultrasound, we measure three dimensions of the bladder: maximal transverse (width), anterior-posterior (height), and longitudinal (length). Then we determine the PVR volume using the Dicuio’s formula (volume [mL] = height [cm] × depth [cm] × transverse diameter [cm] × 0.52) (61). To determine BVE, we measure the bladder volume before voiding (BVvoid) using ultrasound and then we measure voided volume (VV) using a measuring cylinder. Using the equation (VV/BVvoid × 100), we can express BVE by fraction (%) of the voided volume. A combination of lower IPP (< 8.2 mm) and lower BVE (< 70), sawtooth and interrupted wave shape on uroflowmetry might be useful factors to predict DU and UAB.

Despite all non-invasive methods, pressure-flow study is practically the only method by which we can establish an accurate diagnosis of UAB (62). The parameters observed during this study are peak flow (Qmax) and detrusor pressure at peak flow (PdetQmax) (63). Using these parameters, we can assess the contractility of the bladder by using the bladder contractility index (BCI) formula according to the equation Pdet@Qmax+5Qmax (64). With this formula, we can divide bladder contractility into strong (BCI > 150), normal (BCI 100–150), and weak (BCI < 100). Also, we can exclude or confirm the presence of the obstruction in men using the bladder outlet obstruction index (BOOI) formula according to the equation Pdet@Qmax-2Qmax (65). Based on the results of the BOOI formula, men can be divided into obstructed (BOOI > 40), equivocal (BOOI 20–40), and unobstructed (BOOI < 20). BOOI formula does not apply to women. At the moment, the Blaivas and Groutz nomogram is the most common method used to define BOO in women as a Qmax < 12 mL/sec combined with a Pdet@Qmax of > 20 cm H2O in a pressure-flow study (66). There is a potential future test for UAB that includes urine biomarkers, such as nerve growth factor, and bladder wall biopsy with an electron-microscopic histopathologic ultrastructural assessment of the detrusor (67, 68). The research of these diagnostic methods is still ongoing, so further studies are needed to implement them into clinical practice.

**Treatment of underactive bladder syndrome**

The treatment of UAB is focused on improving the QOL and preventing complications. If the patients are asymptomatic, we still need to administer the treatment. Also, we must inform patients about possible side effects of each type of treatment. It is necessary to achieve the status of an empty bladder regardless of the aetiology of UAB to avoid chronic urinary retention, bilateral hydronephrosis, recurrent urinary tract infections (UTI), bladder stone formation, and overflow incontinence. Common methods of treatment are timed voiding, double voiding, straining to void, Credé or Valsalva manoeuvre, clean intermittent catheterisation (CIC), pharmacotherapy, and surgical treatment (35, 69, 70).

In patients with vesicoureteral reflux and high intravesical pressure, the Credé and Valsalva manoeuvres are contraindicated. Constipation should be avoided by dietary fibre intake and exercise, which are usually recommended as first-line treatment (71). Prolonged use of laxatives may lead to some adverse effects. CIC must be recommended to patients who have chronic urinary retention with high PVR. If possible, placement of an indwelling urinary catheter and suprapubic cystostomy should be avoided due to complications, such as catheter encrustation, urethral erosion, and increased risk of UTI and bladder cancer (72). We need to explain the benefits of CIC to each patient to enhance compliance. Silicone catheters are most commonly used because they carry a lower risk of allergic reactions. Patients can perform catheterisation on their own or they are catheterised by caregivers. Recommended daily number of catheterisations ranges between 4 and 6 and the amount of urine discharged at every catheterisation should not exceed 400–500 mL. Silicone catheters are most commonly used. CIC is impractical and inconvenient for elderly, visually impaired and mentally handicapped patients, and for patients with
limited manual dexterity. Complications of CIC are urethral injuries (e.g. false passage, strictures), UTI, and haematuria (73).

There are no effective oral drugs for UAB treatment. Contemporary pharmacotherapy of UAB includes the use of $\alpha$-adrenergic blockers to reduce outlet resistance at the level of the bladder neck and muscarinic agonists or choline esterase inhibitors to increase detrusor contraction (74). These drugs can be used as monotherapy or in combination. $\alpha$-adrenergic blockers, such as tamsulosin at a dose of 0.4 mg once a day and silodosin at a dose of 8 mg once a day, are in most cases considered for the initial stage of UAB treatment in men (75). $\alpha$-adrenergic blocker therapy for women with UAB is an off-label regimen in most countries (76). Bethanechol chloride (BC) and pyridostigmine bromide (PB) are the most common orally administered parasympathomimetic agents used in clinical practice (77). The usual adult oral dose for BC ranges from 10 to 50 mg three or four times a day and from 60 to 180 mg for PB. Their effectiveness is limited due to the downregulation of muscarinic receptors and potentially life-threatening side-effects, such as bradycardia and ventricular tachycardia (32). The European Association of Urology (EAU) states that they should not be prescribed for UAB treatment (75). Prostaglandin E2 (PGE2) can increase the inotropic activity in smooth muscles (72). It prevents the release of noradrenaline from sympathetic nerve endings. Intravesical administration of PGE2 can increase detrusor contractions and decrease maximal urethral closure pressure (75). The effectiveness of PGE2 is limited and it is not recommended for routine treatment.

Onabotulinumtoxin A injections into the external urinary sphincter reduce urethral resistance, eliminate the inhibitory effects of urethralafferent nerves on the detrusor and allow easier voiding with the aid of increased abdominal pressure (72). This therapy has not been approved yet and there is no standard dosage. The efficacy of transurethral resection of the prostate and transurethral incision of the bladder neck in patients with BOO and accompanying UAB is questionable. Patients should be informed that they may not benefit from this type of procedure.

Chronic urinary retention associated with UAB often leads to myogenic decompensation because of an overdistended bladder. Reduction cystoplasty decreases the capacity of the bladder and facilitates bladder emptying, but it does not increase bladder contractility (72, 75). This treatment method should be performed only in well-chosen cases and in patients with residual detrusor contractility. Sacral neuromodulation therapy (SNM) is appropriate for well-chosen patients who have not been helped by more conservative treatments, such as drug therapy (78). SNM uses a surgically implanted device to send electrical impulses to the sacral nerves located in the lower back, which modify the function of the detrusor muscle and pelvic floor muscles. It is one of the more expensive methods of treatment and it is performed in specialised high-volume tertiary referral centres. Transurethral intravesical electrical stimulation and use of the stem cells are novel treatment methods with reports that they can improve detrusor contractility and increase weak individual myocyte contractility (79). Neurovascular latissimus dorsi (LD) detrusor myoplasty is suitable for motivated young patients who do not want to undergo CIC. The LD muscle flap is wrapped around the bladder, attached to the pelvic fascia and ligaments, and it is anastomosed to the deep inferior epigastric vessels and lowest motor branches of the intercostal nerve (80). LD detrusor myoplasty can adequately restore bladder emptying on demand (81). Further studies are needed to implement these surgical and novel treatment methods in clinical practice. Regardless of the type of treatment used, patients should have frequent follow-ups with repeated urodynamic examination where necessary.

**Discussion**

ICS conducted a comprehensive review of the terminology pertaining to the lower urinary tract function and dysfunction and recommended the use of the term DUA (9). UAB has not yet been
defined by the ICS. Furthermore, the current definitions of both conditions do not include possible aetiological risk factors. Based on the aetiology, UAB can be classified into four types: neurogenic, myogenic, and idiopathic (29). Neurogenic UAB is associated with changes in the afferent and efferent signals of the micturition reflex (82). Myogenic UAB is associated with modified contraction mechanisms of detrusor muscle cells, which can result in reduced autonomous activity of the bladder (83). UAB can be the combination of myogenic and neurogenic factors or a combination of two or more neurogenic factors. Idiopathic UAB has an unknown cause or mechanism of apparent spontaneous origin (84).

Based on urodynamic findings, UAB can be classified into three types: DU, acontractile detrusor, and OAB/UAB combination (29). Patients with DUA have impaired detrusor contractility and can void incompletely or they have no urine flow during the urodynamic examination. If there are no detrusor contractions during cystometry and a pressure-flow study, then we are talking about an acontractile detrusor. It is an extreme type of DUA, patients have high PVR, and the emptying of the bladder is performed by increased abdominal pressure or CIC. It is important to note that some patients have UAB and OAB symptoms (17). If we suspect this is the case, a urodynamic assessment is mandatory. DOA is recorded during filling cystometry and DUA during a pressure-flow study. Education about the symptoms and clinical signs of the lower urinary system is of utmost importance for all urologists, urogynecologists, and neuourologists. Taking a medical history in an outpatient setting can be complicated at times and for this reason, it is recommended to use questionnaires, frequency-volume charts, and bladder diaries in the evaluation of symptoms. Physicians must also be well acquainted with performing a physical examination, especially of neurological status. Urodynamic testing is very demanding and one must be very familiar with the methodology to adequately interpret the results. Catheter placement and recording of urodynamic traces must be performed according to the ICS standards. There is still no effective pharmacotherapy of UAB. For now, CIC is the only effective therapy for achieving empty bladder status, but unfortunately, not all patients are willing to perform the catheterisation procedure multiple times a day for an extended period of time. All patients should be offered treatment taking into account the cause of UAB and the most distinct symptomatology. CIC is the main treatment method in the management of patients with high PVR and UAB.

Contemporary research has shown that there are drugs which can have a positive effect on DUA, but in most cases, these studies were not randomised clinical trials. Oral parasympathomimetics can improve detrusor contractions and facilitate bladder emptying, but they do not have a long-lasting effect and they have many serious side effects. ICS and EAU guidelines do not recommend or approve the use of parasympathomimetics for UAB. This therapy is contraindicated in patients with coexisting OAB and UAB symptoms because it may worsen bladder emptying, leading to urine retention and UTI. Therefore, we must perform a thorough neurourologic and urodynamic assessment if we suspect that there are multiple voiding dysfunctions in one patient at the same time. α-adrenergic blockers are useful in men with BOO accompanied by PVR, but their use in women with UAB is not supported by the guidelines. SNM and reconstructive surgical methods are expensive and usually performed in experienced high-volume centres. A large number of patients diagnosed with UAB sometimes do not have access to such centres due to distance or cost of treatment. Research is underway on possible new pharmacotherapeutics and new surgical methods of treating UAB.

Conclusion

Regardless of the complexity of the neuromuscular mechanism of controlling the storage of urine and emptying the bladder, we take the process of voiding for granted. When some form of voiding dysfunction occurs, patients experience how much it can affect the

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QOL (85). UAB is a relatively new term of voiding dysfunction and was recognised in some aspects years before we knew what it is today. It has a high prevalence in the elderly population (86). Despite new insights, UAB is still shrouded in mystery (6). Many diseases can cause the loss of sensation in the bladder and/or detrusor muscle damage (8). It is a great challenge to determine exactly which disease caused the symptoms of UAB. We must do our best to identify the most likely aetiology of UAB in each patient. Classification of UAB needs to be improved to facilitate diagnostic processing and it should be based on aetiology, urodynamic findings, and symptoms. At this point, we have a great knowledge about the symptoms of UAB and about the urodynamic characteristics of DUA. This can improve through further research on the pathophysiology of UAB. Future developments in the pharmaceutical industry, gene therapy, and biomedical applications are expected to close the gap in treatment. We need to raise awareness among those patients who are highly likely to develop UAB in order to initiate treatment at the right time and avoid complications.

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