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Review

Underactive bladder: Pathophysiology and clinical significance

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Abstract Underactive bladder (UAB) is a voiding disorder which generates disabling lower urinary tract symptoms (LUTS) due to the inability to produce an effective voiding contraction sufficient to empty the bladder. The underlying abnormality, that is usually appreciated when performing urodynamic studies, has been defined by the International Continence Society (ICS) as detrusor underactivity (DUA). DUA is a common yet under-researched bladder dysfunction. The prevalence of DUA in different patient groups suggests that multiple aetiologies are implicated. Currently there is no effective therapeutic approach to treat this condition. An improved understanding of the underlying mechanisms is needed to facilitate the development of new advances in treatment. The purpose of this review is to discuss the epidemiology, pathophysiology, common causes and risk factors potentially leading to DUA; to aid in the appropriate diagnosis of DUA to potentially improve treatment outcomes.

1. Introduction

Detrusor underactivity (DUA) is a bladder dysfunction that affects both sexes and causes bothersome lower urinary tract symptoms (LUTS). It is a common diagnosis reported in up to 48% of men and 45% of women who received urodynamic assessment for LUTS [1]. DUA is defined by the International Continence Society (ICS) as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span" [2]. Although a definition exists, there are no recognized diagnostic criteria. Measures of "normal" strength of contraction and contraction duration are not specified. Not having standardized measurement criteria creates conflict and confusion. Urodynamics is the diagnostic tool for DUA; it is an invasive test that might not be available in all health care settings. Therefore, the term underactive bladder (UAB) may be a more appropriate clinical term that can be used to integrate the symptoms and signs of DUA [3].

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Whilst the predominant symptoms relate to voiding dysfunction, there is no pathognomonic symptom that characterizes DUA [4]. The symptoms of DUA vary, and may include voiding symptoms such as weak stream and straining, and storage symptoms such as frequency and the feeling of incomplete emptying. It is likely that the symptoms differ due to the degree of bladder sensation present in any individual case of DUA. Whilst patients usually have a high post void residual (PVR), those with DUA and poor sensation have infrequent voiding and loss of the urge to void. Conversely, patients with DUA and intact sensation suffer frequency and urgency. LUTS experienced by patients with DUA overlap significantly with the pattern of LUTS associated with bladder outlet obstruction (BOO) and hence it is not possible to reliably differentiate the two without an invasive urodynamic study [5]. This has hindered the accurate estimation of the true scale of the condition.

2. Epidemiology

LUTS have a significant impact on the quality of life (QoL) on affected individuals. The Epidemiology of LUTS (Epi-LUTS) study included 30,000 participants over 40 years of age, it concluded that storage LUTS were present in 45.7% of men and 66.8% of women. Voiding LUTS were documented in 57.1% of men and 48% of women [6]. The extent to which DUA contributed to the development of these LUTS remains undetermined.

There is limited knowledge regarding the natural history of DUA and the accompanying symptoms of UAB. Most statements regarding the natural history of UAB are derived indirectly from large epidemiologic studies assessing LUTS. To date no epidemiological work has been able to evaluate DUA. The principal problem is that DUA is a urodynamic diagnosis and it is impractical to perform invasive tests at a community level. Thus our understanding of the incidence, prevalence, underlying risk factors, and natural history of the condition is limited [7]. However the presence of UAB in diverse clinical groups suggests a multifactorial aetiology and pathogenesis [8].

The symptoms that result from DUA are often indistinguishable from symptoms caused by other lower urinary tract dysfunctions. Most cases of LUTS are attributed to detrusor overactivity or stress urinary incontinence (SUI) in women and to benign prostatic hyperplasia (BPH) causing BOO in men. Hesitancy, poor urinary stream, intermittency and straining are common symptoms seen in male patients with BOO [9]. Investigations, such as urinary flow rate, are often used as a screening test for BOO but does not distinguish between BOO and DUA [10]. Additionally, a high PVR could be a result from either DUA or BOO [11]. Whether prolonged BOO results in DUA is still not known, whilst it had been considered to be a possibility in the past it is unlikely to be a common scenario based on clinical observation.

Symptoms such as retention and high PVR in women are more likely due to DUA, this is due to the extremely low incidence of BOO in women (2.7%—8%) [12]. Clinical series of patients with LUTS undergoing urodynamic studies currently provide the best data of prevalence of DUA. It is clear that DUA occurs with increasing age in women just as in men which further supports the view that BOO is unlikely to be an important predisposing factor to DUA in the majority of cases in both men and women.

Review of the literature suggest that in younger men (<50 years), the prevalence of DUA is 9%—28%, which rises to 48% in elderly men (>70 years) [7]. The prevalence of DUA in older women ranges from 12% to 45%, peaking in those who are institutionalized [7]. A likely explanation is that contractility of the bladder becomes impaired with age, resulting in the development of DUA in both sexes. In a study of patients aged over 65 years, who had undergone a urodynamic study for LUTS, and who had no neurological or anatomical conditions, 40.2% of men and 13.3% of women were classified as having DUA [1].

3. Pathophysiology

DUA affects different patient groups, suggesting a multifactorial aetiology. In clinical practice most patients do not have a clearly identifiable cause for DUA. This suggests that DUA may occur secondary to age-related changes, affecting both the detrusor muscle and the central and peripheral innervation of the lower urinary tract. Although it has been assumed that aging leads to a decline in detrusor contractile function, there is no conclusive evidence that this is the cause. The neural axis controlling a detrusor contraction is complex and therefore multiple abnormalities in the pathway can cause impairment of detrusor contraction and result in DUA. Therefore DUA could be idiopathic or result from an iatrogenic injury, or disturbance of its muscular contractile ability, or neurogenic control. The ICS does not classify DUA based on the probable underlying aetiology. Such a classification should form the basis for future research in this field [13].

Idiopathic impaired detrusor contractile function has been defined as being "free of evident neuropathy, free of functional or anatomic BOO, a low or no detrusor pressure (P_{det}) combined with a maximum flow (Q_{max}) of less than 10 mL/s, and a large PVR of more than 150 mL or urinary retention" [14]. People who have no obvious cause for DUA or when aging is the main cause of DUA are labeled as having idiopathic DUA [13]. Idiopathic DUA has been reported to occur in nearly 75% of patients 56—80 years of age and in nearly one-half of the patients who had a history of recurrent acute uncomplicated cystitis [15]. Idiopathic DUA appears to be preceded by a phase of low detrusor contraction velocity before there is a recognized decrease in detrusor contraction strength [16].

Any pathological abnormality that affects the myocytes or other constituents of the detrusor muscle may alter its contractile function. This results in a reduction in the contractile force exerted in the bladder, even if the neural axis is apparently intact [17]. This may result from either altered excitation-contraction-coupling mechanisms of detrusor muscle, change in the ion storage/exchange mechanism, change in the calcium storage and energy generation [18]. In a series reporting urodynamic evaluations coupled with structural studies of endoscopic detrusor biopsies evaluated with electron microscopy. Impaired detrusor contractility was reported to be associated with distinctive and reproducible changes in detrusor ultrastructure [19]. It still has to be determined if this specific

degeneration pattern and structural abnormality is the consequence or the outcome of the DUA.

UAB may result from changes in afferent function, central control mechanism or efferent innervation. Impairment of efferent signaling in the sacral cord, sacral roots, and pelvic nerves may manifest as absent or reduced detrusor contraction as commonly seen with cauda equina syndrome. Whilst in the past when dealing with LUTS there has been a predominant focus on the role of the efferent system. In recent years, the greater significance of the afferent system in many cases is increasingly being acknowledged [20]. Bladder afferent signals ascend the spinal cord to the periaqueductal gray matter, where they project to the limbic system within the cerebrum, which in health exerts an inhibition on the pontine micturition center (PMC). Intact bladder sensation is crucial to the normal function of the efferent limb of the micturition reflex. The afferent system monitors the bladder filling volume during the storage phase, when permission to void is given there is a relaxation of the cerebral inhibition of the PMC. The afferent system is also important in monitoring the magnitude of detrusor contractions during voiding [21]. Urethral afferents also have a major role in the perception of flow through the urethra [22]. The human brainstem also contains specific nuclei responsible for the control of micturition [23]. It is demonstrated by functional MRI studies in asymptomatic patients, where in elderly patients a decreased response in the insular cortex when the bladder was filled [24]. The brain and central nervous system therefore plays an essential role in the integration and fine tuning of both storage and voiding function; which if subject to dysfunction may result in DUA.

4. Diabetes mellitus (DM)

DM is common and often results in lower urinary tract dysfunction by causing diabetes induced peripheral neuropathy or so-called "diabetic cystopathy". This is characterized by impaired bladder sensation, increased capacity, reduced contractility, and increased PVR. Diabetic neuropathy affects approximately one-third of people with DM and results in a whole spectrum of dysfunction, often related to the severity of the DM and the extent to which it is adequately controlled. Diabetic cystopathy disrupts the nerve supply to the bladder resulting in a combination of impairment of voiding efficiency and a decrease in bladder sensation [25,26]. Concomitant conditions such as urinary tract infection, BPH resulting in BOO and bladder outlet weakness stress urinary incontinence may obscure underlying diabetic cystopathy.

DM affects the bladder in diverse pathological pathways, including axonal degeneration and segmental demyelination resulting in autonomic neuropathy and diminished bladder sensation [27]. Bladder ischemia is also often seen in patients with DM, which may damage nerves, leading to smooth muscle injury and DUA [28]. DM also causes an osmotic diuresis due to a high blood glucose level, which may lead to bladder distension and a rise in intravesical pressure, which may in turn affect the bladder by causing compensatory detrusor muscle hypertrophy. It has been suggested that with disease advancement, toxic products of oxidative stress such as free radicals accumulate, lead to nerve and myocyte injury, which clinically manifest themselves as impaired bladder sensation, voiding symptoms and impaired bladder emptying [21]. Nerve growth factor levels, which have been suggested as important in maintaining sensory nerve function, are reduced in patients with DM, leading to an increase in PVR and bladder capacity [29]. DM also has a direct effect on detrusor muscle function. It alters its intracellular signaling and receptor distribution which impairs proper muscle contractility [30]. In DM, non-enzymatic reactions between reducing sugars and protein amine groups result in excessive production of advanced glycation end products (AGEs) that accumulate in tissues. Increased serum AGEs was seen to associate with a significant reduction in parameters reflecting impaired detrusor contractility [31]. It is therefore clear that DM may impair bladder sensation and contractility through a variety of myogenic and neurogenic mechanisms. The control of the disease is essential in avoiding the symptoms of DUA.

5. BOO

When the detrusor muscle is faced with an increased outlet resistance the detrusor might become underactive, which is demonstrated in induced in non-physiological animal models of BOO. In these animal models of induced BOO, the bladder was found to distend owing to the rise in intravesical pressure. After that, the detrusor muscle compensated with hypertrophy and its blood supply increased. With some time of unrelieved obstruction the bladder could not compensate adequately. In this decompensated stage the bladder contractility is impaired, eventually leading to DUA [32]. Permanent contractile failure will result if the obstruction is not relieved. The suggested explanation for these changes is based upon cyclic ischemic and reperfusion injury, which may result in the generation of reactive oxygen species that lead to damage of the myocytes, hence impairment of cellular contractile function and denervation [21]. This is illustrated by reduced response to electrical stimulation, and the replacement of the detrusor muscle with fibrous connective tissue. A color Doppler was used to measure blood flow in obstructive models, a rise in intravesical pressure lead to a fall in blood flow which had a direct effect on neural and muscular detrusor function [33]. Whilst it is tempting to relate the findings from animal models and the hypothesis of ischemic reperfusion injury to explain the development of DUA in humans, it is now recognized that these non-physiological animal models are not translatable to the human condition and certainly do not reflect what is seen in a male patient with BOO. The models rely on acute obstruction, which does not resemble the real clinical picture of long standing progressive obstruction. In addition, many of the models use female animals. Clearly in a clinical setting patients may have symptoms ranging from being completely asymptomatic to having severe LUTS and even retention and there is currently no evidence to suggest a clear progression from BOO to chronic retention.

6. Neurological disease or injury

A large spectrum of neurological diseases or injuries could lead to DUA. Cerebrovascular accident (CVA) or stroke is

frequently associated with bladder dysfunction. The voiding dysfunction occurring in the acute phase of a CVA is urinary retention. In the acute setting, 50% of patients will develop urinary retention and 75% will demonstrate no detrusor contraction [34]. This occurs mainly due to detrusor are flexia from an initial cerebral shock. The long-term outcome of CVA however is most commonly in the form of DOA [34]. DUA occurs in <20% of patients with Parkinson disease [35]. The use of anticholinergic medication has been implicated as a potential contributor to DUA, yet DUA was not demonstrated on urodynamics in a study where those drugs were stopped before urodynamic assessment [36]. In multiple sclerosis, when plaques affect the lumbosacral cord, 20% of patients demonstrate DUA [37]. Multisystem atrophy (or Shy-Dragger syndrome) is a disease that can be misdiagnosed for Parkinson disease. DUA and urinary retention is seen in 52%—95% of patients with multisystem atrophy due to atrophy of efferent parasympathetic nerves [38].

In patients with infectious diseases of the nervous system, DUA can be entirely reversible as reported to occur in patients infected with herpes zoster [39]. But sometimes the neurological effect could be permanent, due to the progressive neuropathies, which occur in patients with acquired immunodeficiency syndrome (AIDS) or neurosyphilis (tabesdorsalis).

An injury at the level of the lumbosacral spinal cord may result in DUA. The injury could be fractures, trauma or a prolapsed intervertebral disc. Similarly, in cauda equina, sacral and pelvic nerves result in DUA. Radical pelvic surgery can injure the pelvic plexus, leading to DUA as well. It is not possible to determine the number of patients with DUA caused by radical pelvic surgery because of the absence of studies that correlate urodynamic findings before and after surgery.

7. Diagnosis

DUA can only be diagnosed by invasive urodynamic testing. Detrusor strength is the best measure of detrusor muscle function. Detrusor muscle contraction speed and duration of the contraction are equally important methods for assessing detrusor muscle function, but are often overlooked. Since the bladder contraction generates both urine flow and intravesical pressure, the urodynamic measurement of detrusor pressure generated to initiate flow is an underestimate to the full bladder contractile function [40]. Although the measurement of detrusor pressure at maximum flow ($P_{det}@Q_{max}$) is easily measured during urodynamic testing, it does not represent the peak contraction strength. When flow is stopped the bladder pressure will reach a maximum value (isovolumetric pressure), but when flow is free the pressure would drop to the minimum allowed to generate flow.

Three techniques were described to obtain an isovolumetric detrusor pressure. Voluntary interruption of voiding is one method, the patient is asked to interrupt the flow by contracting the external sphincter. Mechanical interruption is another way, where the urethra is blocked mechanically midstream (a catheter balloon pulled at the bladder neck is an example). Other means of measuring bladder pressure using interrupted and uninterrupted flow were developed, but have limited role in clinical practice [41].

The watts factor (WF) represents the mechanical power per unit area of bladder surface generated by a contracting detrusor [42]. The advantages of the WF are that it depends minimally on bladder volume and is not affected by the presence of BOO [43]. The WF, nevertheless, involves a complex calculation limiting its clinical application.

The linear passive urethral resistance relation (linPURR) is a two-dimensional format that allows clear identification of individual outflow conditions with distinction of different obstruction types [44]. It assesses detrusor contraction strength by drawing linPURR onto Schafer's pressure/flow nomogram, where the peak of the PURR signifies the detrusor contraction strength.

Bladder sensation evaluation is also an important consideration in the diagnosis of DUA as the afferent nerves have a fundamental role in initiating and maintaining bladder contraction.

8. Conclusion

DUA is a major factor causing significant LUTS, which may have an effect on lower urinary tract function and on the QoL. DUA has received little attention in the scientific literature. Many essential characteristics of this condition remain unclear. Determining a generally accepted urodynamic quantification to define DUA is essential. Thorough epidemiologic studies to determine the true prevalence of DUA are needed. It is also important to understand the natural history of DUA, its pathophysiology and multifactorial aetiology. Further clarification of these mechanisms could support the development of innovative treatment options.

Conflicts of interest

Reem Aldamanhori declares no conflict of interest. Nadir I. Osman has received speaker fees and an educational grant from Astellas. Christopher R. Chapple is a researcher and speaker for Astellas, Pfizer, Recordati, Lilly and Allergan.

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