# Male Lower Urinary Tract Symptoms - An Old Problem from A New Perspective

Hann-Chorng Kuo, M.D.

Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan

#### WHAT ARE LOWER URINARY TRACT SYMPTOMS IN MEN?

Lower urinary tract symptoms (LUTS) include storage symptoms (increased bladder sensation, frequency, urgency, urge incontinence and nocturia), empty symptoms (hesitancy, dysuria, intermittency, small caliber of urine, terminal dribble and residual urine sensation) and painful symptoms (pelvic pain, perineal pain and urethral pain). LUTS are highly prevalent in men and women and increase with age [1]. LUTS are common among elderly men and as a result it is usually considered a synonym of benign prostatic hyperplasia (BPH). However, it as been estimated that only 25% to 50% of men with BPH have LUTS, and only 50% of men with LUTS have urodynamically proven bladder outlet obstruction (BOO) due to BPH or another urethral condition [2].

#### PREVALENCE OF MALE LUTS

LUTS are highly prevalent in men. The overall prevalence of LUTS has been estimated to range from 18.7% to 40% and this increases with age but does not differ by sex or race/ethnicity [3,4]. In men over 65 years old, the prevalence of one or more troublesome LUTS that affects their daily life has been estimated to be 48% [5]. A 5-year longitudinal study of men over 45 years old found that LUTS showed no change in 19% of individuals, worsened in 50%, and improved 31% [6]. The most important risk factor for the development of LUTS was age and there was also a trend towards a higher International Prostate Symptom Score (IPSS) in men with elevated blood pressure and a large waist size [7]. A longitudinal study of black American men found that about 25% of those older than 60 years showed a measurable progression in LUTS severity over time [8].

The prevalence and severity of LUTS increase with age and the progressive increase in the ageing population has increased the social economic burden and severity of LUTS [9]. Among the symptoms in LUTS, the prevalence increase with age is found only to affect urgency, weak stream and nocturia, while the other symptoms are equally distributed across the various age groups [10]. Although the prevalence rates of nocturia, frequency, urge incontinence and nocturnal incontinence are not very high, however, the bothersomeness of these symptoms is very high [11]. In an epidemiological study in eastern Taiwan, nocturia (>2 voids per night) was found to be the most bothersome aspect of LUTS among both aborigines and non-aborigines, with prevalence rates of 31.1% and 19.8%, respectively. About 15% of men reported that their LUTS had great impact on their

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Address correspondence to: Dr. Hann-Chorng Kuo, Department of Urology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien, Taiwan E-mail: hck@tzuchi.com.tw

quality of life [12].

A large multinational study has revealed that 90% of men aged 50 to 80 years suffer from potentially troublesome LUTS and many men have both storage and voiding symptoms [13]. It has been estimated that only 25% to 50% of men with histologically confirmed BPH have LUTS [14], whereas urodynamic BOO is found in only 48% to 53% of men referred for investigation of their LUTS [2,15]. In a study of 185 men with post-prostatectomy LUTS, detrusor overactivity (DO) was found in 10% and detrusor hyperactivity with inadequate contractility (DHIC) in 15%. Most patients with post-prostatectomy LUTS have a small prostate at baseline and a small resected prostate weight [16]. These findings suggest that there might be a tendency to misdiagnose LUTS as BPH, leading to a less favorable surgical result.

#### MALE LUTS AND BPH/BOO

Clinically, diagnosis of BPH and BOO is usually made based on a total prostate volume of more than 40 mL, a maximum flow rate of less than 10 mL/s in combination with a high symptom score of LUTS especially the voiding symptoms [17]. Although the specificity is not high, an initial treatment with alpha-adrenergic antagonists to target the BOO can be given to observe whether a therapeutic effect occurs before an accurate diagnosis is made [18]. However, for men with both storage and voiding symptoms, the clinical diagnosis of lower urinary tract dysfunction becomes more difficult, and an urodynamic pressure flow study usually is needed to accurately identify the pathophysiology and provide appropriate treatment.

BOO is an urodynamic condition implying voiding with a high pressure and/or low flow rate. Patient will develop LUTS (storage and/or empty LUTS) when BOO has developed to a considerable degree. BOO can happen in men and women, in adults and children, and may be associated with both anatomical and neurogenic conditions. In a study investigating men without BOO and LUTS, the maximum flow rate (Qmax) can reach up to 20 mL/s with a mean voided volume of 290 mL. One third of men with LUTS do not have BOO. Many clinical studies have demonstrated that LUTS have a poor diagnostic specificity with respect to BOO and 5% to 35% of patients with BPH and LUTS show not improvement to their symptoms after transrectal ultrasonic physiotherapy (TURP) [19]. Prostate size and uroflowmetry show a better correlation with an urodynamic study than with symptoms alone.

Clinical BPH is defined as having at least two of the following: (1) moderate to severe LUTS (IPSS  $\geq$ 8), (2) an enlarged prostate (total prostatic volume, TPV  $\geq$ 30 mL) and (3) decreased Qmax (<15 mL/s) [20]. Although an enlarged prostate might not indicate the presence of BOO, the mean TPV in patients with BOO is significantly higher than that in patients without BOO [21]. In addition, patients with LUTS that is

suggestive of BPH and with a Qmax of <10 mL/s have a greater improvement in Qmax after TURP compared with those with a Qmax of > 10 mL/s. Patients without evidence of BOO preoperatively also have a poor prognosis after TURP [22]. Patients with postoperative LUTS were found to have a small TPV at the time of surgery, suggesting that a non-BPH etiology might account for their LUTS [16]. Therefore, diagnosis of clinical BPH should be carried out very careful especially when an invasive procedure such as TURP is going to be undertaken.

#### PATHOPHYSIOLOGY OF MALE LUTS

The pathophysiology of LUTS may be bladder dysfunction (bladder hypersensitivity, DO), BOO (bladder neck dysfunction, prostatic obstruction, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia) or a combination of these etiologies [23]. Many men have both storage and voiding symptoms. In men, empty symptoms are more common, but storage symptoms are also encountered frequently [24]. Frequent co-morbidity with prostatic diseases in men adds a significant degree of complexity to the diagnosis and management of male LUTS.

LUTS in men would seem to result from a complex interplay of pathophysiology, including bladder dysfunction and bladder outlet dysfunction such as BPH or poor relaxation of the urethral sphincter. About one third of men with LUTS and who are over the age of 55 years do not have BPO. Men younger than 55 years old are more likely to have poor relaxation of the urethral sphincter as a cause of their LUTS [12]. As a result of LUTS being poorly diagnostic for BPO, patients with LUTS should be carefully investigated to identify possible bladder or bladder outlet dysfunctions.

BPO due to BPH is commonly seen after the age of 60 years [25]. A similar incidence of BPH/BOO in the 56 to 65 years old age group has been found as that in more advanced age group [12]. This earlier study also found a high incidence of DO in patients with BPO (80.9%), and a low incidence of BPO in patients without DO (11.5%), which suggests that bladder dysfunction is highly associated with and secondary to bladder outlet dysfunction. However, 39.3% of patients without BPO had DO, indicating that DO can develop without a strong dependence on aging and without the occurrence of bladder outlet dysfunction. These findings are in agreement with previous reports [26-28].

The presenting symptoms of LUTS are similar in patients with or without BPO. More than 80% of patients without BOO also complained of dysuria. By comparison, urgency has been found to be highly prevalent in patients with DO, with DHIC as well as in patients with bladder outlet dysfunctions such as bladder neck dysfunction and BPO. Urgency has been also noted in one third of the patients with detrusor underactivity, poor relaxation of urethral sphincter and normal urodynamic findings. These results suggest that bladder symptoms are not a reliable indicator of the presence of DO. Patients might feel dysuria because they have urgency sensation due to a small bladder volume. They also might have a tolerable sensory urgency but still feel urge to void. A more detailed questionnaire exploring the severity of urgency might be necessary in order to quantify the urgency and provide a more accurate correlation with urodynamic DO [29].

#### MALE LUTS AND BLADDER CONDITIONS

Frequency and nocturia are the two most common reported bothersome LUTS. In the BACH survey of LUTS, nocturia was reported by 28.4% of people, increased with age, had a higher prevalence in minority populations, and was associated with increasing body mass index, type II diabetes and cardiac disease [30]. A recent study showed that increasingly severe LUTS was associated with a low quality of life (QoL) [31]. Another study found the prevalence of LUTS and erectile dysfunction (ED) significantly increased with age and the presence of LUTS and QoL impairment due to LUTS was an independent risk factor for the presence of ED [32]. Nocturia was the most prevalent form of LUTS in this study. This result is in accordance with previous LUTS surveys [33,34]. Nocturia has multiple attributable factors and is known to increase with age.

In a previous study of a large cohort of men with both storage and voiding symptoms, it was revealed that increasing age was associated with increased incidences of DO and DHIC, especially when the age exceeded 76 years [35]. In contrast, men younger than 65 show a higher incidence of hypersensitive bladder. These bladder dysfunctions may impact on the trend towards an increase in storage LUTS, which appear to be more closely associated with DO in elderly men and hypersensitive bladder in younger men. Overactive bladder (OAB) symptoms in men are often caused by bladder dysfunctions such as DO, DHIC, but also frequently occur in patients with BOO, including BPH, bladder neck dysfunction and poor relaxation of the urethral sphincter [36].

# MALE OAB - A PRIMARY OR SECONDARY BLADDER DISORDER?

#### Bladder hypersensitivity

Among the various etiologies of LUTS due to non-BPH conditions, bladder hypersensitivity and DO are commonly found especially in the elderly men. Sensory urgency may be the presenting symptom of the patients with DO poor relaxation of urethral sphincter, interstitial cystitis, BOO or neurogenic voiding dysfunction. Recent investigations have shown that the urothelial release of neurotransmitters such as acetylcholine (Ach), adenosine triphosphate (ATP) and the neuropeptide substance P, and the expression of TRPV1 and P2X3 receptors in the urothelium have a significant role in human bladder mechanosensation [37,38]. Release of urothelial Ach decreases but ATP production increases with ageing. These physiological changes in the elderly men point to a high prevalence rate of bladder hypersensitivity and OAB and are possibly responsible for the occurrence of DHIC in the elderly men [39].

#### Overactive Bladder

Recent investigations of male LUTS have noted that bladder dysfunction plays an important role in addition to BOO. A multinational large scale study revealed that 90% of men aged 50 to 80 years suffer from potentially troublesome LUTS and many men have both storage and voiding symptoms [13]. OAB symptoms comprise the same symptoms as storage LUTS in BPH and prevalence increases with age. Since most men with OAB do not experience incontinence, men with storage LUTS are often misdiagnosed with clinical BPH [40]. However, the presence of storage LUTS correlates poorly with BOO and male OAB symptoms.

toms may be caused by bladder dysfunctions such as DO or DHIC, or occur in combination with BOO. However, many studies have reported only 45% to 50% of men with LUTS have urodynamically confirmed DO and BOO [15].

DO can be idiopathic or be due to myogenic overactivity, poor cortical perfusion, post-obstructive DO, the ageing process or DHIC. In men with LUTS, we should exclude BOO first. In a recent study of the pathophysiology of male LUTS, only 29.4% of men have BPO and DO makes up 51.1% of male LUTS. Among the patients with BPO, 80.9% of men have DO; however, among the patients with urodynamic DO, only 48% of men have urodynamic BPO [35]. Patients with BPO but without OAB symptoms may develop *de novo* OAB after TURP, which suggests that destruction of the trigone mucosa might result in OAB [41]. Treatment of patients with BPO and OAB should include agents that relieve urethral resistance together with antimuscarinics when the OAB symptoms cannot be resolved after treating with alphablocker or combined 5-alpha reductase inhibitor.

#### Treatment of OAB in men with LUTS

The use of antimuscarinic agents has been the mainstay of the pharmacological treatment of patients with an OAB. These agents can suppress detrusor contractility through inhibiting the muscarinic receptors in the urinary bladder. Recent investigations have shown that ACh is present the urothelium and ACh expression increases with ageing. OAB symptoms or DO may be mediated through an abnormal increase in the urothelial production of Ach and a decrease in the threshold of bladder sensation or detrusor contraction. Patients with BOO and OAB might have both increased outlet resistance and urothelial dysfunction. Therefore, treatment of OAB symptoms by antimuscarinic agent is able to target at urothelial dysfunction without affecting the detrusor contractility. A combination therapy for BOO and OAB involving an alpha-blocker and an antimuscarinic agent is rational and has little effect on the detrusor contractility.

An increase in difficult urination and postvoid residual (PVR) are two adverse events previously believed to be associated with antimuscarinic therapy for OAB. However, recent studies have shown that, in fact, treatment with antimuscarinic agent in combination with alpha-blocker does not cause the hypothesized adverse effects. Based on reported evidence, patients with BOO and an OAB are able to obtain an improvement in their LUTS from antimuscarinic treatment with-

out influencing voiding efficiency. Treatment with an antimuscarinic agent can provide relief affecting urgency sensation or DO without reducing detrusor contractility. After combined therapy for BOO and OAB, the maximum flow rate does not decrease because the bladder capacity has increased through a decrease in the urgency sensation. The voiding efficiency and PVR did not change significantly, which suggests that the suppression of muscarinic receptor hyperactivity by antimuscarinic agents is not accompanied by a decrease in detrusor work in the absence of severe BOO.

#### OTHER CONDITIONS CAUSING MALE LUTS

#### Nocturia and nocturnal polyuria

LUTS are common in elderly and among these symptoms it has been found that nocturia is the third most bothersome aspect of LUTS. The prevalence of nocturia increases to 80% in patients aged over 80 years. Nocturia is one of the most common causes of a disturbed sleep pattern in the elderly. The causes of nocturia include DO, hypersensitive bladder, BOO, nocturnal polyuria or small bladder capacity. When the nocturnal urine volume is >900 mL or alternatively more than 35% of the daily voided volume, nocturnal polyuria is likely. Lack of a diurnal desmopressin rhythm may be a cause of nocturnal polyuria and can be treated with exogenous desmopressin such as DDAVP [42]. In addition, for patients with combined nocturnal polyuria and BOO or OAB, combined multiple medication is often necessary to relieve this type of complex male LUTS.

#### Poor relaxation of urethral sphincter

Among the various causes of non-BOO male LUTS, poor relaxation of the urethral sphincter is the most frequently encountered condition [23]. Patients might have symptoms of hesitancy, intermittency, small caliber urine, or postvoid dribble. Some patients might also have storage symptoms such as urgency or frequency. The causes for poor relaxation of the urethral sphincter might be a learned habit, chronic prostatitis, pelvic floor hypertonicity, occult neuropathy or increased bladder sensitivity. Although this condition does not affect urinary tract function, the symptoms might have a major impact on the patient's quality of life, especially among the younger members of the aged population. Diagnosis can be made by uroflowmetry, combined electromyography study or videourodynamic pressure flow study.

Table 1. Analysis of Pathophysiology of Male LUTS in 1407 Men by Age [35]

| Pathophysiology              | <55 years (172) | 56-65 years (282) | 66-75 years (519) | >76 years (434) | <b>Total</b> (1407) | p value |
|------------------------------|-----------------|-------------------|-------------------|-----------------|---------------------|---------|
| Bladder dysfunction          |                 |                   |                   |                 |                     |         |
| Hypersensitive bladder       | 28 (16.3%)      | 38 (13.5%)        | 56 (10.8%)        | 28 ( 6.5%)      | 150 (10.7%)         | 0.001   |
| Detrusor overactivity        | 32 (18.6%)      | 103 (37.0%)       | 285 (55.0%)       | 302 (70.0%)     | 722 (51.5%)         | 0.000   |
| DHIC                         | 1 ( 0.6%)       | 6 ( 2.1%)         | 20 ( 3.9%)        | 51 (11.8%)      | 65 ( 4.6%)          | 0.000   |
| Detrusor underactivity       | 10 ( 5.8%)      | 31 (11.0%)        | 58 (11.2%)        | 54 (12.4%)      | 153 (10.9%)         | 0.127   |
| Bladder outlet dysfunction   |                 |                   |                   |                 |                     |         |
| BN dysfunction               | 6 ( 3.5%)       | 5 ( 1.8%)         | 5 ( 1.0%)         | 3 ( 0.7%)       | 19 ( 1.4%)          | 0.041   |
| BPO                          | 18 (10.5%)      | 80 (28.4%)        | 167 (32.0%)       | 148 (34.0%)     | 413 (29.4%)         | 0.000   |
| Pseudodyssynergia            | 3 (1.7%)        | 4 ( 1.4%)         | 14 ( 2.7%)        | 9 ( 2.1%)       | 30 ( 2.1%)          | 0.656   |
| Poor relaxation of sphincter | 78 (45.3%)      | 74 (26.2%)        | 90 (17.3%)        | 41 ( 9.4%)      | 283 (20.1%)         | 0.000   |
| Normal UDS finding           | 24 (14.0%)      | 31 (11.0%)        | 35 ( 6.7%)        | 15 ( 3.5%)      | 105 ( 7.5%)         |         |

Abbreviations: DHIC = detrusor hyperactivity with inadequate contractility, BN = bladder neck, BPO = benign prostatic obstruction, UDS = urodynamics

#### Painful symptoms

Several conditions can cause painful symptoms in men. Interstitial cystitis, BOO, poorly compliant bladder and transitional cell carcinoma can cause a painful bladder. Urinary tract infection, urethral stricture, BPO and chronic prostatitis can cause a painful urethra. A painful pelvis or a painful perineum can be due to pelvic floor hypertonicity, chronic prostatitis, spastic urethral sphincter or perianal inflammation. Treatment of such painful symptoms in men is not easy and should be based on an exact diagnosis for the painful symptoms. Digital rectal examination and prostatic massage in order to examination the prostatic fluid, urethrocystoscopy to exclude urethral stricture, and performing random bladder biopsies to investigate the possibility of carcinoma *in situ* are the diagnostic procedures necessary for male painful symptoms.

Transitional cell carcinoma of the bladder usually mimics interstitial cystitis in men with LUTS and painful bladder syndrome. Characteristic glomerulation may appear after cystoscopic hydrodistention and bladder biopsy may reveal nonspecific chronic cystitis. However, when long-term medications such as pentosanpolysulphate or COX-2 inhibitor fail to relieve the symptoms, it is necessary to repeat the cystoscopy, carry out further urine cytology and do multiple random bladder biopsies in order to pinpoint early bladder carcinoma.

#### Postprostatectomy male LUTS

Over half of patients with post-prostatectomy LUTS had a small total prostate volume and resected adenoma weight, indicating their LUTS were non-BPH or non-BOO conditions before TURP. Among the patients with postprostatectomy LUTS, a normal urethra and bladder has been noted in 9.1% of the patients, DO in 9.6% of patients, detrusor underactivity in 18.7% of patients, poor relaxed external sphincter in 19.3% of patients, DHIC in 14.4% of patients and residual BOO in 27.8% patients [16]. Detailed cystoscopy and a videourodynamic study are necessary for these patients especially when they are diagnosed to have residual BPH or BOO and repeat transurethral surgery is being planned. A narrow urethral segment might not necessarily be responsible for the postprostatectomy LUTS. DHIC, bladder hypersensitivity or OAB can also be the cause of male LUTS in the presence of a small BPH.

#### Other urethral conditions

Urethral sphincter pseudodyssynergia in patients with chronic stroke, intracranial lesions, Parkinson's disease or spondylolisthesis can cause severe empty symptoms or storage symptoms in the elderly men [43]. These patients might have BPH but the LUTS are caused by conditions other than BPH. Searching for evidence of BOO is mandatory before proceeding with an invasive procedure for the male LUTS. Otherwise the LUTS is usually not resolved by the procedure. Urethral stricture or urethral meatal stenosis can cause BOO and LUTS, especially in the patients that have had a previous transurethral procedure. A detailed physical examination and urethral dilatation may relieve the LUTS without undertaking any invasive diagnostic procedure.

#### ASSESSMENT OF MALE LUTS

Assessment of male LUTS should include a self-assessed symptom score questionnaire such as American Urogical Association (AUA) symptom score and IPSS [44]. A voiding diary recording the frequency

of urgency episodes and the voided volume provides a great help with the initial diagnosis of OAB and other polyuria conditions. Uroflometry and PVR, prostatic measurement using digital rectal examination, transrectal sonography and transabdominal sonography are also helpful. In order to assess lower urinary tract neurophysiology, a neurological examination is necessary such as bulbocavernous reflex, perineal sensation and spontaneous anal sphincter contraction. Cystometry, urethral sphincter electromyography and a pressure flow study with or without cinefluoroscopy can provide further information on detrusor function and sphincter activity. Cystoscopy can also help us to diagnose urethral stricture or severe prostatic obstruction. After the initial diagnosis, the male patients with LUTS can be classified into LUTS suggestive of BPH, LUTS suggestive of DO, detrusor underactivity or a disease of neurological origin. Patients might have a combination of detrusor dysfunction and BOO or urethral conditions.

Using IPSS subscores as the initial differential diagnosis for bladder-related and urethral-related conditions associated with male LUTS is recently gained attention. Most of the physicians managing male LUTS are general practitioners and not urologists and therefore they do not have adequate equipment to investigate flow rate or the prostate volume. In these circumstances, diagnosis of the causes for male LUTS is largely based on the presenting symptoms. In a recent analysis of male patients with bothersome LUTS, we found the ratio of empty IPSS score to storage IPSS score can be used as the initial diagnostic tool when making a differential diagnosis between the various urethral related conditions (i.e. bladder neck dysfunction, BPO, poor relaxation of the urethral sphincter) and the various bladder related conditions (i. e. hypersensitive bladder, DO). Medication targeting the urethral related conditions such as alpha-blockers and targeting the bladder related conditions using antimuscarinic agents can have a successful rate of more than 70%. It is encouraging to use this simple diagnostic tool to assess male LUTS and then prescribe the first drug for patients who have LUTS. In these circumstances, patients can be referred to a urology specialist only when their LUTS cannot be successfully managed by first line medication.

#### CONCLUSIONS

LUTS in men can be caused by both bladder and bladder outlet dysfunctions that may occur alone or in combination. The presenting symptoms of male LUTS are similar in patients with or without BPO. Many patients without BOO also complain of dysuria. On comparison, urgency was highly prevalent in patients with DO and DHIC as well as in patients with bladder outlet dysfunctions such as bladder neck dysfunction and BPO. Bladder symptoms are not reliable indicators of the presence of DO. LUTS is not useful for the differential diagnosis of BPO or non-BPO in men. The key symptom of OAB, namely urgency, cannot be used to make a definite diagnosis of DO. The etiologies of LUTS may involve both bladder dysfunctions and bladder outlet dysfunctions. Accurate diagnosis of lower urinary tract dysfunction should be based on a comprehensive urodynamic study, which allows the correct selection of therapy that is aimed at the underlying pathophysiology. However, for the first line treatment for male LUTS, a simple approach is to use the ratio of IPSS empty to storage subscores to make the initial differential diagnosis of a urethral or bladder related condition.

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