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Review Article

# Current consensus and controversy on the treatment of male lower urinary tract symptoms/benign prostatic hyperplasia

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**Abstract**

Lower urinary tract symptoms (LUTS) are highly prevalent in men and increase with age. Because LUTS are common among elderly men, they are usually considered synonymous with benign prostatic hyperplasia (BPH). Drugs should be the first-line treatment for BPH and surgical intervention should be performed only when there are complications or LUTS refractory to medical treatment. In addition to medical treatment, several minimally invasive therapies, such as thermal therapy, prostatic lift, laser evaporation, or laser enucleation techniques have been developed. Recent investigations have also revealed that bladder dysfunction such as detrusor overactivity and detrusor underactivity may also contribute to male LUTS. In the treatment of LUTS suggestive of BPH (LUTS/BPH), the following questions should be considered: Is there an obstruction? Are we treating BPH or LUTS? Can management targeting BPH reduce LUTS? Should patients with LUTS be treated before bladder outlet obstruction is confirmed? What is the role of transurethral resection of the prostate (TURP) nowadays? Will new techniques provide better outcomes than TURP? This article discusses the current consensus and controversies in the treatment of LUTS/BPH.

**Keywords:** *Lower urinary tract symptoms, Medical treatment, Overactive bladder, Quality of life, Surgery*

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## Surgical versus drug management of male lower urinary tract symptoms/ benign prostatic hyperplasia

In past years, benign prostatic hyperplasia (BPH) was a surgical disease. In men with moderate to severe lower urinary tract symptoms (LUTS) and a large postvoid residual (PVR) volume, bladder stone formation, gross hematuria, recurrent urinary tract infection, or upper urinary tract deterioration, surgical intervention using open prostatectomy or transurethral resection of the prostate (TURP) was indicated for rapid relief of LUTS [1]. With the advent of medical therapies, nowadays <10% of men with LUTS/BPH are treated surgically. In a trial combining doxazosin and finasteride, significant improvements in the BPH Impact Index and International Prostate Symptom Score (IPSS) – quality of life (QoL) scores were observed in men assigned to combined treatment groups compared with those assigned to placebo. Most patients with LUTS/BPH can be successfully managed by medical treatment [2]. Initial treatment of LUTS/BPH with alpha-adrenoceptor antagonists to target bladder outlet obstruction (BOO) can be given before an accurate diagnosis is made [3]. In patients with a large prostate volume >30 mL, combined alpha-blockers and 5-alpha-reductase inhibitors can effectively reduce the prostatic size by 25% and relieve LUTS [4]. Combination therapy with dutasteride plus tamsulosin also provided significantly superior improvements in patient-reported QoL and treatment satisfaction compared with either monotherapy at 4

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years in men with a moderate-to-severe IPSS. Less than 5% of men treated had complications and needed surgical intervention at the 4-year follow-up [5].

However, there is no consensus regarding the most appropriate timing for surgical intervention in men with LUTS/BPH. Progression of symptoms after long-term medical treatment, occurrence of complications, and patient preference are all indications for surgical intervention. However, many patients refuse surgery because they are afraid of developing urinary incontinence after surgery. With the advent of minimally invasive prostatic surgery, bleeding and postoperative pain can be reduced to a minimum, and patients' acceptance of surgical intervention can also be increased [6]. Therefore, more patients with LUTS refractory to medical treatment are being encouraged to receive minimally invasive prostatic surgery such as laser TURP, even if their prostate volume is small. The results of surgical intervention might not be as good as open prostatectomy, especially in men with storage predominant symptoms after medication for BPH and BOO. We believe an accurate diagnosis and identification of the cause of male LUTS is paramount and can help to improve the quality of treatment. Urodynamic pressure-flow study or video-urodynamic study is mandatory in male patients who desire surgery [7].

## Overactive bladder and benign prostatic hyperplasia – should antimuscarinic agents be the first-line treatment?

Benign prostatic obstruction (BPO) due to BPH is commonly seen in men with LUTS after the age of 60 years [8]. A high incidence of detrusor overactivity (DO) was found in patients with BPO (80.9%), and a low incidence of BPO in patients without DO (11.5%) suggesting the bladder dysfunction is highly associated with and secondary to bladder outlet dysfunction. Interestingly, 39.3% of patients without BPO had DO, indicating that DO can develop without a strong dependence on aging or bladder outlet dysfunction [9,10].

Overactive bladder (OAB) symptoms in men are not only often caused by bladder dysfunction such as DO or detrusor hyperactivity and inadequate contractility (DHIC) but also frequently occur in patients with BOO, including BPH, bladder neck dysfunction, and poor relaxation of the urethral sphincter [11]. In a previously reported cohort with both storage and voiding symptoms, increasing age was associated with increased incidence of DO and DHIC, especially in men over 76 years old [11]. Men younger than 65 years show a higher incidence of hypersensitive bladder.

A multinational large scale study revealed that 90% of men 50–80 years old suffer from potentially troublesome LUTS, and many men have both storage and voiding symptoms [12]. 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 and are often undergo unnecessary prostate surgery when alpha-blocker therapy has failed [13].

The use of antimuscarinic agents has been the mainstay of pharmacological treatment of patients with an OAB. Treatment of OAB symptoms by antimuscarinic agents can target urothelial dysfunction without too much affecting detrusor contractility. Combination therapy for BOO and OAB involving an alpha-blocker and an antimuscarinic agent is rational and has little effect on voiding efficiency [14].

An increase in difficult urination and PVR are two adverse events previously believed to be associated with antimuscarinic therapy for BOO and OAB. However, recent studies have shown that, in fact, treatment with combined antimuscarinic agents and alpha-blockers does not cause these hypothetical adverse events [14]. Based on reported evidence, patients with BOO and OAB were able to obtain improvement in storage LUTS from antimuscarinic treatment without influencing voiding efficiency [15]. The voiding efficiency and PVR did not significantly change, suggesting 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.

## Underactive bladder and benign prostatic hyperplasia – will transurethral resection of the prostate benefit patients?

Chronic urinary retention is a debilitating bladder disorder that greatly impacts QoL as well as health. In elderly patients with chronic medical disease (such as diabetes mellitus [DM] and chronic heart failure) or neurological diseases (such as cerebrovascular accident, Parkinson's disease, and dementia), chronic urinary retention due to an underactive bladder (UAB) is frequently encountered and difficult to manage. The pathophysiology of chronic urinary retention may involve neurogenic, myogenic, and bladder outlet pathologies [16]. Patients with UAB usually have a diminished bladder fullness or urgency sensation and cannot contract the detrusor sufficiently to complete bladder emptying. Patients with UAB usually void with abdominal straining, and an intermittent flow

pattern is noted. The bladder sensation may be normal, or the first sensation or urge sensation is reduced [17].

UAB in elderly patients usually presents with difficult urination, urinary retention, and LUTS. Urodynamic detrusor underactivity (DU) was found in nearly two-thirds of incontinent institutionalized elderly [18]. DU is also common in older patients, in those with general weakness and medical diseases such as DM, debilitating disease, and cancer in the terminal stage and after major surgery [19]. UAB may be chronic or temporary. In clinical practice, we have observed patients with BOO and normal detrusor contractility who developed transient DU after TURP or immediately after an acute illness such as a stroke. These patients may regain spontaneous voiding within 1–3 months. However, some patients develop chronic DU and spontaneous voiding may not return in the short term.

Patients with chronic urinary retention usually have low voiding pressure or DU. In video-urodynamic study, it is difficult to differentiate whether patients have BOO or not. Chronic BOO can result in structural and functional changes in the bladder wall. Detrusor contractility may be reduced in patients with chronic urinary retention or a large PVR due to BPH with BOO [20]. Patients with chronic BOO might also have a low detrusor pressure and large PVR. Differentiation between idiopathic DU and DU resulting from chronic BOO is not an easy task. The total prostate volume (TPV) and cystoscopy should be checked for the possible existence of BOO due to an enlarged prostate. Patients with clinical UAB and a TPV >40 mL are likely to have BOO, but patients with a TPV <30 mL might not have prostate obstruction.

Detrusor, bladder neck, and urethral sphincter dysfunction are usually characterized as motor neuron diseases [21]. Afferent nerves of the pudendal nerve are postulated to have a potential modulatory effect on sympathetic neuronal control in various neuropathic and nonneuropathic bladder dysfunctions [22]. Bladder neck dysfunction seems to represent sympathetic hyperactivity or dysfunction and poor accommodation, which are considered secondary to abnormal adrenergic detrusor innervation [23]. Clinically, transurethral incision of the bladder neck (TUI-BN) or TURP to ablate urethral smooth muscle not only disrupts the continuity of the tight bladder neck but also might abolish the inhibitory effect on detrusor contractility [24]. Patients with idiopathic DU may regain adequate detrusor contractility and resume spontaneous voiding [25,26]. A poorly relaxed urethral sphincter is thought to cause increased urethral afferent activity, which inhibits bladder afferent signaling leading to poor bladder sensation and UAB. Therefore, application of sacral neuromodulation in patients with Fowler's syndrome can restore normal voiding [27]. Patients with stroke and incomplete bladder emptying might also develop UAB/DU due to spasticity of the external sphincter [28]. In young men with LUTS, bladder neck dysfunction, dysfunctional voiding, and DU are the main urodynamic abnormalities [29,30]. Treatment targeting the bladder, urethral smooth muscle, or urethral sphincter hyperactivity might restore normal detrusor contractility and improve voiding efficiency in patients without BPO who have incomplete bladder emptying.

We have previously performed TUI-BN to decrease bladder outlet resistance in patients with UAB and DU [25]. Postoperative video-urodynamic study revealed that detrusor pressure increased significantly compared with baseline data in patients who had low detrusor contractility or DU before the operation (from 8.7 ± 9.8 to 28.3 ± 13.8 $cmH_2O$, $P = 0.021$). Four (67%) of 6 patients with DU could void with the aid of abdominal pressure after TUI-BN. Interestingly, we observed a recovery of detrusor contractility in some patients after the surgical procedure. This phenomenon is observed not only in neurogenic bladder but also in nonneurogenic DU [24,26], suggesting a micturition facilitating reflex might be triggered after TUI-BN.

It is also possible that the inhibitory effect of adrenergic hyperactivity on detrusor contractility can be modulated after TUI-BN, resulting in recovery of detrusor function that was inhibited through unknown mechanisms. In a recent clinical study, 78.9% of patients with an acontractile bladder had significant return of detrusor contractility after laser enucleation of the prostate [31]. Since the prostatic urethra is innervated mainly by the sympathetic adrenergic nerves, ablation of the prostatic urethra might abolish the sympathetic hyperactivity which inhibits detrusor contractility.

## Surgical procedure for benign prostatic hyperplasia – do new techniques provide better outcomes?

TURP is the gold standard surgical procedure for male LUTS due to an enlarged prostate after the failure of medical treatment. The procedure, although not complication-free, has been accepted as safe and effective for elderly men for more than 50 years. Open prostatectomy has been abandoned except in special cases in which TURP is not feasible or the estimated prostate size is over 100 mL. With the advent of minimally invasive prostatic surgery such as bipolar TURP, transurethral laser evaporation or enucleation, transurethral prostate lift, and laparoscopic

or robotic-assisted prostatectomy, more urologists are using innovative techniques to treat BPH, especially in patients with bleeding tendencies, anticoagulant therapy, or a huge prostate [32-34]. These techniques have been welcomed by young urologists. Head to head comparisons of innovative procedures and TURP have not been well conducted. Recent evidence has shown that most of the procedures have similar treatment outcomes and complication rates [35,36].

Each innovative BPH surgical procedure has its specific indications, advantages, and disadvantages. For incidence, bipolar TURP and laser TURP are safe for elderly men with bleeding tendencies, anticoagulant therapy, or poor heart and lung function. However, the economic burden is a problem in developing countries. Prostate lift is another promising procedure. Patients can be treated under local anesthesia, and the therapeutic effect is satisfactory. However, the procedure is also expensive, and long-term efficacy has not yet been determined. Laparoscopic or robotic-assisted prostatectomy, although minimally invasive, requires general anesthesia and is very expensive. There seems no acceptable reason to use these innovative surgical procedures to treat men with a healthy general condition or a TPV $n < 100$ mL or those who cannot afford the high surgical expenses. The most important thing is to make an accurate diagnosis of BPO, make sure that the LUTS originate from an enlarged prostate, and ensure that the surgical procedure can relieve the LUTS. Surgery with traditional TURP or any innovative procedure will be good for the patients. Although minimally invasive techniques have been well developed, urologists should balance the costs of the surgery against patient benefits.

## Precision medication for treatment of male lower urinary tract symptoms/ benign prostatic hyperplasia

Patients with LUTS suggestive of bladder dysfunction due to OAB can be started on antimuscarinic agents or beta-3 adrenoceptor agonists [37,38]. However, the treatment for OAB using antimuscarinics in adults 65 years old or older should be done cautiously because the risk of several cholinergic or noncholinergic adverse events might increase [39]. The guidelines of the European Association of Urology advise that initial treatment of LUTS and OAB be conservative, including lifestyle interventions, physiotherapy, pharmacotherapy, and is of an empirical nature [40]. Patients with LUTS suggestive of bladder neck dysfunction, small prostatic obstruction, and poor urethral sphincter relaxation can be started on alpha-blockers. In patients with an enlarged prostate >40 mL, combined alpha-blockers and 5-alpha-reductase inhibitors can be used for a more efficacious treatment outcome and prevention of complications and BPH-related surgery. Medical treatment provides satisfactory results in most of men with LUTS/BPH. Surgical procedures may be considered when the treatment result is not satisfactory based on improvement in QoL, development of BOO-related complications, or patient preference.

## Conclusions

The pathophysiology of LUTS could be bladder dysfunction, bladder neck dysfunction, prostatic obstruction, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia, or a combination of these etiologies. The diagnosis and treatment of male LUTS is precision medicine. In patients with LUTS/BPH, we should make a tentative diagnosis of bladder dysfunction or bladder outlet dysfunction and lifestyle modification, and medical treatment should be given first. Surgical treatment should be reserved for cases in which initial management has failed. Although minimally invasive techniques have been well developed, urologists should balance the costs of the surgery against patient benefits.

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### Conflicts of interest

There are no conflicts of interest.

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