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Review Article

Pathophysiology of benign prostate enlargement and lower urinary tract symptoms: Current concepts

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Abstract

Lower urinary tract symptoms (LUTS) are highly prevalent in the aging population, particularly in men. Historically, prostate enlargement was thought to be responsible for most cases of male LUTS. Several risk factors for the development of benign prostate enlargement/hyperplasia (BPE/BPH) have been identified, including age, genetics, hormones, growth factors, inflammation, and lifestyle factors. However, as our knowledge continues to evolve, male LUTS are no longer managed entirely in a prostate-centric fashion. In this article, we review current concepts in the epidemiology, etiology, and pathophysiology of BPE/BPH and male LUTS.

Keywords: *Benign prostate enlargement, Benign prostate hyperplasia, Bladder outlet obstruction, Lower urinary tract symptoms*

Introduction

Lower urinary tract symptoms (LUTS) represent one of the most common and bothersome conditions seen in daily urologic practice, affecting at least one in every four men older than 40 years [1]. LUTS include a range of storage (irritative), voiding (obstructive), and postmicturition symptoms, have a negative impact on health-related quality of life (QoL) and are associated with high personal and societal costs [2,3]. Although structural anomalies, neurological disease, vesicogenic conditions, and infections can play roles, benign prostate enlargement/hyperplasia (BPE/BPH) is still by far the most influential factor leading to male LUTS [4]. In this article, we review current concepts in the epidemiology, etiology, and pathophysiology of LUTS and BPE/BPH.

Pathophysiology of male lower urinary tract symptoms

The pathophysiology of LUTS could include bladder dysfunction (including bladder hypersensitivity, detrusor overactivity [DO]), bladder outlet obstruction (BOO), (including bladder neck dysfunction, prostatic obstruction, urethral stricture, poorly relaxed urethral sphincter, urethral sphincter dyssynergia), or a combination of these etiologies [5]. Many men have both storage and voiding symptoms. In men, empty symptoms are more common, but storage symptoms are encountered frequently [6]. The frequent comorbidity with prostatic diseases in men adds complexity to the diagnosis and management of male LUTS.

Epidemiology

Benign prostate hyperplasia (BPH) *per se* is rather a histologic diagnosis describing a hyperproliferative process of epithelial and stromal cells in the transition zone of the prostate [7]. It may not be of much clinical significance unless it is an imaging-proven benign prostate enlargement resulting in BOO and associated with bothersome LUTS [8]. The prevalence of BPE/BPH and LUTS rises markedly with aging. It is estimated that nearly 50% of all men at the age of 60 have histological BPH, and by 80 the prevalence approaches 90% [9]. Moderate to severe LUTS were reported by 26% of men 40–49-year-old and almost doubled in those 70-year-old or older [10]. There is a subtle ethnic difference in the prevalence of LUTS on a global scale [2,9,11].

BPE/BPH-related LUTS are rarely life-threatening, yet its impact on QoL can be significant and should not be underestimated in an aging population [12]. Apart from physical functioning, LUTS may also have a detrimental effect on mental health and social economy. In men with severe LUTS, the annual risk of having at least one fall increased by 33% compared with men who had mild symptoms [2]. Falls in the elderly are a major concern and can result in pain, fracture, disability, and sometimes mortality [13]. The severity of LUTS is also strongly correlated with anxiety, depression, insomnia, and sexual dysfunction [2,11]. With billions of dollars already spent directly each year in the treatment of LUTS and urinary obstruction, more ancillary health-care expenditures can be expected, especially in an era of rapidly increasing male longevity [13,14].

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LUTS in bladder outlet obstruction

BOO is an urodynamic condition implying voiding with high pressure and/or a low-flow rate. The patient develops LUTS when BOO has developed to a considerable degree. BOO can occur in men and women, in adults and children, and in anatomical and neurogenic conditions. In a study, investigating men without BOO and LUTS, the maximum flow rate (Qmax) reached 20 mL/s with a mean voided volume of 290 mL [15]. One-third of men with LUTS do not have BOO. Many clinical studies have demonstrated that LUTS have a poor diagnostic specificity for BOO and the symptoms of 5%–35% of patients with BPH and LUTS did not improve after transurethral resection of the prostate (TURP) [16]. The prostate size and uroflowmetry have better correlation with urodynamic study than symptoms alone.

Clinical BPH is defined as having at least two of the following: (1) moderate to severe LUTS (international prostate symptom score >8), (2) an enlarged prostate (total prostatic volume [TPV] >30 mL), and (3) decreased Qmax (<15 mL/s) [17]. 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 [18]. In addition, patients with LUTS suggestive of BPH and a Qmax of <10 mL/s have more improvement in Qmax after TURP than those with a Qmax of >10 mL/s. Patients without evidence of BOO preoperatively also have a poor prognosis after TURP [19]. Patients with postoperative LUTS were found to have a small TPV at the time of surgery, suggesting a non-BPH etiology might account for their LUTS [20]. Therefore, a diagnosis of clinical BPH should be made carefully, especially when an invasive procedure such as TURP is contemplated.

Etiology of male lower urinary tract symptoms/benign prostate hyperplasia

The precise molecular etiology of BPE/BPH is complicated and poorly understood, although several risk factors for the development of BPE/BPH and LUTS have been identified. These include age, genetics, hormones, growth factors, inflammation, and lifestyle factors.

Age and genetics

Age itself is the major risk factor for BPE/BPH and LUTS. The aging process involves changes in cellular mitogenesis and hormonal homeostasis in the prostate gland, which later proceed to chromosomal aberration and apoptosis [21]. Aging is also associated with inflammation and microvascular disease, which provoke ischemia and oxidative stress, providing a favorable environment for BPH [22]. A genetic link for clinical BPH in men younger than 60 years has been studied over the past few years. Evidence suggests that it is an inheritable disease, possibly in an autosomal dominant fashion. Moreover, the genetic factor is said to account for a 72% increased risk in developing moderate or severe LUTS in elderly men [13].

Hormones

Sex steroid hormones have been affirmatively linked with the development and maintenance of BPE/BPH. Androgen is perhaps the most extensively studied hormone of all. In the prostate, testosterone is converted to dihydrotestosterone (DHT) by type II 5α reductase through DHT/androgen receptor signaling and may influence cell proliferation, differentiation, morphogenesis, and functional maintenance [23]. The use of 5α reductase inhibitors in a clinical setting was found to decrease serum concentrations of DHT and slow progression of clinical BPH [13]. Although not yet conclusive, estrogens (both endogenous and exogenous) and selective estrogen receptor modulators may have a role in regulating stromal-epithelial interactions involved in prostatic cellular growth [24]. To date, there is no clear and consistent link between other sex steroid hormones and BPE/BPH.

Growth factors

Several growth factors and their corresponding receptors have been identified in prostatic epithelium and stroma, which can stimulate or inhibit cell division and differentiation processes. These include epidermal growth factor, fibroblast growth factor, and transforming growth factor-β, but this list is by no means exhaustive. Activation of these growth factors alone or in combination can induce stromal cell growth, followed by significant tissue remodeling, which is responsible for prostate enlargement [25].

Inflammation

There is a growing body of evidence that suggests that inflammation is closely linked to the development of BPE/BPH and LUTS. From a histological point of view, inflammatory infiltrates are the most prevalent feature coexisting with BPH, and the degree of inflammation is correlated with prostate volume and weight [26]. From an immunological point of view, inflammation may activate the release of cytokines and raise the concentration of growth factors, resulting in an abnormal proliferation of prostatic cells [27]. From a serological point of view, an increased level of C-reactive protein has been observed in men with LUTS, which is likely indicative of systemic inflammation [13].

Metabolic syndrome, lifestyle factors, and obesity

In a recent systematic review of metabolic syndrome (MetS) and BPE/BPH focusing on subsets of MetS and their relationship with the TPV and LUTS, it was reported that the TPV was significantly larger in men with MetS than those without. Furthermore, the differences in TPV were significantly higher in obese participants and those with low serum high-density lipoprotein cholesterol levels. Interestingly, in contrast to other studies, there were no differences in LUTS symptom scores between men with and without MetS [28]. Heavy smoking, low physical activity, and high protein intake can also substantially alter the risks of symptomatic BPH and LUTS [29].

Pathophysiology of benign prostate enlargement/hyperplasia

The hyperplastic process in the prostate begins in the periurethral region, namely, the transition zone. As discussed earlier, this process is influenced by multiple factors, leading to an increase in the cell number and size through epithelial and stromal proliferation or apoptosis. As enlargement takes place, prostatic intrusion into the urethral lumen or bladder neck can considerably change bladder outlet resistance by causing mechanical obstruction. Despite the fact that the size of the prostate does not correlate closely with symptoms, the larger the size, the greater the likelihood of future clinical deterioration.

The prostatic capsule is another key to the development of LUTS by transmitting the pressure of tissue expansion to the urethra and increasing urethral resistance [30]. Growing evidence has shown that, just as in BOO secondary to BPE/BPH, these anatomical and functional changes may, in turn, induce significant alterations in the morphology and physiology of the urothelium and detrusor muscles, which lead to bothersome LUTS [31].

Despite significant success in the use of alpha-blockers and 5 alpha-reductase inhibitors in reducing the risk of LUTS progression, 20% of men with BPE/BPH will still experience prostate-related urinary retention and may require surgery within 1 year after drug initiation [32]. Knowledge about why cellular and molecular differences in BPE/BPH progression lead to profound symptoms in some but not all men remains unclear. In recent years, several biomarkers have been proposed that might be useful in identifying those whose disease is more likely to progress than others and in stratifying individuals into subpopulations for therapeutic purposes.

Prostatic-specific antigen (PSA) and its isoforms have been examined. Studies have demonstrated that there is a strong correlation between the prostate volume and PSA level, implying serum PSA could be used as a biomarker for BPE/BPH progression in the absence of prostate malignancy. It was also concluded that symptomatic men with a PSA $\geq$1.5 ng/mL are at higher risk for developing significant progressive BPH in the long run [33]. PSA isoforms, on the other hand, provide minimal information in the clinical setting [34].

As the technology for gene-expression profiling has continued to advance, DNA microarrays have been employed to identify a set of genes that could potentially differentiate symptomatic BPH, asymptomatic BPH, and prostate cancer. One example is JM-27, an androgen-regulated gene, which is located on the X-chromosome and encodes proteins belonging to a family of MAGE/GAGE [35]. It was dramatically up-regulated in diseased prostatic tissue [36]. It was found that the serum level of JM-27 can separate patients with aggressive BPH from the asymptomatic population with a sensitivity of 90% and a specificity of 77% [37]. Research on other biomarkers such as P25/26, nucleotide polymorphisms, inhibitors of androgen receptors and others have been undertaken, and may perhaps offer early BPE/BPH detection and monitoring of disease progression and therapeutic response in the near future.

LUTS in non-BPH conditions

Bladder hypersensitivity

Sensory urgency may be the presenting symptom in the patients with DO, poor relaxation of the urethral sphincter, interstitial cystitis, BOO, or neurogenic voiding dysfunction. Recent investigations found the urothelial release of neurotransmitters such as acetylcholine, adenosine triphosphate, and the neuropeptide substance P, and the increased expression of the transient potential receptor vanilloid receptor subfamily and purinergic receptor P2X3 indicate that the urothelium plays an important role in the transduction of bladder sensation [38,39]. Adenosine triphosphate production increases with aging. These physiological changes in elderly men indicate that bladder hypersensitivity and overactive bladder (OAB) are responsible for DO and inadequate contractility in elderly men [40].

Polyuria

A number of patients have a large daily urine output (>2800 mL). Patients may have polydipsia and high water intake, and therefore, they have a frequency with a voided volume >350 mL and are likely physiologically normal [41]. The metabolic status of these patients should be checked with evaluations of diuretic intake and conditions such as diabetes, azotemia, hyperlipidemia, and sleep apnea syndrome.

Psychological factors

Psychological, social, and psychiatric factors might also cause frequency in male patients. These patients may have high levels of distress and anxiety. The symptoms may worsen in relation to work or stress and several diseases such as uremia, infection, or cancer.

Urothelial dysfunction

Sensory urgency might be a micromotor urgency due to micromotion of the detrusor during rapid bladder filling such as in diuresis. Patients may have severe urgency when their bladder volume is small. This condition might be the cause of urothelial dysfunction such as in trigonal mucosal dysfunction. Increased nerve growth factor levels have been found in bladder biopsies of patients with sensory urgency, chronic cystitis, and interstitial cystitis compared with levels in controls [42]. Intravesical onabotulinumtoxinA has been found to decrease symptoms of OAB and interstitial cystitis. The production of nerve growth factor was reduced after onabotulinumtoxinA treatment in patients with neurogenic or idiopathic DO [43].

Overactive bladder

DO can be due to idiopathic reasons, myogenic overactivity, poor cortical perfusion, postobstructive DO, the aging process, or detrusor hyperactivity with impaired contractility (DHIC). In men with LUTS, BOO should be excluded first. Patients with benign prostatic obstruction (BPO) but without OAB symptoms might develop *de novo* OAB after TURP, suggesting the destruction of the trigone mucosa might result in OAB [44]. Treatment of patients with BPH with BOO and OAB should include agents relieving the urethral resistance and antimuscarinics as well when OAB symptoms cannot be resolved after treating with an alpha-blocker alone or combined with a 5 alpha-reductase inhibitor.

Nocturia and nocturnal polyuria

Nocturia is the third most bothersome LUTS. The prevalence of nocturia increases to 80% in patients over 80-year-old. It is one of the most common causes of a disturbed sleep pattern in the elderly. The causes of nocturia include DO, a hypersensitive bladder, BOO, nocturnal polyuria, or a small bladder capacity. When the nocturnal urine volume >900 mL or more than 35% of the daily voided volume, nocturnal polyuria is likely. Lack of diurnal desmopressin rhythm can be the cause of nocturnal polyuria and can be treated with exogenous desmopressin [15]. For patients with combined nocturnal polyuria and BOO or OAB, combined multiple medications are necessary to relieve the complex male LUTS.

Poor relaxation of the urethral sphincter

Among the various causes of non-BOO male LUTS, poor relaxation of the urethral sphincter is most frequently encountered [15]. 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. Learned habits, chronic prostatitis, pelvic floor hypertonicity, occult neuropathy, or increased bladder sensitivity have been postulated to lead to poor relaxation of the urethral sphincter. These voiding symptoms might have a great impact on QoL, especially in young men.

Pain symptoms

Several bladder or bladder outlet conditions can cause pain in men. Interstitial cystitis, BOO, a 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. Treatment of pain symptoms in men is not easy and should be based on the exact diagnosis of the pain.

Transitional cell carcinoma of the bladder usually mimics interstitial cystitis in men with LUTS and painful bladder syndrome. Urine cytology and repeat random bladder biopsy are necessary to find early bladder carcinoma.

Postprostatectomy male lower urinary tract symptoms

Over half of patients with postprostatectomy LUTS had a small total prostate volume and resected adenoma weight, indicating their LUTS were non-BPH or non-BOO conditions before TURP [20]. Detailed cystoscopy and video urodynamic study are necessary for these patients especially when they are diagnosed with residual BPH or BOO and are planning to undergo repeat transurethral surgery. DHIC, bladder hypersensitivity, or OAB can also cause male LUTS in the presence of a small BPH.

Other conditions

Urethral sphincter pseudodyssynergia in patients with chronic stroke, intracranial lesions, Parkinson's disease, and spondylolisthesis can cause severe empty symptoms or storage symptoms in elderly men [45]. These patients might have BPH, but the LUTS are caused by conditions other than BPH. Urethral stricture or urethral meatal stenosis can also cause BOO and LUTS, especially in patients who have had transurethral procedures.

Conclusions

LUTS in men can be caused by both bladder and bladder outlet dysfunctions occurring alone or in combination. The presenting symptoms in male LUTS are similar in patients with and without BPO. LUTS are not useful for the differential diagnosis of BPO and non-BPO in men. Accurate diagnosis of lower urinary tract dysfunction should be based on a comprehensive urodynamic study, which will enable correct selection of therapy aimed at the underlying pathophysiology.

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Conflicts of interest

There are no conflicts of interest.

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