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REVIEW

Voiding dysfunction in men: pathophysiology and risk factors

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Introduction

Benign prostatic hyperplasia (BPH) refers to histologic changes within the prostate. Benign prostate growth induces physiological changes in men that in some cases lead to bothersome lower urinary tract symptoms (LUTS). These LUTS exert their effects in an individual's life by disrupting their daily activities and can be associated with a diminishing quality of life. Although a benign prostatic obstruction is relatively common in those with LUTS, in approximately one-third of men with significant LUTS, there is no evidence of a benign prostatic obstruction.[1] To further understand the relationship between LUTS, BPH and bladder outlet obstruction, the physiological changes that occur as a man develops BPH must be understood. Although the precise relationship is the focus of future research, understanding both the physiology and the risk factors associated with prostate growth can assist in understanding some of the interactions between the three components. By understanding the changes that occur as a male develops BPH, we can try to identify risk factors and the most efficient measurements used to diagnose individuals with this condition. Identifying these may allow for more efficient diagnosis of individuals suffering from this disease.

Terminology

A more robust understanding of male voiding dysfunction is predicated on the use of rare terminology. The challenge is to change the terms to make them more pragmatic and user friendly. In the past, the term 'prostatism' was used to describe a wide variety of LUTS, making it relatively non-specific and the source of a substantial amount of confusion. This changed in the early 1990s when Abrams[2] introduced more specific terminology. He explained that BPH should be used to describe only histologic changes of hyperplasia. Benign prostate enlargement should refer to the gross enlargement of the prostate gland, which is typically determined through a digital rectal examination (less accurate) or a transrectal ultrasound. Benign prostatic obstruction should be used to describe urodynamic confirmation of bladder outlet obstruction caused by the prostate. BPH, benign prostate enlargement and LUTS can coexist or occur independently. The term LUTS encompasses voiding (painful urination, weak stream, hesitance and intermittency), postmicturition (terminal dribble and feeling of incomplete emptying) and filling (nocturia, frequency, urgency and urgency incontinence) symptoms and was proposed in 1994 by Abrams.[3] Although LUTS can result from BPH, it can originate from many other sources, including alterations in bladder function, comorbities or neurological disorders. To clarify terminology, the fourth International Consultation on BPH suggested using 'LUTS' or 'LUTS suggestive of BPH' instead of 'prostatism' when referring to men with urinary symptoms and the possibility of an enlarged prostate.[4] Moreover, the types of urinating symptom need to be properly explained. In the past, obstructive and irritative symptoms were the most common terms utilized. Currently, the more appropriate terms are voiding (that is, decreased urinary stream, sense of incomplete bladder emptying and hesitancy) and storage symptoms (urgency, frequency, nocturia and urge incontinence).

Economic burden

BPH is a progressive chronic disease that will develop in approximately 90% of men by the age of 80 years.[5] Autopsy data published by Berry *et al.*[6] on more than 1000 prostate specimens found histologic evidence of BPH in more than 40% of men of 50–59 years and in almost 80% of men of

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70–79 years. As this is such a large proportion of men, understanding the physiology and relationships between BPH, LUTS and bladder outlet obstruction is imperative. In general BPH/LUTS is a very common condition and its prevalence tends to increase linearly over time. Therefore, there is a large number of men who should be targeted for prevention measures. By implementing prevention and developing methods of diagnosing men earlier, the costs associated with BPH may be reduced. In 2000, the total direct cost of BPH was estimated to be $1.1 billion, whereas the outpatient prescription drugs contributed another $194 million annually.[7] The total cost to society from BPH in the United States has been approximated to be $4 billion annually.[8]

Explanation of symptoms

Symptoms associated with BPH can be classified as obstructive or irritative. Obstructive symptoms include a decrease in the flow, hesitancy, intermittency, terminal dribbling and inability to fully empty the bladder. A decrease in the force and flow of the stream associated with urethral compression from prostate enlargement are some of the main and early characteristics of BPH. Hesitancy tends to occur, as the detrusor needs time to overcome the urethral resistance. Intermittency is typically seen because the detrusor cannot sustain the pressure needed to urinate during the entire voiding period. Terminal dribbling and inability to completely empty the bladder also occur due to the failure of the detrusor to sustain the pressure necessary to void for the entire duration. Irritative symptoms include nocturia, frequency, urgency and dysuria. Nocturia and frequency tend to occur for several different reasons. Incomplete emptying tends to leave residual urine in the bladder, therefore, resulting in slower intervals between voids. Also, having an enlarged prostate causes the bladder to trigger a voiding response more frequently than the normal population. These symptoms may be attributed to the increased sensitivity of a hypertrophied detrusor to small volume changes. The frequency symptoms tend to be heightened at night because the urethral and sphincteric tone is slightly reduced during sleep. Urgency and dysuria tend to be rather uncommon but can arise from detrusor instability where detrusor contractions and sphincteric relaxations are not synchronized.[9]

Normal anatomy and voiding

To understand the changes that occur when an individual develops BPH, the normal anatomy and voiding must be explored. The anatomy of the adult prostate is based on McNeal's seminal work.[10] The prostate is divided into four discrete regions: the peripheral zone, the central zone, the transition zone (TZ) and the anterior zone. The peripheral zone is composed of the postero-inferior part of the gland, representing approximately 70% of volume. The central zone comprises 25% of the prostate volume, containing the ejaculatory ducts and is the zone that is typically involved in inflammatory processes (such as prostatitis). The TZ is composed of two lateral lobes along with periurethral glands, representing 5% of the volume.[11] All BPH nodules originate in the preprostatic region, which contains the periurethral glands and the TZ.[12] The vascular supply to this area is from the urethral branches of the inferior vesical artery, which travels from the bladder neck to the verumontanum.[13] A normal prostate weighs around 20 g and contains the prostatic urethra.

The bladder is a muscular organ that functions in the storage of urine and in normal individuals has a capacity of approximately 500 ml.[14] The bladder has two main parts: a body that lies above the urethral orifices and a base made up of the trigone and bladder neck. The urethra extends from the bladder and can be broken down into four segments: the preprostatic portion (bladder neck), the prostatic urethra, the membraneous urethra and the penile urethra.[15] The two sphincteric elements are an internal involuntary smooth muscle sphincter at the bladder neck and a voluntary skeletal sphincter in the membraneous urethra segment. In the relaxed state when the bladder is filling, the bladder neck will remain closed. When the motor nerves of the bladder are stimulated to contract, the bladder neck opens. By voluntarily relaxing the muscles in the urethra sphincter, urine passes from the bladder through the urethra and exits the body.[9]

Lower urinary tract symptoms and bladder outlet obstruction

BPH symptoms can be derived from a static and a dynamic component. The static component is enlargement of the prostate gland, and is caused by excessive growth of stromal and epithelial elements. Growth of the prostate gland is triggered through the presence of androgens, the most important being testosterone and dihydrotestosterone, a substance that induces cellular proliferation. Concomitantly, there is an increase in smooth muscle that leads to increased urethral resistance. The detrusor response to increased resistance is initially to generate higher pressures to overcome the outlet resistance. The bladder's response to obstruction is very important because one-third of men who had their obstruction surgically removed continue to suffer from voiding dysfunction.[16] The

two main types of changes that occur in the bladder are detrusor instability and detrusor acontractility. Detrusor instability (clinically termed overactive bladder or OAB) is associated with symptoms of frequency and urgency, whereas detrusor acontractility tends to be related to deterioration in the force of urinary stream, hesitancy, intermittency, increased residual urine and eventually can lead to bladder decompensation where the bladder is no longer able to generate sufficient pressure to empty. After bladder decompensation, the deposition of collagen and elastin between smooth muscles leads to weakened contractions by the bladder. This can eventually lead to diverticula formation.[9] This is analogous to the model of hypertensive cardiomyopathy where an increase in peripheral vascular resistance leads to cardiomyopathy and congestive heart failure.[17]

The bladder response to generate higher forces is accomplished through a 2 to 10-fold increase in bladder mass through hypertrophy of bladder smooth muscle cells.[18] The remodeling of the bladder can be rather extensive because in the rat the bladder weight increases from the normal 80 to 140 mg in 3 days, 170 mg in 10 days, 640 mg in 42 days and 1000 mg in 90 days.[19] This increase in mass was reversible when the obstruction was removed, but the de-obstructed bladder showed differences in cellular and intercellular structure when compared with the control and hypertrophic urinary bladders. Although this is the process that occurs in rats, it shows how drastic the change in bladder size can be when an obstruction is present.[20] By increasing the thickness and musculature of the bladder, complete emptying of the bladder is possible. During the hypertrophy process, pressure 2–4 times larger than normal intravesical pressure may be reached by the trabeculated bladder in an attempt to empty the bladder and push urine past the obstruction. This pressure tends to lead to diverticula formation. Diverticula are basically pouches that have no muscle wall and therefore are unable to contract and force their contents into the bladder even once the obstruction is removed. Their presence leads to a constant presence of residual volume in the bladder. Residual volume can cause infections and to prevent them from coming back the diverticula may need to be surgically removed.[9]

Prostatic capsule

The anatomy and unique aspects of the prostate, specifically the presence of the prostatic capsule, greatly influences the development of BPH. The only other documented species that develops BPH naturally is the dog. However, symptoms of BPH are unusual in dogs because they don't possess a prostatic capsule. It is thought that the capsule is the structure that transfers the pressure from the urethra tissue growth, leading to an increase in urethral resistance. Therefore, the presence of a capsule is thought to be directly related to the development of BPH. This assertion is further supported by clinical evidence where an incision of the prostatic capsule (transurethral incision of the prostate) leads to significant improvement in outflow obstruction. This result is independent of the prostate size, as the size remains the same after this procedure.[16]

Estrogens

The role of estrogens, specifically estradiol, is increasingly being recognized as a possible factor in the development of BPH. In the case of the dog, the interaction between estrogens and androgens is relatively clear. Estrogens seem to be involved in the induction of the androgen receptor.[21] As their prostate contains many high-affinity estrogen receptors, the administration of estrogen leads to stimulation of the stroma and an increase in collagen production.[22–24] In humans, estrogen's influence on BPH development is less clear. Most of the circulating estrogens are produced by the peripheral conversion of testosterone and androstenedione to estrone and estradiol. In hyperplasic prostates, serum estradiol and estriol levels are positively correlated with prostate size.[25] Although the estrogen receptor β levels are lower in the TZ stromal cells than normal tissue, there may be enough receptors to have an active role in BPH development. On the basis of knowledge that estrogen receptor β knockout mice develop BPH, the receptors may have an antagonistic (inhibitory) role in the development of BPH.[26] In contrast, estrogen receptor α levels (upregulated by estradiol) have been shown to correlate with FGF-2 and FGF-7 concentrations, both putative growth factors for BPH.[27] The role and exact interactions between estrogen levels, estrogen receptors and the relative concentration of estrogens to androgens remains relatively unclear.

Hereditary BPH

Men with a family history of BPH typically have a higher risk of BPH development than the general population. The exact mechanism is still unknown, but there is a predisposition to younger age of onset and larger glands in patients with a family history of BPH. This is supported by the Sanda *et al.*[28] study where a fourfold greater risk of prostatectomy in the first-degree relatives of study subjects was found. These individuals had a family history positively

associated with prostate volume. In the United States Finasteride Trial, 69 men with 'familial (greater than or equal to three affected family members) BPH were compared with 345 BPH controls without a family history of BPH. The familial BPH group had a significantly larger mean prostate volume (82.7 vs 55.5 ml) compared with BPH controls, but both groups had similar androgen levels.[29] Pearson *et al.*[30] analyzed the North American Finasteride Trial and discovered that subjects with a family history of BPH developed BPH at an earlier age than controls. Although the probability of incurring bothersome BPH during a male's life was approximately the same in both groups, the risk of surgery/hospitalization was greater for individuals with early onset of the disease and larger prostates. Fathers and brothers of patients with BPH had a greater risk of bothersome BPH and brothers had an increased risk of surgery. On the basis of these studies, an autosomal or codominant Mendelian pattern of inheritance is thought to operate. Research into specific gene alterations in hereditary BPH is ongoing and will likely lead to significant advances in diagnosis and treatment in the future.

Risk factors

Although evidence for comorbidity, environmental, dietary or lifestyle-related risk factors are generally weak, some have been shown to be related to BPH disease or disease-related events. The relationship between the risk factors and disease development is poorly understood and these risk factors should be interpreted cautiously because many studies use loose definitions of BPH. The prostate, lung, colorectal and ovarian cancer screening trial ($n = 34\,694$) found statistically significant but slightly decreased rates for BPH and transurethral resection of the prostate among Asian men, current smokers and alcohol consumers. There was not any specific dose in the last two categories that corresponded to the lowered levels. There was no statistical difference between black and white males. Aspirin or ibuprofin use slightly increased the rates of these parameters.[31] Smoking cigarettes tends to increase testosterone and estrogen levels due to the nicotine level, and therefore should have a positive and inductive effect on BPH development.[15] However, individuals who smoke regularly develop other health problems, which may make them a poor candidate for surgery.

In the Olmsted County Study, light-to-moderate smokers were found to be less likely to develop moderate-to-severe LUTS, whereas heavy smokers and never smokers showed the same risk. Smokers also had a lower risk of having a prostate volume over 40 ml and a flow rate less than 15 ml s^{-1}.[32] The decreased rates associated with alcohol use may be due to alcohol decreasing plasma testosterone levels and production along with an increase in the clearance of testosterone.[33] Morrison[34] reported a multivariate adjusted risk reduction of 0.49 and Sidney *et al.*[35] found an age-adjusted risk reduction of 0.75 for this inverse relationship regarding the risk of having surgery for BPH when consuming three alcoholic drinks per day. It should also be noted that a patients' poorer health due to drinking alcoholic beverages may deters physicians from offering surgery as a possible treatment option.

In the Mass Male Aging Study, cigarette smoking and vigorous exercise were protective against BPH, although there was no specific dose response. In contrast, heart disease was positively correlated to BPH development. BPH classification was based on a broad definition where subjects were included who had frequent or difficult urination and they were told by a physician that they had an enlarged prostate or underwent BPH-related surgery.[36] Hypertension and symptomatic BPH are associated and may share a common link due to either increased sympathetic tone or α-adrenoreceptor responsiveness.[37] Hammarsten *et al.*[38] also discovered that prostate volume and growth rates are correlated with hypertension, obesity and insulin levels, suggesting that BPH may be an unrecognized component of the metabolic syndrome. Michel *et al.*[37] retrospectively examined 9867 men who were examined at a large BPH clinic and found a positive correlation between hypertension and International Prostate Symptom Score (IPSS) and a negative correlation with maximum flow rates (independent of age). These relationships were statistically significant but relatively weak. The influence of body mass index (BMI) and obesity on LUTS/BPH has been examined, but there are a few caveats. A digital rectal examination is typically used to diagnose BPH, but obese patients may have anatomical obstacles that make it difficult to determine if the prostate is enlarged. Also, patients with a high BMI may be less likely to undergo surgery. In terms of the biology, adipose tissue is the main way that testosterone is converted to estrogen; therefore, men with lower BMIs have higher serum testosterone levels.[39] In the Kaiser Permanente cohort study, BMI was negatively correlated with BPH-related surgery.[35] Both Soygur *et al.*[40] and Daniell[41] found a positive association between obesity and prostate size but no such correlation was found between obesity and symptom severity. Men between the age of 40 and 75 years in the Health Professionals Follow-up Study without cancer or previous prostatectomy provided measurements such as weight, height, and waist and hip circumferences. Adjustments for age, smoking and BMI were performed and they discovered that abdominal obesity was related to prostatectomy (Odds ratio, 2.38) and with frequent urinary symptoms (Odds ratio, 2.00). This suggests

that abdominal obesity in men may increase the frequency and severity or urinary obstructive symptoms along with the need for a future prostatectomy.[42] In our data sets in more than 400 men, we found that waist circumference may be the best predictor of both proxies for BPH, that is, symptoms, flow rate and prostate size as well as metabolic dysfunction.

Best predictors of progression

Prostate volume/size

An enlarged or hyperplasic prostate has been one of the main warning signs for the development of BPH. Although it has been shown to be one of the most consistent markers for future disease progression, an enlarged prostate does not always lead to LUTS or cause problems for the individual. In terms of prostate growth, the baseline prostate volume is positively correlated with increases in prostate volume over time.[43] In the Olmsted County group, a total prostate volume greater than 30 ml was a statistically significant risk factor for treatment.[44] In the Proscar Long-term Efficacy and Safety Study, a total prostate volume of greater than 40 ml at baseline was a significant risk factor for acute urinary retention (AUR) and the incidence of surgery. The incidence of AUR or surgery was 8.9, 11.7 and 22.0% in patients with baseline prostate volumes of 14–41, 41–57 and 58–150 ml, respectively. Subjects in the highest volume group also showed higher rates of symptom progression and worsening flow rates.[45] The poor correlation between prostate size and symptoms occurs because multiple other factors influence the development of LUTS such as age, medications, comorbid conditions, diet and bladder physiology.[46] A more useful way to predict symptoms, flow rates and high detrusor pressure is by using the TZ volume instead of using the total volume, because prostatic hyperplasia only occurs in the TZ and periurethral glands.[47,48] The TZ index (ratio of TZ volume to total volume) has also been examined as a factor in disease parameters. Kaplan *et al.*[48] determined that a TZ index greater than 0.50 was a statistically useful cutoff point.

PSA (this will be discussed in a separate article in this supplement by Dr Roehrborn).

Other predictors

Symptom score

The symptom severity is typically quantified using the American Urological Association (AUA) Symptom Index, which is also known as the IPSS.[49] This index is composed of seven questions that relate to the symptoms associated with LUTS, with a maximum value of 35. Patients with scores between 0 and 7 are classified as mildly symptomatic, those with scores between 8 and 19 are moderately symptomatic and those with scores between 20 and 35 are severely symptomatic. This index is typically used to identify changes in disease progression over time, where most patients identify a decrease in three points as a clear improvement.[50] It has been shown by Moon *et al.*[51] that socioeconomic factors do not seem to have an effect on the responses given to the questionnaire and by Barry *et al.*[52] that the responses generated from the questionnaire are the same regardless of whether it is self-administered, read to the patient, mailed in or administered in an alternative way. This does not exclude the possible differences that may arise in terms of how the questionnaire or symptoms are perceived by patients.

By observing the changes in symptom score as individual's age, a clear relationship emerges. In an international study of 7588 Asian men, 18, 29, 40 and 56% of men in their 40s, 50s, 60s and 70s, respectively, have moderate-to-severe symptoms.[53] These results are similar to those reported in Europe, North America and in studies done under less stringent conditions.[54,55] Even though differences may arise in the absolute number of individuals with moderate-to-severe symptoms in each study, there is an obvious trend toward higher symptom scores as a patient ages in all reported studies.

The baseline AUA symptom score has been shown to be useful in predicting BPH progression. In the case of the Olmsted County population, men with moderate-to-severe LUTS had three times the risk of AUR and five times the risk of surgery when compared with individuals with mild LUTS.[44] In a clinical study of 500 men who decided not to undergo surgery to treat BPH, 10% of patients with mild symptoms later had a prostatectomy performed, whereas 24 and 39% of those with moderate-to-severe symptoms at baseline underwent the same procedure.[56] In terms of the Proscar Long-term Efficacy and Safety Study placebo group, individuals with mild, moderate-low, moderate-high and severe baseline symptoms underwent surgery 7.7, 6.9, 10.1 and 13.9%. Although surgery tends to be positively correlated with increasing symptom score, it is difficult to categorize this as a marker for disease progression. In the same study, the incidence of AUR was also correlated to the baseline symptom score, but not as prominently.[57] It should be noted that the baseline symptom score, however, is generally not a risk factor for disease progression. This can be attributed in some ways to the difficulty for men with high symptom scores to have a four-point or greater symptom score decrease. This is mainly due to a regression to the mean phenomenon or a 'ceiling effect'.

Maximum flow rates

Noninvasive urinary flow rates are a surrogate marker for outlet obstruction. Decreased maximum

urinary flow rates may be secondary to outlet obstruction, decreased contractility or a combination of the two. In diagnosing outlet obstruction, Reynard *et al*.[58] calculated sensitivities of 82 and 42% and specificities of 38 and 70% for maximum flow rates of 15 and 10 ml s^{-1}, respectively. It is generally accepted that a maximum flow rate less than 10 ml s^{-1} indicates a high probability of obstruction, while a flow rate greater than 15 ml s^{-1} indicates a low probability, with the 10–15 ml s^{-1} interval representing an intermediate range. This tends to be less useful predictor of BPH because the maximum flow rate has a slight dependency on the volume voided.[59] To correct for this relationship, some individuals have developed nomograms, but there has not been one that has become universally accepted.[60–68] Another weakness of using the maximum flow rate to diagnose BPH is that is tends to have diurnal and day to day variability.[50,69] Most BPH trials tend to use flow rates less than 10–15 ml s^{-1} as entry criteria. Lower baseline flow rates do correlate with higher rates of BPH progression, but ultimately, it would require urodynamic studies to determine if this is due to bladder function or symptoms secondary to obstruction. When a cutoff flow rate of 12 ml s^{-1} was used, community-dwelling men with lower flow rates had approximately three times the risk of surgery and AUR than those with higher flow rates over time.[44,70] The men with lower baseline flow rates also saw a more rapid deterioration in their flow rates over time.[71] In the placebo arm of the medical therapy of prostate symptoms, men with a maximum flow rate <10.6 ml s^{-1} at baseline had a greater risk of overall progression, symptomatic progression and incidence of surgical intervention.[72]

Maximum flow rates have been seen to exhibit an age-related component. The decrease in urinary flow rates with age is approximately linear. For instance, in the Olmsted County Study, the median flow rate decreased from 20.3 to 11.3 ml s^{-1} in men of 40–44 years and 59–75 years, respectively.[59] When using thresholds such as an IPSS score greater than seven and a maximum flow rate less than 15 ml s^{-1}, the Olmsted Study showed that 17% of men in their 50s, 27% of men in their 60s and 35% of men in their 70s would satisfy the criteria.[73] This demonstrates the association between aging and decreasing urinary flow rates.

Post-void residual volume

Post-void residual urine volume (PVR) is, like noninvasive flow rate, a measure of both bladder and outlet function. It represents the volume of fluid remaining after the completion of micturition. Studies have shown that in normal males PVR ranges from 0.09 to 2.24 ml, with a mean of 0.53 ml.[74] PVR tends to be difficult to interpret in clinical practice due to its relatively large test–retest variability.[75] In a selected cohort of the Olmsted County population that was followed for up to 12 years (median of 7.7 years), PVR increased slowly at a rate of 2.2%. Men with baseline moderate-to-severe LUTS showed a rapid increase in PVR during the study period. Even though patients with elevated PVR do not often suffer severe health consequences, elevated or rising PVR values do represent a risk factor for predicting future BPH-related events.[76] In the Olmsted County study, men with PVR >50 ml had three times the risk of AUR compared with those with lower PVR values.[77] A retrospective study of 942 men by Mochtar *et al*.[78] were treated with α blockers ($n=389$) or watchful waiting ($n=553$). Hazard ratios for interventional therapy necessity were 2.1 for PVR >50 ml, 2.5 for PVR >100 ml and 4.1 for PVR <300 ml. Statistical significance was not maintained when multivariate analysis was performed, although there was a trend toward higher rates of surgery when PVR was >300 ml (Hazard ratios 1.8, 0.4–8.6). In medical therapy of prostate symptoms, subjects in the placebo arm with a baseline PVR greater than 39 ml had statistically significant higher progression rates, including symptom score progression, rates of AUR and surgical therapy.[72] In patients on medical therapy, however, baseline PVR did not predict outcomes.[79] Overall, in clinical trials, the importance of PVR as a predictor of BPH progression may be underestimated, as most trials exclude patients with large baseline PVRs. Therefore, by aiming future research toward individuals with high baseline PVR measurements, a strong relationship may be established in patients with large PVRs.

Sexual dysfunction

There are three cellular mechanisms that appear to play a role in the development of LUTS and sexual dysfunction. Recently, McVary[80] detailed alterations in three cellular mechanisms that are frequently associated with LUTS and ED: (1) reduced nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling; (2) increased autonomic activity mediated, in part, by α-adrenergic receptors and (3) increased Rho-kinase activation. An impetus to further evaluating these associations stemmed in part from recognition of the role for the NO/cGMP pathway in male sexual function and the effects of phosphodiesterase type 5 inhibitors. Phosphodiesterase type 5 inhibition increases NO-stimulated cGMP concentrations in corpus cavernosal tissue, resulting in smooth muscle relaxation and increased blood flow that promote erection with sexual stimulation. However, recent studies have demonstrated that phosphodiesterase type 5 inhibition, either as a monotherapy or in combination with an α-adrenergic receptor antagonist, also improves male LUTS presumably through a NO/cGMP-mediated relaxation of smooth muscle in the

bladder neck, urethra and prostate.[81,82] Conversely, the α-adrenergic receptor antagonist alfuzosin, which is believed to relieve LUTS through inhibition of prostatic smooth muscle contraction, also improved sexual function in a long-term study of men with LUTS.[83] Studies in animal models also suggest that α-adrenergic receptor activation plays a role in the development of BPH and detrusor overactivity.[82] Finally, the activation of Rho-kinase, which promotes smooth muscle contraction through inhibition of myosin light-chain phosphatase, was associated with the proliferation of human and rat prostatic smooth muscle and α-adrenergic receptor-mediated contractions in rat prostatic smooth muscle *in vitro*. Rho-kinase activation was also associated with an increase in corpus cavernosal smooth muscle tone in rabbits with bladder outlet obstruction.[82] Clearly, these studies suggest important modulatory roles for NO/cGMP, α-adrenergic and Rho-kinase signaling in lower urinary tract and sexual functions.

Conclusions

Benign prostatic hyperplasia is a disease that affects a large proportion of males and is known to be associated with rather bothersome LUTS. We know that LUTS can be attributed to a variety of sources, such as prostatic enlargement, changes in bladder function or neurophysiologic alterations, such as increased sympathetic tone. The ability of LUTS to result from such a wide range of events further complicates the relationship between BPH, LUTS and bladder outlet obstruction. Although BPH tends to result from a prostatic obstruction followed by changes in the detrusor, an obstruction is not necessary for this condition to arise. By focusing research efforts on determining the exact relationship between the three components, tailored treatment options can be used for patients with the disease and prevention methods can be targeted. Currently, the diagnosis of BPH has been based on the identification of risk factors strongly associated with BPH. One of the most important risk factors that should be considered is familial BPH or an individual's history because this should alert the individual to begin monitoring the main parameters correlated with BPH at a younger age. The parameters that are most strongly associated with BPH and used to predict future BPH-related events are age, PSA levels, prostate volume and sexual dysfunction. Baseline maximum urinary flow rate, AUA symptom score and post-void residual volume are typically moderate predictors of the disease, but tend to be used to evaluate symptom progression. Therefore, by focusing research efforts on identifying more effective correlations to BPH, we can become more efficient in the diagnosis of BPH.

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