

BPH: Epidemiology and Comorbidities

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Abstract

Recently published data suggest that clinical benign prostatic hyperplasia (BPH), which is hallmarked by the occurrence of moderate-to-severe lower urinary tract symptoms (LUTS), occurs in about one quarter of men in their 50s, one third of men in their 60s, and about half of all men 80 years or older. Although effective treatments for LUTS/BPH are available, this condition often occurs in the context of common, age-related comorbidities such as cardiovascular disease, hypertension, and erectile dysfunction. Alpha₁-selective adrenergic receptor (α₁-AR) antagonists (eg, alfuzosin, doxazosin, tamsulosin, terazosin) remain the cornerstone of therapy for LUTS/BPH. In addition, 5-alpha-reductase inhibitors (ie, dutasteride, finasteride) have been associated with improvements in LUTS/BPH in men with larger prostates, especially when used in combination with α₁-AR antagonists. Although all these drugs have been shown to be beneficial for the treatment of BPH, there are differences in side-effect profiles. When selecting an appropriate course of therapy, these side effects and any impact they may have on existing comorbid conditions must be considered.

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Introduction

Overview. Benign prostatic hyperplasia (BPH) is characterized by the nonmalignant overgrowth of prostatic tissue surrounding the urethra, ultimately constricting the urethral opening and giving rise to associated lower urinary tract symptoms (LUTS) such as urgency, frequency, nocturia, incomplete bladder emptying, and weak urine stream.^{1,2} Left untreated, serious complications can occur in men with BPH, including acute urinary retention (AUR), renal insufficiency and failure, urinary tract infection, and bladder stones.² The exact etiology of BPH is not known; however, the similarity between BPH and the embryonic morphogenesis of the prostate has led to the hypothesis that BPH may result from a “reawakening” of embryonic induction processes in adulthood.³ It

has also been postulated from anatomic and histologic studies of BPH at autopsy that BPH originates in the innermost aspect of the prostate gland (transition zone), which is located along the axis of the proximal urethra.³

Not all men with histologic BPH develop LUTS that requires intervention. Several processes, such as prostatic infarction, acute or chronic inflammation as a result of ongoing prostatitis, or in some cases, incidental adenocarcinomas of the gland, may foster the development of symptomatic BPH.³ The development of symptoms also depends on the enlargement of the individual prostate. As BPH nodules that originate in the transition zone grow, the remainder of the gland becomes compressed; if sufficient elasticity is present in the rest of the gland, little or no urethral compression will result. Conversely, if the remainder of the gland cannot expand freely, urethral constriction and obstruction of the urinary tract may occur.³ There is also a dynamic component to BPH, which can show substantive variation between individuals, relating to the neuronal control over prostatic smooth muscle tone by alpha_{1A}-adrenergic receptors (α_{1A}-ARs).⁴ The interindividual differences in the static and dynamic components of BPH will determine which men are affected by LUTS and the degree of symptom bother.

Prevalence and Impact. Histologically distinguishable BPH is present in about 8% of men aged 31 to 40 years, and this prevalence increases markedly with age to about 90% by

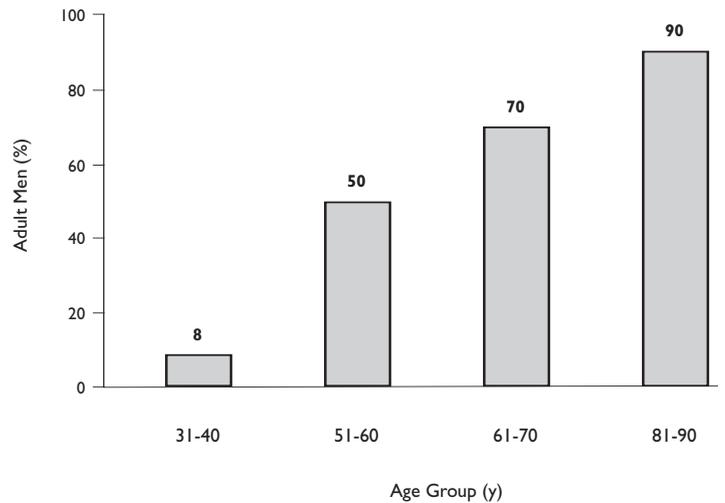
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the ninth decade of life (Figure 1),⁵⁻⁷ establishing BPH as a chronic disease that spans decades. Nonetheless, as noted above, not all men with BPH will go on to develop LUTS requiring treatment. The Urologic Diseases in America BPH Project examined the US prevalence of moderate-to-severe LUTS, defined by an American Urological Association (AUA) Symptom Index (SI) score of ≥ 8 .¹ Results from the Olmsted County Study (OCS) showed a progressive increase in the prevalence of moderate-to-severe LUTS, rising to nearly 50% by the eighth decade of life (Figure 2).^{2,8} The presence of moderate-to-severe LUTS was also associated with the development of AUR as a symptom of BPH progression, increasing from an incidence of 6.8 episodes per 1000 patient-years of follow-up in the overall OCS population to a high of 34.7 episodes in persons 70 years or older with moderate-to-severe LUTS.^{2,9} Risk factors were also established for BPH in OCS; these include age, prostatic volume, and peak urinary flow rate (Q_{max}).² The odds of developing moderate-to-severe symptoms increased progressively after age 50 years (Table), and were 3.5- and 2.4-fold greater in men with a prostate volume >50 mL and in those with a flow rate of <10 mL/sec, respectively.²

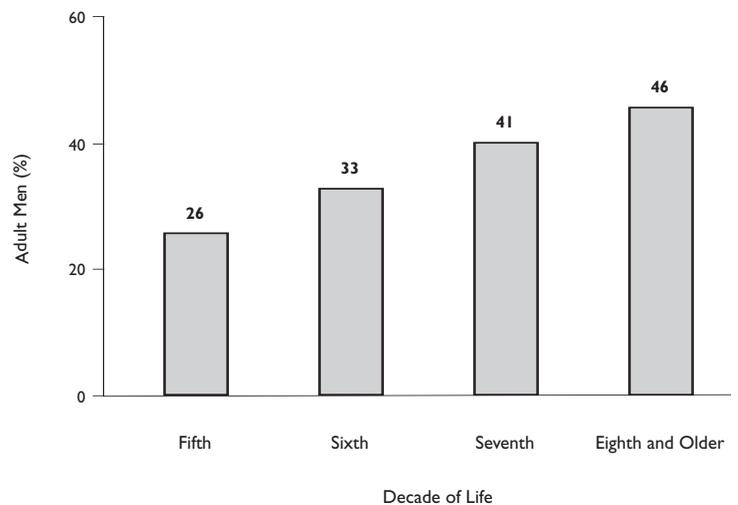
Although BPH is not a life-threatening condition, the impact of BPH on quality of life (QOL) can be significant and should not be underestimated. A self-administered questionnaire completed by 117 patients reported sleep, anxiety/worry over the condition, mobility, leisure, activities of daily living, and, to a larger extent, the effect on sexual activities as the most important concerns among patients with prostate symptoms (International Prostate Symptom Score [IPSS] >7).¹⁰ The impact of BPH-associated LUTS has also been studied in a community-based population in the United Kingdom. A random sample of approximately 1500 individuals aged 50 years or older was assessed for BPH symptoms and their impact on QOL using a self-administered survey.¹¹ Moderate-to-severe LUTS was seen in 41% of the patients (as assessed by an IPSS of ≥ 8), although only 18% reported they had been diagnosed with BPH.¹¹ Respondents experienced decrements in both QOL

Figure 1. Presence of Histologic BPH at Autopsy by Age Group



BPH indicates benign prostatic hyperplasia.
Source: Reference 7.

Figure 2. Prevalence of Moderate-to-severe LUTS (AUA SI Score ≥ 7) in the United States From a Population-based Study (Olmsted County Study)



LUTS indicates lower urinary tract symptoms; AUA SI, American Urological Association Symptom Index.

Source: Reference 8.

and health status as symptomatic severity increased, with most men experiencing problems with mobility, self-care, activities of daily living, pain or discomfort, and anxiety or depression. Despite the high preva-

Table. Odds of Developing Moderate-to-severe LUTS After the Fifth Decade of Life

Decade of Life	Odds Ratio
Sixth	1.9
Seventh	2.9
Eighth	3.4

LUTS indicates lower urinary tract symptoms.
 Source: Reference 2.

lence of LUTS reported in this survey, only 11% were aware of the pharmacologic or surgical interventions available to treat BPH; watchful waiting was the most common primary treatment (34%).¹¹ The findings of this study underscore the need for better education about BPH and its treatments.

Given the potential impact of BPH symptoms on overall health, greater communication between patients and their healthcare providers is warranted to facilitate the diagnosis of LUTS. In this regard, primary care physicians (PCPs) have been taking a greater role in the treatment of BPH; one study found that 86% of PCPs had prescribed BPH medications in the preceding year, although 66% admitted rarely or never using the AUA SI.¹² Among the available drugs, a median of 12 and 2 patients per year had been prescribed alpha₁-selective adrenergic receptor (α₁-AR) antagonists and finasteride, respectively, in this study.¹² For patients, the most important parameters motivating them to seek treatment of BPH are symptom severity and degree of bother associated with LUTS; these are also important considerations when assessing BPH and deciding when treatment is indicated.¹³

Medical Treatments. The advent of medical therapy has obviated the need for surgery in many patients with BPH.¹ α₁-AR antagonists are considered first-line medical therapy. They exert their effects by blocking α₁-AR-mediated contraction of the prostatic smooth muscle cells and bladder neck.^{1,14} There are 3 α₁-AR subtypes: α_{1A}, α_{1B}, and α_{1D}; terazosin, doxazosin, and alfuzosin are α₁-AR antagonists that show equal affinity for all α₁-AR subtypes.^{4,15-17} Tamsulosin is

selective for the α_{1A}- and α_{1D}-AR subtypes but has less affinity for the α_{1B} subtype, which regulates blood pressure via vascular smooth muscle contraction.¹⁵⁻¹⁸ α₁-AR antagonists are comparably effective in patients with BPH/LUTS, causing a 35% to 40% improvement in total symptom scores and a 15% to 30% improvement in Q_{max}.¹⁹ Furthermore, results suggest that α₁-AR antagonists that do not require titration (eg, tamsulosin, alfuzosin) can be started at their appropriate therapeutic doses and accordingly have a more rapid onset of action than those requiring titration (eg, doxazosin, terazosin).^{19,20} Differences in the safety and tolerability profiles among α₁-AR antagonists have been reported¹⁹⁻²¹ and will be discussed in the following article.

Androgen reduction therapy with 5-alpha-reductase inhibitors (eg, finasteride) has been found to decrease prostatic size by 20% to 30% within 3 to 6 months of treatment, underscoring the importance of androgens on BPH progression.²² Patients undergoing up to 4 years of finasteride therapy do not experience any additional regression, but no further growth of the gland is observed. Of note, the partial reduction in prostate size observed after androgen withdrawal may not always be sufficient to decrease resistance in the urethra²²; thus, symptom improvement may not be as dramatic and quantifiable when comparing with placebo or with the immediate benefit after surgery (eg, transurethral resection of the prostate). The use of finasteride either alone or in combination with an α₁-AR antagonist (doxazosin) has also been examined in the Medical Therapy of Prostatic Symptoms study; results of this study will be discussed in the following review article (see “Treatment and Pharmacologic Management of BPH in the Context of Common Comorbidities”). Overall, combination therapy yielded better symptom control; however, the use of finasteride as monotherapy or with doxazosin was associated with a significantly higher incidence of sexual side effects.²¹

Comorbidities in Aging Men

Cardiovascular (CV) Disease and Hypertension. CV disease, including coronary artery disease and stroke, accounts for 25%

to 55% of deaths worldwide.²² Hypertension is a well-established risk factor for CV disease, and like BPH, the prevalence of hypertension increases with age.²³ Although BPH and hypertension appear to involve separate disease processes, it has been postulated that age-related increases in sympathetic tone may play a role in their pathophysiologies.²³ Studies from both the United States (Third National Health and Nutrition Examination Survey [NHANES III]) and the United Kingdom suggest that about 50% to 65% of people over the age of 60 years are hypertensive.²³ These may be conservative estimates, because hypertension, like BPH, is a largely underdiagnosed condition.^{24,25} Using these estimates, however, it can be extrapolated that if about 50% of men have BPH by age 60 years and 50% have hypertension by age 60 years, then approximately 25% of men 60 years and older have BPH with comorbid hypertension.²³ It is important, therefore, for urologists and cardiologists to recognize the frequent coexistence of these conditions and to consider hypertension and BPH in patients 60 years or older when deciding on a course of treatment.²³

The Framingham Heart Study evaluated the prevalence of CV disease and its associated risk factors in an average American population over a period spanning more than 30 years. Data from a community-based, prospective cohort in the Framingham study have been used to estimate the residual lifetime risk (ie, the lifetime cumulative incidence, unadjusted for other mortality causes) for developing hypertension (defined as blood pressure $\geq 140/90$ mm Hg).²⁶ Among those aged either 55 or 65 years, the lifetime residual risk for developing hypertension was 90%, as was the risk for developing stage 1 high blood pressure (defined as $\geq 140/90$ mm Hg in spite of treatment).²⁶ This risk was found to be 60% higher among men over the period studied (1976-1998) compared with an earlier period (1952-1975). This temporal trend may be in part related to a concomitant trend in obesity.²⁶ These findings suggest a very high likelihood of hypertension comorbidity with BPH in men aged 65 years or older.

In a retrospective study that assessed BPH symptom severity (using IPSS or Q_{max})

and blood pressure in more than 9800 patients who had BPH, the authors observed an increase of 0.13 points and 1.60 points in IPSS with each year of age and measured incidence of hypertension, respectively.²⁷ Similarly, in logistic regression analysis, the risk of hypertension was increased by 5.3% and 5.0% with each year of age and each IPSS point, whereas Q_{max} was not a predictor.²⁷ Findings of this study are consistent with a possible pathophysiologic relationship between BPH and hypertension, which may be related to increased sympathetic activity in the aging man.

Diabetes. The prevalence of CV disease and hypertension in the aging man may also relate in part to a high incidence of type 2 diabetes in this population. Heart disease is the leading cause of death among diabetic patients, and the risks for heart disease and stroke among persons with diabetes is about 2- to 4-fold higher than in healthy individuals.²⁸ In addition, about 73% of adults with diabetes have hypertension or take blood pressure-lowering medications.²⁸ Prevalence statistics suggest that about 21 million people in the United States (6.2% of the entire population) have diabetes, including about 15 million diagnosed and another 6 million undiagnosed individuals.²⁸ Among the overall male population, the incidence is roughly 10.5%, or 11 million. As with BPH, the prevalence of diabetes appears to increase with age. In the 60-or-older population, about 10 million people are estimated to have diabetes, or about 20.9% of the population.²⁸ If one assumes that about one half of these persons are men, the incidence of diabetes in the men older than 60 years could be roughly estimated at 5 million. Because about 70% to 90% of men in this age group can also be expected to have BPH (Figure 1), there could be as many as 3.5 million to 4.2 million men with diabetes and coexistent BPH. Although it cannot be assumed that these men will have pathologic BPH as opposed to clinically inert disease, the likelihood of BPH and diabetes coexisting in this population should be considered when treating either condition. A further complication in the treatment of patients with comorbid LUTS caused by BPH and

diabetes is the presence of erectile dysfunction (ED), which has been found to occur in 25% of patients with long-term (10 or more years) type 1 diabetes.²⁹

Metabolic Syndrome. The metabolic syndrome is characterized by the simultaneous presence of a number of risk factors for heart disease, including abdominal obesity, proatherosclerotic dyslipidemia, high blood pressure, insulin resistance or glucose intolerance, and a prothrombotic and proinflammatory state in the blood.³⁰ The prevalence of metabolic syndrome is believed to be on the order of 50 million individuals in the United States.³⁰ Metabolic syndrome places the afflicted individual at increased risk for CV disease, including stroke and peripheral vascular disease. The American Heart Association has recommended lifestyle interventions (ie, smoking cessation, weight loss, increased physical activity, and dietary modifications) to reduce the risk of these complications.³⁰ A recent study suggests that declining androgen levels in men may negatively contribute to metabolic syndrome, because men in the upper tertile of testosterone levels were at reduced risk of having 3 or more features of metabolic syndrome (odds ratio, 0.24; $P < .04$).³¹ Recent results from NHANES III also indicate that serum C-reactive protein level, a feature of metabolic syndrome, may be associated with intraprostatic inflammation in BPH.³² The potential association between metabolic syndrome and BPH requires further study; however, physicians should be aware of metabolic syndrome as another potential comorbidity in older men at risk for BPH.

ED. ED is a common comorbid condition in the aging man.^{5,6} The Massachusetts Male Aging Study (MMAS) examined the prevalence of ED among men aged 40 to 70 years.³³ The prevalence of minimal, moderate, or complete impotence was 52%, and complete impotence tripled from 5% to 15% between ages 40 and 70 years, with a strong age association.³³ CV disease, diabetes, and hypertension were also associated with a higher probability of impotence, and the findings of this important study established

impotence as a significant health concern in aging men. A more recent study of 2412 men aged 40 to 70 years from 4 countries examined the prevalence of ED, defined by AUA criteria as “the persistent inability to achieve and/or maintain an erection sufficient for sexual activity.”³⁴ Among the 1335 who were classified as healthy (eg, no comorbid CV disease, hypertension, diabetes), there was a 16.1% overall prevalence of ED, whereas among those with concomitant conditions, it was nearly doubled (31.5%).³⁴ Risk factors for ED in this study included age (8% increase per year between 40 and 70 years) and smoking (odds ratio, 2.3 for >30 cigarettes/day). In addition, there was an inverse relationship with ED for both physical activity and educational level.³⁴ Despite the fact that men with a diagnosis of prostate disease were excluded from the analysis, 7.6% of interviewees reported moderate LUTS; 1.1% reported severe LUTS. In view of the known effect of LUTS on ED, the odds ratio for ED was 2.2 and 4.9, respectively, when considering men with moderate or severe LUTS.³⁴ The findings of this study have several implications. First, this study reaffirms the benefits of healthier lifestyles, including weight control, physical activity, and avoidance of smoking, on erectile function. Second, the findings identify a sizable proportion of even “healthy” men with “occasional insufficiencies in erectile function” (mild ED)—about 40% across all age groups. Finally, they underscore the coexistence of these 2 disorders and the contribution of LUTS to ED, even among men with no previous diagnosis of prostate disease.

BPH is the most common cause of LUTS in men 50 years of age or older,⁵ and the treatment of BPH symptoms may improve sexual function in men whose ED may be related to the coexistence of LUTS.³⁴

When determining a course for the treatment of BPH, physicians should consider the presence of age-related comorbidities and the potential for a given treatment to negatively affect these conditions.

Summary

BPH occurs at a high frequency in the aging man and is usually present with 1 or

more comorbidities. Accordingly, the choice of BPH treatment should be guided by the presence of medical conditions such as diabetes, metabolic syndrome, CV disease, ED, and hypertension. The use of an α_1 -AR antagonist with the least potential to interfere with blood pressure or to cause CV side effects, for example, is most appropriate for the treatment of LUTS in patients with comorbid CV disease or hypertension, as well as in those who are at a higher risk of orthostatic hypotension and falling.¹⁹ Furthermore, given the frequent occurrence of ED in this population, those drugs that effectively treat LUTS, thereby improving sexual function without causing bothersome sexual side effects such as impotence or decreased libido, have the most potential for long-term control of BPH.

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