Pathophysiology of Lower Urinary Tract Symptoms in the Aging Male Population

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Nearly all men will develop histological benign prostatic hyperplasia by the age of 80, but the degree of prostatic enlargement resulting from the hyperplasia is highly variable. Historically, it has often been assumed that the pathophysiology of lower urinary tract symptoms (LUTS) in men is the result of bladder outlet obstruction associated with prostatic enlargement. The observation that prostatic enlargement, bladder outlet obstruction, and LUTS are all age-dependent has been interpreted to indicate that these phenomena were causally related, but there is insufficient evidence for this. Undoubtedly, some men's prostatic enlargement causes obstruction and symptoms. Based on the available data, however, this subset appears to be extremely small. Because of the many urological and nonurological conditions that cause LUTS and age-dependent changes in bladder and neurological function, it is unlikely that there exists a single dominant etiology for the aging male population. If this is the case, then the optimal management of LUTS will require different and possibly combination therapies.
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Key words: • Benign prostatic hyperplasia • Lower urinary tract symptoms • Bladder outlet obstruction • Urinary retention • Transurethral prostatic resection

Benign prostatic hyperplasia (BPH) refers to a proliferative process of the cellular elements of the prostate, an enlarged prostate, or the voiding dysfunction resulting from prostatic enlargement and bladder outlet obstruction. It is estimated that BPH affects at least 50% of men in their 60s and that close to 90% of men in the United States will develop histologic evidence of the condition by age 80.[1] Thus, histological BPH appears to be an inescapable part of the aging process and its prevalence is expected to increase as the US population continues to age.

Table 1
Benign Prostatic Hyperplasia: Clinical Manifestations

Lower urinary tract symptoms • Voiding or obstructive symptoms • Storage or irritative symptoms
Impaired bladder emptying
Detrusor instability
Urinary tract infections
Chronic urinary retention
Chronic renal insufficiency
Hematuria*

*Only as a diagnosis of exclusion.

Histologically, BPH describes a process of rapid growth of both the stromal and epithelial cells of the prostate gland. BPH arises in the periurethral and transition zones of the prostate.[2] The relative proportion of stromal and epithelial hyperplasia is highly variable in men with clinical BPH. In a group of 26 men with BPH, the individual cellular composition of the hyperplastic component of the prostate ranged from 16.1% to 56.1% in connective tissue, from 20.2% to 59.3% in smooth muscle, from 4.3% to 24.8% in the epithelium, and from 5.3% to 21.9% in the epithelium lumen.

Although nearly all men develop histological BPH, the degree of prostatic enlargement resulting from hyperplasia is highly variable. The volume of the prostate is most accurately determined using imaging studies such as ultrasound, computerized tomography, and magnetic resonance imaging. Oesterling and colleagues[3] measured the prostate volumes of 464 men between 40 and 80 years of age, selected at random from the population of Olmsted County, MN. The overwhelming majority of men had prostate volumes ranging between 20 g and 60 g. A statistically significant correlation existed between age and prostate volume (P = .0001; r^2 = .185). Although prostate volume was age dependent, there was substantial overlap between the 10-year categorical age groups.

The size of the prostate is a very weak determinant of symptom severity and bladder outlet obstruction.

Lower urinary tract symptoms (LUTS) include *voiding or obstructive symptoms* such as hesitancy, poor and/or intermittent stream, straining, prolonged micturition, feeling of incomplete bladder emptying, dribbling, etc, and *storage or irritative symptoms* such as frequency, urgency, urge incontinence, and nocturia. The severity of LUTS is best measured using quantitative symptom indices. The most widely accepted instrument for quantifying symptom severity is the American Urological Association (AUA) symptom index.[4] Results from population-based studies have shown that the prevalence of moderate-to-severe LUTS and reductions in Q_{max} both increase with patient age.[5] Because the development of LUTS and prostatic enlargement are both age dependent, the development of LUTS in the aging male population has often been attributed to the enlarging prostate or BPH. In fact, until recently, the constellation of obstructive and irritative symptoms observed in aging men was termed “prostatism."

The fact that the development of benign prostatic enlargement (BPE), LUTS, and bladder outlet obstruction (BOO) are *temporally* related does not imply these events are *causally* related. The classic LUTS considered the hallmark of BPH occurs with the same frequency in age-matched women.[6] It is now widely recognized that the differential diagnosis of LUTS in the aging male population includes both urological and neurological conditions. Parkinson’s disease, a cerebrovascular accident, diabetes mellitus, congestive heart failure, bladder cancer, prostate cancer, urinary tract infection, overactive bladder, urethral stricture, and bladder neck hypertrophy may all cause LUTS identical to BPH.[7] Nevertheless, LUTS in the presence of some degree of prostatic enlargement have been sufficient to establish the clinical diagnosis of BPH.

Pathophysiology of BPH: Historical Perspective

The clinical manifestations attributed to BPH include LUTS, impaired bladder emptying (PVR), acute urinary retention (AUR), detrusor instability (DI), urinary tract infection (UTI), chronic urinary retention (CUR), chronic renal insufficiency (CRI), and hematuria (Table 1). Historically, it has been thought that these signs and symptoms resulted from bladder dysfunction arising from BOO due to

the enlarged prostate. Prostatic enlargement promoted BOO due to dynamic and static factors. Smooth muscle hyperplasia contributed to the dynamic obstruction and the generalized hyperplasia of both stromal and epithelial elements contributed to the static obstruction. Bladder outlet obstruction predisposed directly to AUR. Long-term BOO also promoted bladder dysfunction, which was manifested by poor contractility or detrusor instability. The incomplete bladder emptying resulting from impaired bladder contractility caused LUTS, UTIs, CUR, and CRI. The detrusor instability also contributed to LUTS. Hematuria may be attributed to BPH only as a diagnosis of exclusion. This is one clinical manifestation not explained by BOO.

The medical therapies widely used today for treatment of BPH are targeted to diminishing bladder outlet obstruction in order to reduce prostate volume and relax prostate smooth muscle tension.[7] Clinical data demonstrate that androgen suppression and α-blockade relieve and increase urinary flow rates in men with BPH; these data have been used to support the hypothesis that the pathophysiology of "prostatism" is due to bladder outlet obstruction.

Relationships Between LUTS, Bladder Outlet Obstruction, and Prostate Volume

Historically, it has often been assumed that the pathophysiology of LUTS in men is the result of bladder outlet obstruction associated with prostatic enlargement.[8] The observation that prostatic enlargement, bladder outlet obstruction, and LUTS are all age dependent was interpreted to indicate that these phenomena were causally related,[9] but there is insufficient evidence for this. The relationships between prostate volume, bladder outlet obstruction, and LUTS are optimally defined by measuring these parameters in a group of men selected at random from the community. Jacobsen, Girman, and Lieber[5] measured prostate volume using transrectal ultrasonography, peak flow rate, and the AUA symptom score in 464 men between the ages of 40 and 80 years, selected at random from the residents of Olmsted County, MN (Table 2). The *P* and r^2 values for the pairwise relationships between prostate volume and peak flow rate, prostate volume and symptom score, and peak flow rate and symptom score are shown in Table 2. These observations demonstrate that the size of the prostate is a very weak determinant of symptom severity and BOO, and that BOO is only a minor determinant of symptom severity.

Table 2
Relationships Between LUTS, Bladder Outlet Obstruction, and Prostate Enlargement

		Pairwise Comparisons					
		PV vs PFR		PV vs AUASS		PFR vs AUASS	
Reference	No.	*P*	r_2	*P*	r_2	*P*	r_2
Jacobsen et al[5]	466	< .001	.034	< .001	.045	< .001	.123
Barry et al[10]	198	.06	.020	.22	.008	.27	.005

LUTS, lower urinary tract symptoms; PV, prostate volume; PFR, peak flow rate; AUASS, American Urological Association symptom score.

Barry and coworkers[10] reported the relationships between prostate volume, peak flow rate, and symptom scores in a cohort of men participating in a clinical trial examining different treatment options for BPH. The pairwise correlations between prostate volume and peak flow rate, prostate volume and symptom score, and peak flow rate and symptom score were not clinically or statistically significant (Table 2). The findings from both of these research groups[5,10] strongly suggest that the widely held concept of the pathophysiology of LUTS in the aging male population—typically bladder outlet obstruction arising from enlarged prostate—is a gross oversimplification.

One explanation for the poor correlation between bladder outlet obstruction and symptom severity is that peak flow rate is not a reliable proxy for bladder outlet obstruction. Only a weak correlation exists between peak flow rate and synchronous pressure flow studies. Because pressure flow studies are invasive, these measurements have not been performed in a community population. Investigators have failed to show a clinically or statistically significant correlation between the severity of bladder outlet obstruction, based on detrusor pressures at peak flow rate, and severity of LUTS.[11]

Studies comparing LUTS, bladder outlet obstruction, and prostate size among different races provide additional evidence that prostate size is not an important factor leading to the development of LUTS and lowered peak flow rate. The AUA symptom score, peak flow rate, and prostate volume were measured in community-based surveys of men in the United States (Olmsted County, MN) and Japan (Shimomaki-nura) (Table 3).[12] The Japanese men had smaller prostates, higher peak flow rates, and more severe symptoms.

Table 3
International Prostate Symptom Score, Peak Flow Rate, and Prostate Volume in Caucasian (American) and Asian (Japanese) Men

Race	IPSS (% ≥ 8)	PFR (mL/sec)	PV (cm^3)
Caucasian	25.5	17.2	29.5
Asian	36.6	21.3	23.5

IPSS, international prostate symptom score; PFR, peak flow rate; PV, prostate volume.

The observation that Asian men had smaller prostates, higher symptom scores, and higher peak flow rates provides further evidence that the severity of LUTS is not explained by bladder outlet obstruction or prostate volume.

Oesterling and associates[3] reported the distribution of prostate size in a cohort of randomly selected men living in Olmsted County, MN. Interestingly, the mean prostate volume and the distribution of prostate volumes were almost identical to subjects with both LUTS (AUA symptom score ≥ 8) and bladder outlet obstruction (peak urinary flow rates from 4 to 15 mL/sec) who were enrolled in the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study (VA-COOP) (Figure 1).[13] The fact that a random population of men has the same mean prostate volume and distribution of prostate volume as a group of age-matched men with clinical BPH provides further evidence that prostate size is relatively unimportant in the development of LUTS and BOO.

Additional evidence questioning the influence of prostatic enlargement on the pathophysiology of LUTS in the aging male comes from studies comparing the incidences of symptoms in men and women. Lepor and Machi[6] administered the AUA symptom score to a group of 101 men and 99 women between the ages of 55 and 79 years. Subjects were attending a general health symposium with no emphasis on genitourinary diseases. Mean AUA symptom scores were equivalent in men (6.9) and women (7.7). The AUA score was subgrouped into obstructive and irritative scores. The obstructive symptom scores in men (2.7) and women (2.9) were not significantly different. Similarly, the irritative scores in the men (4.2) and women (4.8) were not significantly different. The development of LUTS characteristic of BPH is a non–gender-specific event associated with aging. It is conceivable that the pathophysiology of LUTS in men and women is different. Nevertheless, the observation that the prevalence of LUTS characteristic of clinical BPH is equivalent in men and women suggests that important nonprostatic mechanisms likely exist for the development of symptoms.

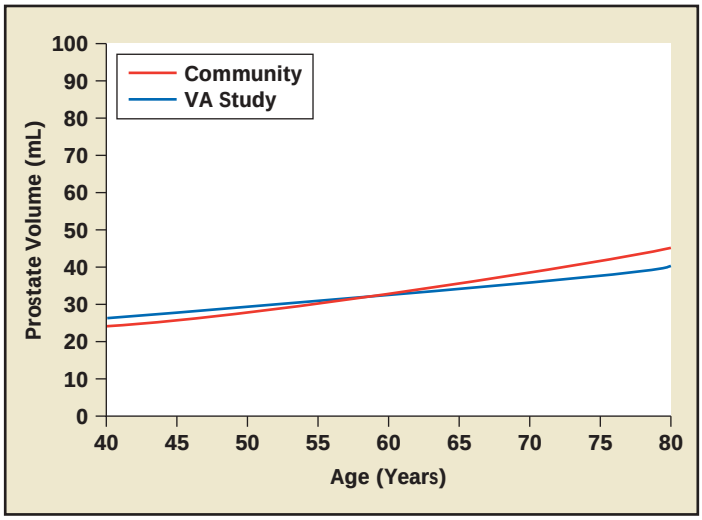

Figure 1. *Estimated median prostate volume as a function of age for the VA Study, and Olmsted County Community Study. Adapted from Boyle et al,[13] with permission from the publisher, Elsevier Science.*

In summary, there is no clinically significant relationship between prostatic enlargement and LUTS in men with clinical BPH. There is only a weak relationship between LUTS and bladder outlet obstruction. Therefore, factors other than prostatic enlargement and bladder outlet obstruction must contribute to the development and severity of LUTS.

Does the Prostate Mediate LUTS?

Despite the observation that both men and women develop LUTS, the unequivocal effectiveness of transurethral resection of the prostate (TURP) strongly suggests that the prostate and/or prostatic urethra must play an important role in the pathophysiology of clinical BPH. Schwartz and Lepor[14] have also demonstrated that in men with clinically localized prostate cancer and LUTS, radical prostatectomy has the same beneficial effect on symptoms as does TURP. This provides further evidence that the prostate is an important factor in the pathophysiology of LUTS in men.

Table 4
Comparison of Prostatic α_1 Adrenoceptor Density, Phenylephrine Responsiveness, and Cellular Composition in Men With Symptomatic and Asymptomatic BPH

Tissue Source	α_1AR Density (fmol/mg wet wt)	Phenylephrine (gT/g wet wt)	S/E Ratio E_{max}
TURP	.17	11.4	5.5
Cystoprostatectomy	.19	27	2.7

BPH, benign prostatic hyperplasia; α_1AR, α_1 adrenoceptor; S/E, stromal:epithelial; E_{max}, maximal tension; TURP, transurethral resection of prostate.

Lepor and Rigaud[15] reported the treatment outcome for 30 men with clinical BPH undergoing TURP. Overall, 87% of the patients experienced marked or moderate improvement in their symptomatology. In this prospective study, the relationship between changes in peak flow rate and changes in obstructive symptom score was not statistically significant (P = .49; r^2 = .25). Similarly, changes in peak flow rate versus changes in irritative symptom score were not statistically significantly (P = .9; r^2 = .085). Schaeffer has reported that symptom improvement following prostatectomy is equivalent in men with and without pressure flow evidence of bladder outlet obstruction. These studies suggest that TURP relieves LUTS and decreases bladder outlet obstruction via independent mechanisms.

Identifying Prostatic Factors Contributing to the Pathophysiology of Clinical BPH

Caine and coworkers[16] reported in 1976 that α-blockers are effective for the treatment of BPH. Over the last 20 years, over 20 randomized clinical trials have consistently demonstrated the safety and efficacy of various α_1-blockers for the treatment of BPH.[7] It is indisputable that α_1 receptors are abundant in the human prostate,[17] and these receptors mediate the tension of prostate smooth muscle.[18] It has been assumed that the efficacy of α_1-blockers is mediated via relaxation of prostate smooth muscle. The observation by Shapiro and colleagues[19] that 40% of the area density of BPH tissue is smooth muscle provides further evidence that prostate smooth muscle is likely an important factor in the development of clinical BPH.

The most appropriate study design to elucidate the pathophysiology of clinical BPH would be a comparison of biochemical and histological properties in tissue specimens derived from age-matched men with and without clinical BPH. Ideally, the specimens would be derived from men with prostates of equivalent size. Several investigators have made comparisons between tissue specimens derived from the inner (transition zone) and outer (peripheral zone) regions of the prostate. In the enlarged prostate, the outer and inner zones correspond to the surgical capsule and the hyperplastic tissue, respectively. These comparisons do not provide insight into the pathophysiology of clinical BPH but instead compare regional differences in the prostate.

Between 1986 and 1989, our laboratory investigated the pathophysiology of clinical BPH utilizing inner gland tissue specimens derived from men undergoing TURP for clinical BPH (symptomatic BPH) and men undergoing cystoprostatectomy for bladder cancer (asymptomatic BPH). Preoperatively, symptom scores, peak flow rate, and prostate volumes were routinely measured. Alpha$_1$ receptor density was observed to be equivalent in tissue specimens obtained from men with symptomatic and asymptomatic BPH (Table 4).[18] The contractile response to α_1 agonists was also similar between these groups (Table 4).[17] These studies suggested that the development of clinical BPH was not due to up-regulation of the α_1 receptor or increased responsiveness of prostate smooth muscle to α_1 agonists.

Although other investigators have reported that the α_1 receptor is up-regulated in men with BPH, these studies compared tissues from different regions of the prostate and not inner gland tissue from men with and without clinical BPH. In our studies, the stromal:epithelial ratio was greater in men with symptomatic BPH, suggesting that the cellular composition of the inner gland (transition zone) may represent an important factor contributing to the pathophysiology of clinical BPH (Table 4).[20]

Because the neurotransmitter for the α_1 receptor is norepinephrine, another plausible mechanism contributing to

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the pathophysiology of clinical BPH is increased adrenergic innervation. Spitsbergen and coworkers[21] have reported that the frequency of micturition in the spontaneous hypertensive rat (SHR) is greater than in controls, implying that the increased levels of norepinephrine may mediate voiding dysfunction. Lepor and colleagues[22] reported an inverse relationship between the AUA symptom score and catecholamine level in consecutive men undergoing prostatic biopsy for an elevated prostate-specifc antigen (PSA) or abnormal digital rectal examination who had no evidence of prostate cancer. This observation strongly suggests that the pathophysiology of clinical BPH is not due to increased adrenergic innervation.

In summary, the studies from our laboratory identified the cellular composition of the prostate as the only parameter contributing to the pathophysiology of clinical BPH.

Do α-Blockers Relieve LUTS by Relaxing Prostatic Smooth Muscle Tension?

In order to further define the role of prostate smooth muscle in the pathophysiology of clinical BPH, 26 men with clinical BPH who were candidates for medical management completed the Boyarsky symptom score and underwent uroflowmetry and transrectal ultrasound-guided biopsy of the prostate before initiating therapy with the α_1-blocker terazosin.[23] The mean percentage smooth muscle was quantified from the biopsy specimens. The pairwise relationships between baseline peak flow rate and percentage smooth muscle, baseline total symptom score and percentage smooth muscle, percentage change in peak flow rate and percentage smooth muscle, and percentage change in the symptom score and percentage smooth muscle are shown in Table 5. These pairwise relationships demonstrate a statistically and clinically significant relationship between the baseline peak flow rate and the percentage smooth muscle, and no significant relationship between the baseline total symptom score and percentage smooth muscle. These observations suggest that the amount of prostate smooth muscle contributes to bladder outlet obstruction and not to symptomatology.

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These observations provide further evidence that LUTS and bladder outlet obstruction are not causally related. The relationship between the increase in peak flow rate and the percentage smooth muscle was highly significant, suggesting that the improvement in bladder outlet obstruction secondary to terazosin is related to relaxation of prostatic smooth muscle. A very weak and statistically insignificant relationship was observed between the percentage change in the total symptom score and the percentage smooth muscle, suggesting that the symptom improvement associated with terazosin is most likely not mediated via relaxation of prostate smooth muscle. An important implication of these findings is that nonprostatic smooth muscle α_1-mediated mechanisms may account for the symptom improvement elicited by α_1-blockers in men with BPH.

The study correlating response to α-blockers with the cellular composition of the prostate suggests that prostate smooth muscle density contributes to the severity of bladder outlet obstruction and accounts for the α_1-mediated reduction of bladder outlet obstruction in men with clinical BPH. Prostate smooth muscle density does not appear to be a major factor contributing to the severity of LUTS or to α_1-mediated improvement in symptomatology in men with clinical BPH.

Table 5
The Role of Prostatic Smooth Muscle in the Pathophysiology of BPH

	Linear Correlation		
Pairwise Comparisons	*P*	*r*	r^2
% SM vs baseline AUASS	.59	.11	.012
% SM vs baseline PFR	.02	−.44	.194
% SM vs AUASS	.19	−.27	.073
% SM vs PFR	< .0001	−.75	.563

BPH, benign prostatic hyperplasia; SM, smooth muscle; AUASS, American Urological Association symptom score; PFR, peak flow rate.

Pathophysiology of LUTS—Clinical Correlations

If the pathophysiology of LUTS is partly due to BOO resulting from prostate smooth muscle tension, then the improvement in symptom scores in men undergoing α-blocker therapy should be directly proportional to the increase in peak flow rates. The

overwhelming clinical evidence derived from the medical therapy literature provides evidence suggesting that decreases in symptom scores are not proportional to increases in peak flow rate.

An analysis of the VA-COOP study provides insights into the pathophysiology of clinical BPH.[24] In this multicenter clinical trial, 1229 men with clinical BPH were randomized in equal proportions to receive placebo, terazosin, finasteride, or combination therapy. This study represented the first comparison of an α_1-blocker and a 5α-reductase inhibitor and was the first to examine a combination of both drugs.

Over the entire 52 weeks of the randomized study, changes in peak flow rate and AUA symptom score were not significantly different between placebo and finasteride. The changes in peak flow rate and AUA symptom score between placebo and terazosin were highly statistically significant, whereas this relationship between terazosin and combination therapy was not statistically or clinically significant. The equivalent effectiveness of placebo versus finasteride and terazosin versus combination therapy is compelling evidence that finasteride has a limited role in the medical management of BPH.

A subset analysis of the VA study failed to demonstrate a statistically or clinically significant relationship between changes in AUA symptom score and changes in peak flow rates for men receiving terazosin, suggesting that α_1-blockers relieve LUTS via a mechanism unrelated to relieving bladder outlet obstruction.

A subset analysis of the VA study examined the symptom improvement according to baseline peak flow rate quartile groups.[25] Interestingly, improvements in the AUA symptom scores were equivalent in the lowest baseline peak flow rate quartile group (peak flow rate < 8.6 mL/sec) and the highest quartile baseline peak flow rate group (peak flow rate > 12.4 mL/sec), suggesting that α_1-mediated symptom improvement may not be related to relaxing prostate smooth muscle. If this is the case, men with LUTS and no evidence of bladder outlet obstruction should also respond to α_1-blockers.

Lepor and colleagues[26] have recently reported that symptom improvements in age-matched men with prostate volumes of equivalent size were equivalent in men with normal and abnormal baseline peak flow rates. The assumption that men with LUTS must also have bladder outlet obstruction has likely limited the clinical utility of α-blockers in men with LUTS. Thus, men with lower urinary tract symptoms secondary to prostatitis, interstitial cystitis, radiation cystitis, and other clinical entities, may also respond to α_1-blockers.

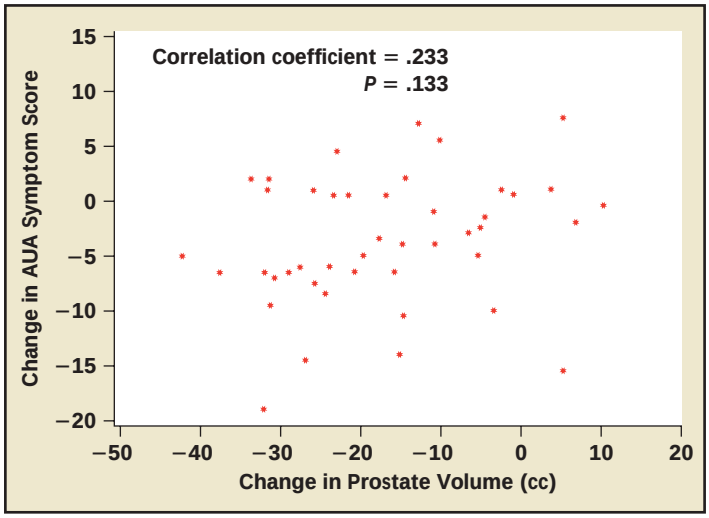

Figure 2. *Scatter plot for pairwise correlation relationships in finasteride group between changes in prostate volume and American Urological Association (AUA) symptom score in subjects with baseline prostate volumes greater than 50 cm³.*

Do 5α-Reductase Inhibitors Relieve LUTS by Reducing Prostate Volume?

Androgen deprivation in general has a limited utility for improving LUTS in men with BPH. Only in men with very large prostates does the effect on LUTS become clinically significant. Even in men with large prostates (> 50 cm³), α-blockers have a 3-fold greater treatment-related effect on relieving LUTS.

The proposed mechanism of action for the efficacy of finasteride in men with BPH is reduction of prostate volume. Figure 2 shows the relationship between changes in prostate volume and changes in AUA symptom score for the 251 subjects randomized to the finasteride group in the VA study.[25] The *P* values for both these pairwise relationships were not statistically significant. The mechanism for the minimal efficacy associated with finasteride is not related to reduction of prostate volume.

Conclusion

What is the pathophysiology of LUTS in men with BPH? The development of microscopic BPH, bladder outlet obstruction, and LUTS is associated with aging. The overwhelming clinical evidence suggests that these three age-dependent parameters are not causally related. Undoubtedly there are some men whose prostatic enlargement causes obstruction and symptoms. Based on the available data, however, this subset must be small.

We know that TURP and radical prostatectomy result in highly significant improvements in LUTS. Obviously, the mechanisms of symptom improvement in these cases must be related to the prostate, bladder neck, or prostatic urethra, because only these tissues are resected or excised. Because men without bladder outlet obstruction respond equally well to prostatectomy, a plausible mechanism for the pathophysiology of BPH and the effectiveness of TURP may be a nonobstruction mechanism involving neurological pathways. Therefore, drugs that influence the sensory afferent in the lower urinary tract, or the neural pathways that process this input, may represent an entirely new therapeutic strategy for men with LUTS.

We also know that α_1-blockers represent an extremely effective pharmacological strategy for the treatment of BPH. There is increasing evidence that men with LUTS and no evidence of bladder outlet obstruction respond to α_1-blockers. The mechanism for α_1-mediated symptom improvement appears to be independent of bladder outlet obstruction. It is plausible that sensory innervation of the prostate may represent a target for α_1 antagonists.

Because of the many urological and nonurological conditions that cause LUTS and the age-dependent changes in bladder and neurological function, it is unlikely that there exists a single dominant etiology for LUTS in the aging male population. If this is the case, then the optimal management of LUTS will require different and possibly combination therapies.

The available data suggest that we should not direct our pharmacological strategies exclusively towards reducing prostate volume or diminishing bladder outlet obstruction. Only incremental advances in the medical management of BPH will be derived by developing subtype-selective α_1 antagonists or more complete inhibitors of 5α-reductase. The quantum advances in the medical management of BPH will require a better understanding of the pathophysiology of LUTS and novel therapeutic strategies for treating LUTS with or without coexisting BPH. ■

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Main Points

- Approximately 90% of men will develop histologic evidence of benign prostatic hyperplasia (BPH) by age 80, and a statistically significant correlation also exists between age and prostate volume.
- Medical therapies widely used today for treatment of BPH are targeted to diminish bladder outlet obstruction, thereby reducing prostate volume and relaxing prostate smooth muscle tension.
- Clinical data demonstrate that androgen suppression and α-blockade relieve symptoms and increase urinary flow rates in men with BPH.
- The observation that prostatic enlargement, bladder outlet obstruction, and lower urinary tract symptoms (LUTS) are all age dependent has been interpreted to indicate that these phenomena are causally related, but there is insufficient evidence for this assumption.
- The unequivocal effectiveness of transurethral resection of the prostate strongly suggests that the prostate and/or prostatic urethra must play an important role in the pathophysiology of clinical BPH.
- Prostate smooth muscle density does not appear to be a major factor contributing to the severity of LUTS or to the α_1-mediated improvement in symptomatology in men with clinical BPH.
- 5α-reductase inhibitors may not relieve symptoms in men with large prostates simply by shrinking the prostate.

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