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REVIEW

Pathology of benign prostatic hyperplasia

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The epidemiology of benign prostatic hyperplasia (BPH) is complex and not fully understood. The androgenic hormones testosterones and dihydrotestosterone play at least a permissive and important role. Growth factors and other hormones including estrogens may also play a role. BPH is a truely hyperplastic process resulting in growth of glandular-epithelial and stromal/muscle tissue in the prostate, leading to often measurable growth taking on different shapes and configurations which may impact symptoms and secondary outcomes. It is important to recognize that BPH is a histological conditions, which is one but not the only cause of lower urinary tract symptoms, and may or may not be associated with prostate enlargement and bladder outlet obstruction. Recognizing the different entities and determining their presence in individual patients may help with therapeutic decision making.
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Introduction

Benign prostatic hyperplasia (BPH) is a pathologic process that contributes to, but is not the sole cause of, lower urinary tract symptoms (LUTS) in aging men.[1] Despite intense research efforts in the past five decades to elucidate the underlying etiology of prostatic growth in older men, cause-and-effect relationships have not been established. For example, androgens are a necessary but not a clearly causative aspect of BPH. Notions held earlier that the clinical symptoms of BPH (prostatism) are simply because of a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of LUTS is because of age-related detrusor dysfunction. Bladder outlet obstruction itself may induce a variety of neural alterations in the bladder, which contribute to symptomatology. Moreover, bothersome LUTS may be seen in men with polyuria, sleep disorders and a variety of systemic medical conditions unrelated to the prostate bladder unit.

Etiology of BPH

Histopathologically, BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. The observation of a new epithelial gland formation is normally seen only in fetal development and gives rise to the concept of embryonic reawakening of the stroma cell's inductive potential.[2] The precise molecular etiology of this hyperplastic process is uncertain. The observed increase in cell number may be because of epithelial and stromal proliferation or to impaired programmed cell death or apoptosis leading to cellular accumulation. Androgens, estrogens, stromal–epithelial interactions, growth factors and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process.

The role of androgens

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty and aging.[3] Patients castrated before puberty or who are affected by a variety of genetic diseases that impair androgen action or production do not develop BPH. Examples for such are the eunuchs having served at the imperial court in the Forbidden City in Peking and the Skoptzy.[4] It is also known that prostatic levels of dihydrotestosterone (DHT) as well as the androgen receptor remain high with aging, despite the fact that peripheral levels of testosterone are decreasing with age. Moreover, androgen withdrawal leads to partial involution of established BPH.[5] Assuming normal ranges, there is no clear relationship between the concentration of circulating androgens and prostate size in aging men

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Table 1 Absence of significant relationship between serum testosterone and serum PSA and prostate volume

Baseline testosterone category (ng per 100 ml)[a]	*No. of individuals (n = 4254)*	*Age (years)*	*PSA ($ng\,ml^{-1}$)*	*Prostate volume (ml)*	*BMI (kg/m^2)*	*Baseline SFI score*
⩾300	3092	66.5	4.0	54	27.0	6.8
275–<300	291	65.3	3.8	56	28.2	6.6
250–<275	269	66.2	3.9	55	28.1	6.4
225–<250	225	65.3	4.0	57	29.0	7.2
200–<225	143	64.8	3.9	56	30.1	5.9
175–<200	115	66.5	4.0	56	29.5	6.8
150–<175	67	66.2	3.6	56	29.5	5.8
<150	52	68.7	4.0	61	31.0	5.6

Abbreviation: BMI, body mass index; PSA, prostate specific antigen; SFI, sexual function inventory.
Adapted from Marberger *et al.*[6]
[a]For nanomoles per liter, divide by 28.8.

or more specifically in men with BPH enrolled in clinical trials[6] (Table 1).

In the brain, skeletal muscle and seminiferous epithelium, testosterone directly stimulates androgen-dependent processes. In the prostate, however, the nuclear membrane-bound enzyme steroid 5α-reductase converts the hormone testosterone into DHT, the principal androgen in this tissue (Figure 1).[3] Overall, 90% of total prostatic androgen is in the form of DHT, principally derived from testicular androgens. Adrenal androgens may constitute 10% of total prostatic androgen, although the importance of this stored hormone source in the etiology of BPH is negligible. Inside the cell, both testosterone and DHT bind to the same high-affinity androgen receptor protein. DHT is a more potent androgen than testosterone because of its higher affinity for the androgen receptor.[7] The hormone receptor then binds to specific DNA-binding sites in the nucleus, which results in increased transcription of androgen-dependent genes and ultimately stimulation of the protein synthesis. In contrast, androgen withdrawal from androgen-sensitive tissue results in a decrease in protein synthesis and tissue involution. Besides inactivation of key androgen-dependent genes (for example, prostate-specific antigen), androgen withdrawal leads to the activation of specific genes involved in programmed cell death.[8,9] In addition to these direct effects many growth factors and their receptors are regulated by androgens. Thus, the action of testosterone and DHT in the prostate is mediated indirectly through autocrine and paracrine pathways. The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life, and levels of androgen receptors[10,11] as well as DHT[12] in the prostate remain high throughout aging.

Two steroid 5α-reductase enzymes have been discovered, each encoded by a separate gene.[13] Type I 5α-reductase, the predominant enzyme in extraprostatic tissues, such as skin and liver, is normally expressed in the 5α-reductase deficiency syndrome and is inhibited by the dual inhibitor dutasteride but not substantially by finasteride. Type II 5α-reductase is the predominant prostatic 5α-reductase, although it is also expressed in extraprostatic tissues. Mutations in the type II enzyme are responsible for the clinical phenotype observed in the 5α-reductase deficiency syndrome.[14] The type II is sensitive to inhibition by both five alpha reductase inhibitors.[15]

These data demonstrate that the stromal cell plays a central role in androgen-dependent prostatic

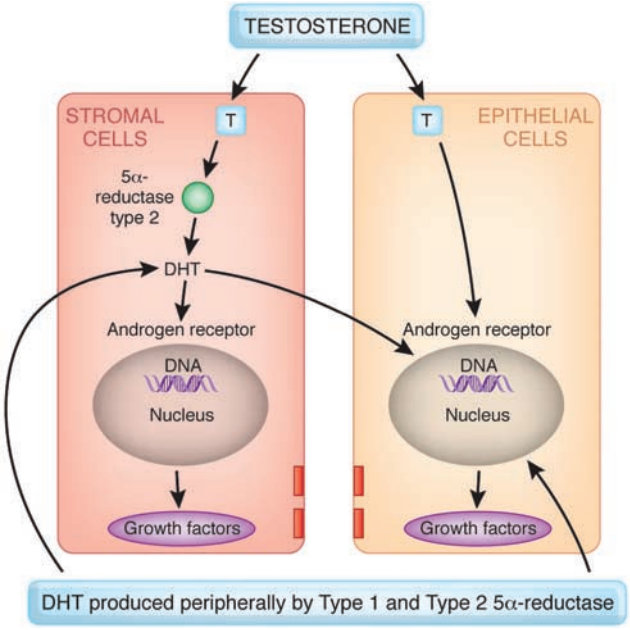

Figure 1 Testosterone (T) diffuses into the prostate epithelial and stromal cell. T can interact directly with the androgen (steroid) receptors bound to the promoter region of androgen-regulated genes. In the stromal cell, a majority of T is converted into dihydrotestosterone (DHT)—a much more potent androgen, which can act in an autocrine manner in the stromal cell or in a paracrine manner by diffusing into epithelial cells in close proximity. DHT produced peripherally, primarily in the skin and liver, can diffuse into the prostate from the circulation and act in a true endocrine manner. In some cases, the basal cell in the prostate may serve as a DHT production site, similar to the stromal cell.[1]

growth and that the type II 5α-reductase enzyme within the stromal cell is the key androgenic amplification step. Thus, a paracrine model for androgen action in the gland (Figure 1) is evident.

The role of growth factors

Growth factors are small peptide molecules that stimulate, or in some cases inhibit, the cell division and differentiation processes.[16] Cells that respond to the growth factors have on their surface receptors specific for that growth factor that in turn are linked to a variety of transmembrane and intracellular signaling mechanisms. Interactions between growth factors and steroid hormones may alter the balance of cell proliferation versus cell death to produce BPH (Figure 2) Subsequent to the first description of the basic fibroblast growth factor in BPH by Story,[18] a variety of growth factors have been characterized in normal, hyperplastic and neoplastic prostatic tissue.[19] In addition to bFGF (FGF-2), acidic FGF (FGF-1), Int-2 (FGF-3), keratinocyte growth factor (FGF-7), transforming growth factors (TGF-β) and epidermal growth factor have been implicated in prostate growth. TGF-β is a potent inhibitor of proliferation in normal epithelial cells in a variety of tissues. In models of prostatic cancer, there is evidence that malignant cells have escaped the growth inhibitory effect of TGF-β. There is mounting evidence of interdependence between growth factors, growth factor receptors and the steroid hormone milieu of the prostate.[16] Although data on the absolute level of growth factor and growth factor receptors in hyperplastic as opposed to normal tissue are conflicting, it is likely that growth factors play some role in the pathogenesis of BPH.

Pathology

McNeal[20] first showed that BPH first develops (Figures 3–5) in the periurethral 'transition zone' of the prostate (Figure 4). The transition zone consists of two separate glands immediately external to the preprostatic sphincter. The main ducts of the transition zone arise on the lateral aspects of the urethral wall at the point of urethral angulation near the verumontanum. Proximal to the origin of the transition zone ducts are the glands of the 'periurethral zone' that are confined within the

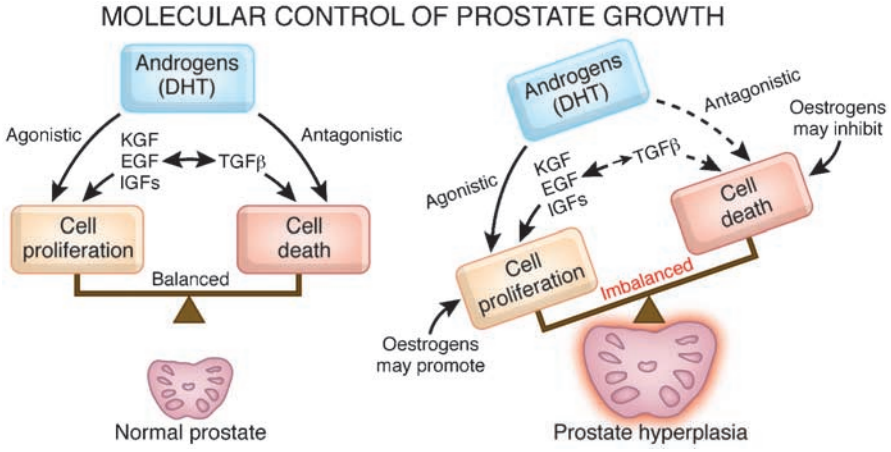

Figure 2 Balance between growth stimulatory and inhibitory factors involved in cellular homeostasis in the prostate gland. The respective roles of androgens (testosterone and dihydrotestosterone (DHT)) are shown. The right hand panel illustrates the imbalance and abnormal growth in benign prostatic hyperplasia (BPH).[17]

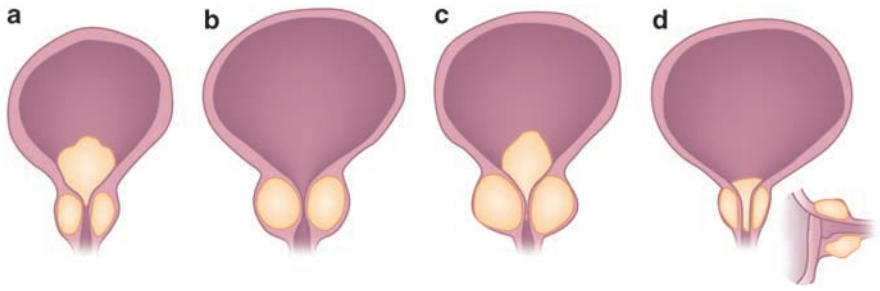

Figure 3 Different gross appearances of hyperplastic prostatic tissue obstructing the prostatic urethra forming 'lobes.' (**a**) Isolated middle lobe enlargement. (**b**) Isolated lateral lobe enlargement. (**c**) Lateral and middle lobe enlargement. (**d**) Posterior commissural hyperplasia (median bar).

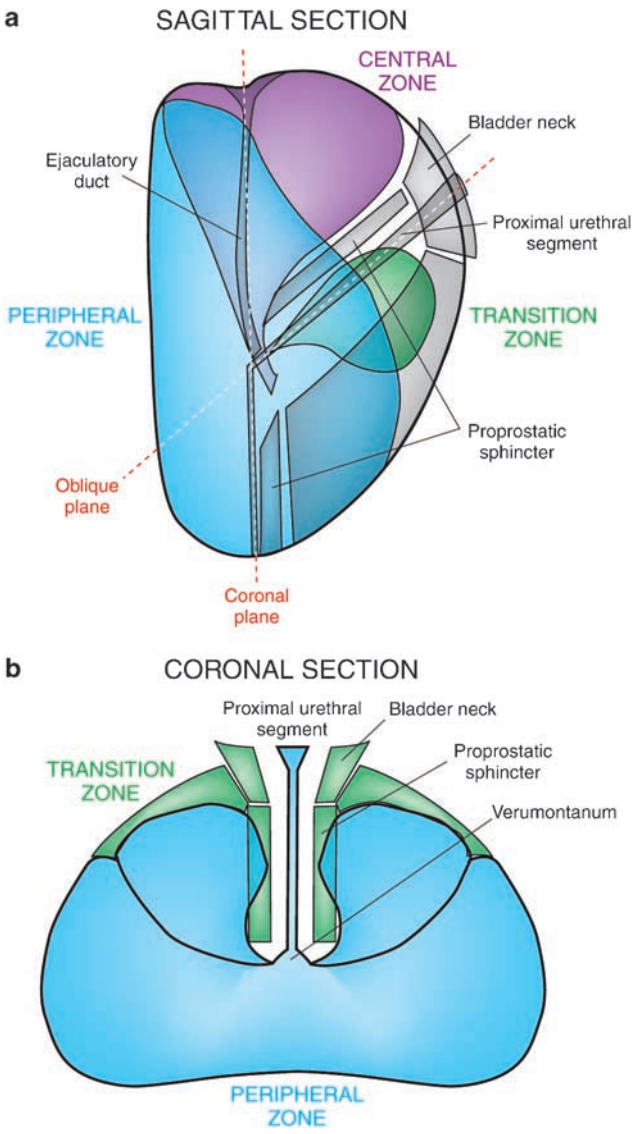

Figure 4 (**a**) Sagittal (top panel) and (**b**) coronal (bottom panel) section of the prostate showing peripheral zone (PZ), transition zone (TZ), central zone (CZ), the verumontanum (V), the proximal urethral segment (UP), as well as preprostatic sphincter (s), bladder neck (bn) and ejaculatory duct (E). OC, oblique plane (bottom view) and C, coronal plane.

preprostatic sphincter and course parallel to the axis of the urethra. All BPH nodules develop either in the transition zone or in the periurethral region. The transition zone also enlarges with age, unrelated to the development of nodules[21] (Figure 4).

One of the unique features of the human prostate is the presence of the prostatic capsule, which plays an important role in the development of LUTS.[22] In the dog, the only other species known to develop naturally occurring BPH, symptoms of bladder outlet obstruction (BOO) and urinary symptoms rarely develop because the canine prostate lacks a capsule. Presumably, the capsule transmits the 'pressure' of tissue expansion to the urethra and

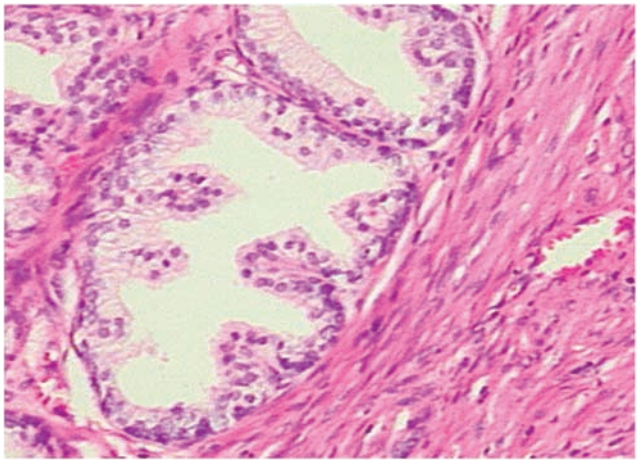

Figure 5 Panel shows glandular tissue to the left and stromal tissue to the right.

leads to an increase in urethral resistance. Thus, the clinical symptoms of BPH in men may be not only because of age-related increases in prostatic size but also to the unique anatomic structure of the human gland. Clinical evidence of the importance of the capsule can be found in series that clearly document that incision of the prostatic capsule (transurethral incision of the prostate) results in a significant improvement in outflow obstruction, despite the fact that the volume of the prostate remains the same.

The size of the prostate does not correlate with the severity of symptoms or the degree of obstruction. Thus, other factors such as dynamic urethral resistance, the prostatic capsule, and anatomic pleomorphism are more important in the production of clinical symptoms than the absolute size of the gland.

Histological features

BPH is a true hyperplastic process (Figure 5). Histologic studies document an increase in the cell number.[21] McNeal's studies show that the majority of early periurethral nodules are purely stromal in character. In contrast, the earliest transition zone nodules represent the proliferation of glandular tissue that may be associated with an actual reduction in the relative amount of stroma. During the first 20 years of BPH development, the disease may be predominantly characterized by an increased number of nodules, and the subsequent growth of each new nodule is generally slow. Then a second phase of evolution occurs in which there is a significant increase in large nodules. In the first phase, the glandular nodules tend to be larger than the stromal nodules. In the second phase, when the size of individual nodules is increasing, the size of glandular nodules clearly predominates.

There is a significant pleomorphism in stromal–epithelial ratios in resected tissue specimens. Studies from primarily small-resected glands show a predominance of fibromuscular stroma.[23] Larger

glands, predominantly those removed by enucleation, show primarily epithelial nodules. However, an increase in stromal–epithelial ratios does not necessarily indicate that this is a 'stromal disease'; stromal proliferation may well be because of 'epithelial disease.'

Importance of smooth muscle

Regardless of the exact proportion of epithelial to stromal cells in the hyperplastic prostate, there is no question that prostatic smooth muscle represents a significant volume of the gland.[24] Although the smooth muscle cells in the prostate have not been extensively characterized, presumably their contractile properties are similar to those seen in other smooth muscle organs. The spatial arrangement of smooth muscle cells in the prostate is not optimal for force generation; however, there is no question that both passive and active forces in prostatic tissue play a major role in the pathophysiology of BPH. Stimulation of the adrenergic nervous system clearly results in a dynamic increase in prostatic urethral resistance. Blockade of this stimulation by α-receptor blockers clearly diminishes this response.

Active smooth muscle tone in the human prostate is regulated by the adrenergic nervous system.[25] The α_1-adrenoreceptor nomenclature has been standardized to reconcile differences in nomenclature based on pharmacologic and molecular studies. Receptor-binding studies clearly show that the α1A is the most abundant adrenoreceptor subtype present in the human prostate.[26,27] Moreover, the α1A receptor clearly mediates active tension in human prostatic smooth muscle. It is still unclear whether other factors may regulate smooth muscle contraction. The presence of type IV and type V phosphodiesterase isoenzymes in the prostate implies that phosphodiesterase inhibitors may be appropriate candidate therapies for BPH-related LUTS.[28,29]

Autonomic nervous system overactivity may contribute to LUTS in men with BPH.[30,31] The activity of the autonomic nervous system, as measured by a standard set of physiologic tests, plasma and urinary catecholamines correlates positively with symptom score and other BPH measures.

The bladder's response to obstruction

Current evidence suggests that the bladder's response to obstruction is largely an adaptive one. However, it is also clear that many lower tract symptoms in men with BPH or prostate enlargement are related to obstruction-induced changes in bladder function rather than to outflow obstruction directly. Approximately one third of men continue to have a significant irritative or storage symptoms after surgical relief of obstruction.[32] Obstruction-induced changes in the bladder are of two basic types. First, the changes that lead to 'detrusor instability' or decreased 'compliance' are clinically associated with symptoms of frequency and urgency. Second, the changes associated with decreased 'detrusor contractility' are associated with further deterioration in the force of the urinary stream, hesitancy, intermittency, increased residual urine and (in a minority of cases) detrusor failure. Acute urinary retention should not be viewed as an inevitable result of this process. Many patients presenting with acute urinary retention have more than adequate detrusor function, with evidence of a precipitating event leading to the obstruction. Independent of obstruction, aging produces some of the same changes in bladder function, histology and cellular function. There is a suggestive evidence from animal models that atherosclerosis and the resultant chronic bladder ischemia or hypoxia induced by other mechanisms (for example, increased bladder wall tension) may contribute to bladder pathology.[33,34]

The complex interrelationship between BPH, LUTS, prostatic enlargement and BOO

From the foregoing discussion it is clear that BPH itself is actually only a histological diagnosis, which

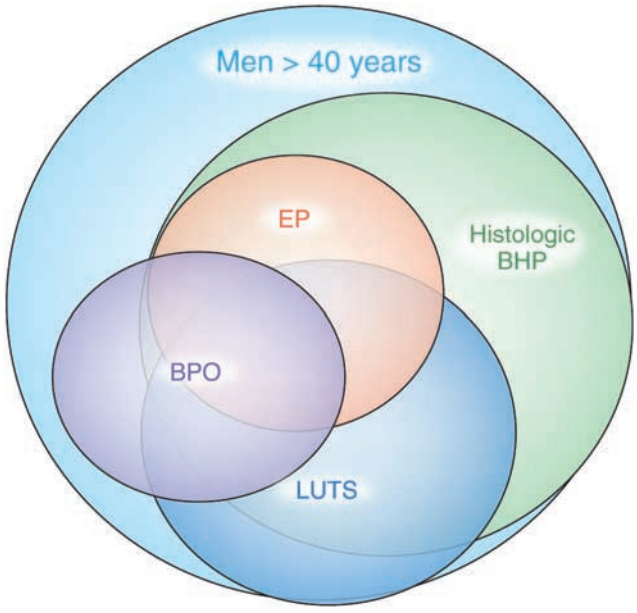

Figure 6 Among all men over the age of 40 years, in an age-dependent manner approximately 50% will develop histological hyperplasia or benign prostatic hyperplasia (BPH); of those, 50% will have bothersome lower urinary tract symptoms (LUTS), which may also be caused by other conditions; some will develop a significant enlargement of the prostate (EP), which can only exist in men with histological BPH; some will develop bladder outlet obstruction (BOO), which may also exist owing to causes other than BPH and EP. Treatment should take into consideration whether the patient has LUTS with or without EP and with or without BOO.

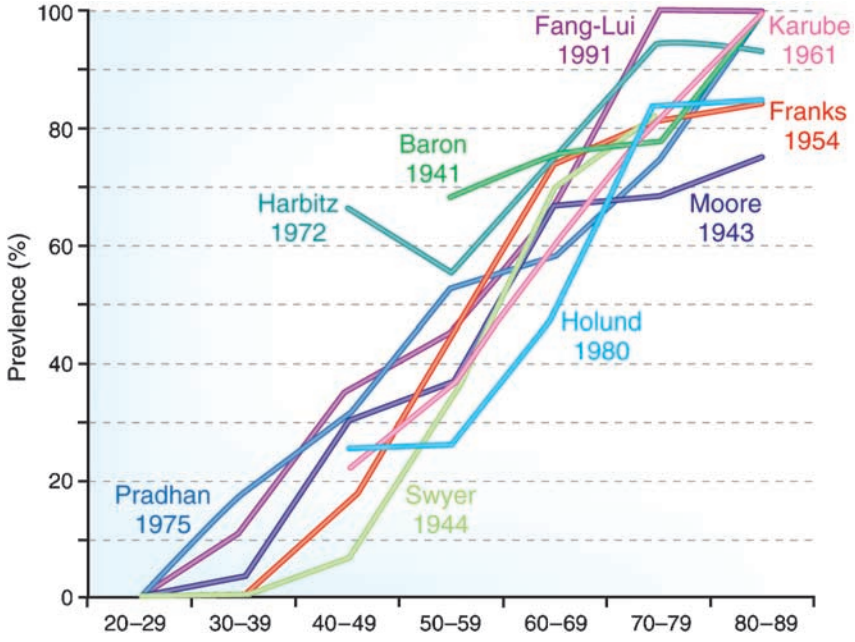

Figure 7 Prevalence of histological benign prostatic hyperplasia (BPH) by age group in nine autopsy series from around the world.[1]

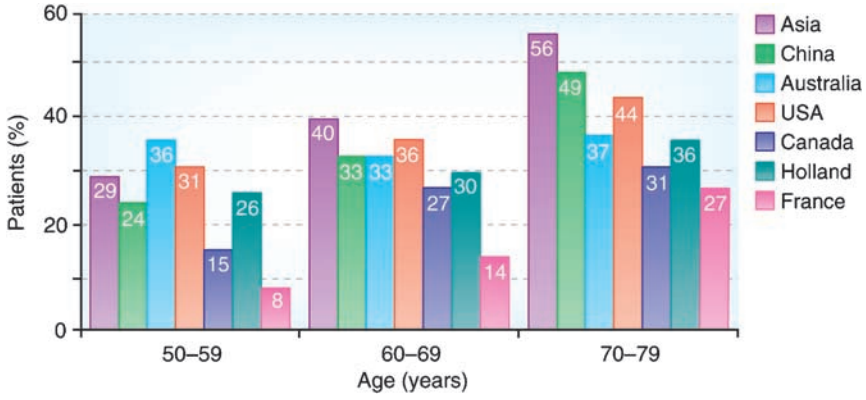

Figure 8 Presence of bothersome lower urinary tract symptoms (LUTS) in seven series from different continents/countries and ethnic groups.[35]

in itself is without much clinical significance. However, it becomes a clinical entity when associated with bothersome LUTS, significant prostatic enlargement and/or BOO. Figure 6 illustrates this complex relationship. Among all men over the age of 40 years, in an age-dependent manner, approximately 50% will develop histological hyperplasia or BPH;[1] of those, 30–50% will have bothersome LUTS, which may also be caused by other conditions;[35–39] some will develop a significant enlargement of the prostate, which can only exist in men with histological BPH; some will develop BOO, which may also exist because of causes other than BPH and enlargement of the prostate. Treatment should take into consideration whether the patient has LUTS with or without enlargement of the prostate and with or without BOO.

Figure 7 shows that across a wide range of continents/countries and ethnic groups, the incidence of histological hyperplasia increases linearly with age, starting approximately at the age 40 years. Figure 8 illustrates that approximately 30–50% of men with BPH—depending on age—will develop bothersome LUTS indicated by a symptom score of >7 points on the international prostate symptom score instrument.

It is interesting to note that prostate size does have an impact on various aspects of life, not only LUTS. In the Olmsted County Study increasing prostate size was associated with increasing symptom, bother, interference and even sexual dissatisfaction (Figure 9).[39] In the Medical Therapy for Prostate Symptoms study, increasing transition zone of the prostate was significantly associated with a

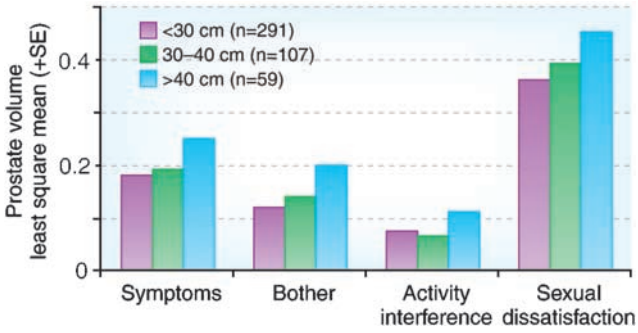

Figure 9 With increasing prostate size, symptoms, bother, interference and sexual dissatisfaction increase.[39]

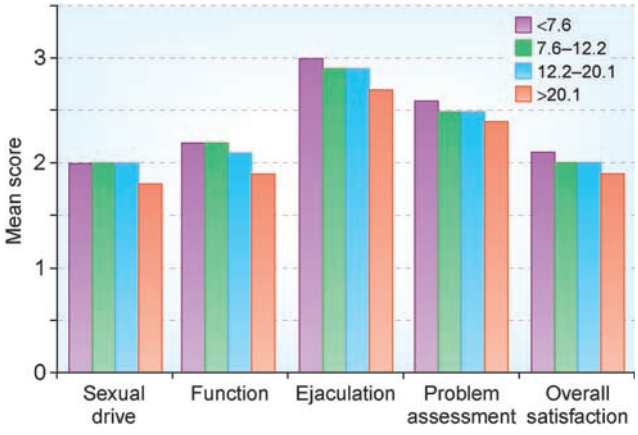

Figure 10 In the Medical Therapy for Prostate Symptoms study, five domains of sexual function showed a deterioration when stratified by increasing prostate size, here in quartiles of the transition zone of the prostate.[40]

deterioration in five domains of sexual function (Figure 10).

Conclusions

When evaluating and treating men presenting with LUTS, health care providers must keep in mind the complexity of the potentially underlying condition. For one, these symptoms should not be universally attributed to the prostate, and the terms 'prostatism' is therefore to be avoided, drawing undue attention to the prostate as the sole cause. The presence of histological stromo-glandular hyperplasia alone is not a condition in need of treatment, except when associated with bothersome symptoms. The presence or absence of noticeable enlargement and/or obstruction, and the anatomy of the prostate (lateral versus middle lobes) all play an important role in deciding what the best strategy for treatment might be. Further and more detailed understanding of the etiology, the interrelationship between androgens and growth factors, the potential role of ischemia, the autonomic nervous system and the PDE5 receptor may all aid our ability to develop better and more targeted treatment for more patients presenting with bothersome LUTS in an ever-increasing number.

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