Chapter

# 156

# Medical Treatment of Benign Prostatic Enlargement

RSK SINHA

## PATHOPHYSIOLOGY OF BPH

Prostate closes off the bladder neck during sexual climax to prevent retrograde ejaculation. However, its primary function is secretory; it produces alkaline fluid that comprises approximately 70% of the seminal volume.

The clinical symptoms are not only due to mass-related increases in urethral resistance but also because of obstruction-induced bladder dysfunction. The bladder wall becomes thickened, trabeculated, and irritable when it is forced to hypertrophy and increase its own contractile force. This increased sensitivity (detrusor instability), even with small volumes of urine in the bladder, is believed to cause ensuing urinary frequency and lower urinary tract symptoms (LUTS).

Chronic renal failure and uremia is end-stage bladder outlet obstruction sequel. While this complication is much less common now, chronic bladder outlet obstruction secondary to BPH may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross hematuria, and bladder calculi.

## CLINICAL MANIFESTATIONS

BPH is a common problem affecting the quality of life (QOL) for approximately one third of men older than 50 years. Histologic evidence of BPH occurs in up to 90% of men by age 80 years.

Prostatic enlargement acts as a clamp on a hose, constricting the flow of urine. Nerves within the prostate also may have a role in causing the following common symptoms:

- Urinary frequency: daytime or nocturia causing disturbed sleep.
- Urinary urgency: sensation of imminent loss of urine without control
- Hesitancy: difficulty initiating the urinary stream, hesitant, interrupted, weak urinary stream
- Incomplete bladder emptying: feeling of persistent residual urine regardless of frequency of urination
- Straining; need strain or push to initiate and maintain urination
- Decreased force of stream: loss of force of urinary stream over time
- Dribbling.

## PHYSICAL EXAMINATION

Assessment of the suprapubic area for signs of bladder distention and a cursory neurological examination for overall sensory and motor deficits should be made. The digital rectal examination (DRE) is an integral part of the evaluation for men with presumed BPH to assess prostate size, contour, nodularity and areas suggestive of malignancy. The normal prostate volume in a young adult is approximately 20g.

## LAB STUDIES

- Urinalysis: for sediment, presence of blood, leukocytes, bacteria, protein, or glucose.
- Urine culture: may be useful to exclude infectious causes of irritative voiding.
- Electrolytes, BUN, and creatinine: if patients have high post-void residual urine volumes.
- Prostate-specific antigen (PSA): Although BPH does not cause prostate cancer; men in the age range for BPH are at risk for cancer and should be screened

accordingly. Men with larger prostates may have slightly higher PSA levels.

### IMAGING STUDIES

- Ultrasound (abdominal, renal, transrectal); Imaging of the prostate using TRUS is recommended in selected patients.
  - — TRUS-guided biopsy may be indicated for patients with elevated PSA levels.
  - — Imaging of the upper tracts is indicated if patients present with concomitant hematuria, history of urolithiasis, elevated creatinine level, high postvoid residual volume, or history of upper urinary tract infection.
- Other diagnostic studies, such as CT scanning or MRI, have no role in the evaluation and treatment of patients with uncomplicated BPH.

### OTHER TESTS

International Consultation on Benign Prostatic Hyperplasia, in conjunction with the World Health Organization and the International Union Against Cancer has suggested following tests:

- **Recommended:**
  - — **International prostate symptom score (IPSS):** Developed to quantitate and validate responses to the questions asked, this set of 7 questions has been adopted worldwide and yields reproducible and quantifiable information regarding symptoms and response to treatment. Each question allows the patient to choose 1 of 6 answers indicating increasing severity of symptoms on a scale of 0-5; the total score ranges from 0-35. Questions concern incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia.
  - — **Bother score:** This helps assess perceived QOL due to urinary symptoms, and the score ranges from 0 (delighted) to 6 (terrible). How would you feel if you were to spend the rest of your life with your urinary condition just the way it is now? (Delighted = 0, pleased = 1, mostly satisfied = 2, mixed = 3, mostly dissatisfied = 4, unhappy = 5, terrible = 6)
  - — **Voiding diary (frequency voiding chart):** When these are filled out for several 24-hour periods, the information helps quantify the degree of frequency and volume output. The information also may help identify patients with polyuria and or distinguish these patients from those with polydipsia.
- **Optional:**
  - — **Flow rate:** Flow rate is useful in the initial assessment and to help determine the response to treatment. It should be performed prior to embarking on any active treatments, including medical treatment. A maximal flow rate (Qmax) is the single best measurement, but a low Qmax does not help differentiate between obstruction and poor bladder contractility. For more detailed analysis, a pressure flow study is required. A Qmax value of greater than 15 mL/s is considered by many to be normal. A value of less than 7 mL/s is widely accepted as low. The results of flow rate measurements are somewhat effort- and volume-dependent; therefore, the best plan to make a reasonable determination of significance is to obtain at least 2 tracings with at least 150 mL of voided volume each time.
  - — **Residual urine:** Obtain this value as soon after voiding as possible to gauge the severity of bladder decompensation. It can be obtained invasively with a catheter but is best determined noninvasively with a transabdominal ultrasonic scanner.
  - — **Pressure flow studies:** Important for determining the presence of bladder outlet obstruction, especially prior to any invasive therapy. Urodynamic studies are the only way to help distinguish patients with poor bladder contraction ability (detrusor underactivity) from those with outlet obstruction.
  - — **Endoscopy** of the lower urinary tract.

### MEDICAL TREATMENT

The medical therapeutic options for BPH have evolved significantly over the last 3 decades, giving rise to the receptor-specific alpha-blockers that comprise the first line of therapy.

#### Alpha-1 Receptor Blockade in BPH

A significant component of the BPH complex and its associated symptoms is believed to be related to the smooth muscle tension in the prostate stroma, urethra, and bladder neck. The smooth muscle tension in these areas is mediated by the alpha1-adrenergic receptors; therefore, alpha-adrenergic receptor-blocking agents should theoretically decrease resistance along the

bladder neck, prostate, and urethra by relaxing the smooth muscle and allowing passage of urine.

BPH is predominantly a stromal proliferative process, and a significant component of prostatic enlargement is due to smooth muscle proliferation. The stromal-to-epithelial ratio is significantly greater in males with symptomatic BPH relative to those with asymptomatic BPH.

The 3 subtypes of the alpha-1 receptor are 1a, 1b, and 1c. Of these, the alpha-1a receptor is most specifically concentrated in the bladder neck and prostate. Provided that the alpha-1a subtype is predominant in the prostate, bladder neck, and urethra, but not in other tissues, drugs that are selective for this receptor (e.g. tamsulosin) may have a potential therapeutic advantage. Tamsulosin is considered the most pharmacologically uroselective of the commercially available agents because of its highest relative affinity for the alpha1a-receptor subtype.

- Selective alpha-adrenergic receptor blockers
  - — The alpha-blocking agents administered in BPH studies can be subgrouped according to receptor subtype selectivity and the duration of serum elimination half-lives.
    - ■ Selective short-acting alpha-1 blockers include prazosin, alfuzosin, and indoramin.
    - ■ Selective long-acting alpha-1 blockers include terazosin and doxazosin.
    - ■ Partially subtype (alpha-1a)–selective agents include tamsulosin.
- Nonselective alpha-blockers
  - — Phenoxybenzamine was the first alpha-blocker studied for BPH. Its nonselective nature causes it to antagonize both the alpha1- and alpha2-adrenergic receptors, resulting in a higher incidence of adverse effects.
  - — Because of the availability of more alpha1-receptor–specific agents, it currently is not often used for the treatment of BPH.

Hormonally inspired medical management emerged from the discovery of a congenital form of pseudohermaphroditism secondary to DHT deficiency (due to a lack of 5-alpha-reductase activity). This deficiency produced a hypoplastic prostate. Type II 5-alpha-reductase is an enzyme responsible for the conversion of testosterone to DHT. DHT promotes growth of prostatic tissue. The 5-alpha-reductase inhibitors block the conversion of testosterone to DHT, causing lower intraprostatic levels of DHT. This leads to inhibition of prostatic growth, apoptosis, and involution.

### 5-Alpha-Reductase Inhibitors

- The inhibition of 5-alpha-reductase selectively blocks androgen action in tissues whose function is dependent on continuing production of DHT, including prostate and hair follicles.
- Finasteride, a 4-aza-steroid, has demonstrated type II 5-alpha-reductase blocking activity resulting in the inhibition of DHT-receptor complex formation. This effect causes a profound decrease in the concentration of DHT in plasma, which, in turn, results in a consistent decrease in prostate size. A third of men treated with this agent exhibit improvement in urine flow and symptomatology.
- A newer agent recently introduced, dutasteride, has affinity for both type I and type II 5-alpha-reductase receptors.
- Both agents actively reduce serum DHT levels by more than 80%, improve symptoms, reduce the incidence of urinary retention, and decrease the likelihood of surgery for BPH. These agents may not work in all men and may take several months before activity is noted. However, for those in whom they are effective, the impact may be profound.

### Phytotherapeutic Agents

- Pharmaceuticals derived from plant extracts are widely used throughout the world for the treatment of various medical ailments. The attraction to phytotherapeutic agents appears to be related to the perception of therapeutic healing powers of natural herbs, the ready availability, and the lack of adverse effects.
- Most of the phytotherapeutic agents used in the treatment of LUTS secondary to BPH are extracted from the roots, seeds, bark, or fruits of plants listed below. Some suggested active components include phytosterols, fatty acids, lectins, flavonoids, plant oils, and polysaccharides. Some preparations derive from a single plant; others contain extracts from 2 or more sources.
- Each agent has one or more proposed modes of action. The following modes of action are suggested:
  - — Antiandrogenic effect
  - — Antiestrogenic effect
  - — Inhibition of 5-alpha-reductase
  - — Blockage of alpha receptors
  - — Antiedematous effect
  - — Anti-inflammatory effect
  - — Inhibition of prostatic cell proliferation

  - — Interference with prostaglandin metabolism
  - — Protection and strengthening of detrusor
- The origins of phytotherapeutic agents are as follows:
  - — Saw palmetto, i.e. American dwarf palm (*Serenoa repens, Sabal serrulata*) fruit
  - — South African star grass (*Hypoxis rooperi*) roots
  - — African plum tree (*Pygeum africanum*) bark
  - — Stinging nettle (*Urtica dioica*) roots
  - — Rye (*Secale cereale*) pollen
  - — Pumpkin (*Cucurbita pepo*) seeds
- The mechanisms of action of some selected phytotherapeutic agents are as follows:
  - — Saw palmetto (American dwarf palm): Extracts of the berries are the most popular botanical products for BPH. The active components are believed to be a mixture of fatty acids, phytosterols, and alcohols. The proposed mechanisms of action are antiandrogenic effects, 5-alpha-reductase inhibition, and anti-inflammatory effects. The recommended dosage is 160 mg orally twice daily. Studies show significant subjective improvement in symptomatology without objective improvements in urodynamic parameters. Minimal adverse effects include occasional GI discomfort.
  - — African plum tree (*P africanum*): Suggested mechanisms of action include inhibition of fibroblast proliferation and anti-inflammatory and antiestrogenic effects. This extract is not well studied.
  - — Rye (*S cereale*): This extract is made from pollen taken from rye plants growing in southern Sweden. Suggested mechanisms of action involve alpha-blockade, prostatic zinc level increase, and 5-alpha-reductase activity inhibition. Significant symptomatic improvement versus placebo has been reported.

## SUGGESTED READING

1. Barry MJ, Cockett AT, Holtgrewe HL, et al. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol 1993;150(2 Pt 1):351-8.
2. Barry MJ, O'Leary MP. Advances in benign prostatic hyperplasia. The developmental and clinical utility of symptom scores. Urol Clin North Am 1995;22(2):299-307.
3. Girman CJ, Jacobsen SJ, Guess HA, et al. Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. J Urol 1995;153(5):1510-5.
4. Girman CJ, Epstein RS, Jacobsen SJ, et al. Natural history of prostatism: impact of urinary symptoms on quality of life in 2115 randomly selected community men. Urology 1994;44(6): 825-31.
5. International Scientific Committee. The evaluation and treatment of lower urinary tract symptoms (LUTS) in older men. Proceedings of the 5th International Consultation on BPH; Paris, France 2000;519-32.
6. Leveillee RJ, Patel V, Bird VG. Prostate Hyperplasia, Benign. www.emedicine.com/med/topic1919.
7. McConnell JD. Epidemiology, etiology, pathophysiology and diagnosis of benign prostatic hyperplasia. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, (Eds). Campbell's Urology. 7th ed. Philadelphia, Pa: WB Saunders 1998;1429-52.