

UCSF Benign Prostatic Hyperplasia (BPH) Review

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Introduction and Epidemiology

Benign prostatic hyperplasia (BPH) is an enlargement of the prostate that is very common and leads to troublesome lower urinary tract symptoms (LUTS) in some men. It is not the same as prostate cancer. BPH is a benign, non-cancerous enlargement. When physicians examine prostate tissue under the microscope, BPH changes can be seen in about 25% of 40 year-old men and about 75% of 70 year-old men. The microscopic changes do not always lead to symptoms. Approximately 30% of men will have lower urinary tract symptoms that lead them to seek medical care. Although physicians have commonly attributed these symptoms to prostate enlargement, we now know that many men with symptoms have minimally enlarged prostates. Also, some men with very large prostates do not have bothersome symptoms. So symptoms and prostate size are not directly correlated. In general however, the likelihood of having severe LUTS, or having an episode where a man is unable to urinate (urinary retention), or having a procedure to relieve symptoms, is higher for men with larger prostates.

Although most men seek care for the symptoms of BPH, urinary tract obstruction due to longstanding BPH can cause some major health problems such as bleeding from the prostate, recurrent infections, bladder stones, inability to urinate, kidney insufficiency or kidney failure.

Men with lower urinary tract symptoms due to BPH have many effective medications to relieve symptoms, slow the growth of their prostate and decrease the risk of future urinary difficulties. New procedures have decreased the risk of interventions to relieve obstruction, some of which can be performed in the urologist's office or as an outpatient procedure. Traditional surgical therapies for BPH such as transurethral resection of the prostate (**TURP**) are performed more safely, with a shorter hospital stay, quicker recovery and with fewer surgical problems than in the past.

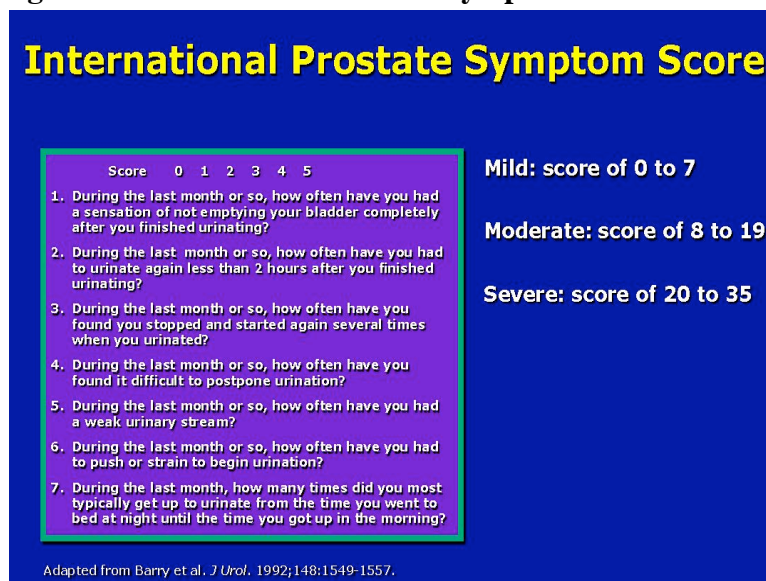
Anatomy and Physiology

The prostate is a gland, present in all men; its primary physiologic role is to make ejaculatory fluid or semen. It is situated at the base of the bladder, deep in the male pelvis, and surrounds the proximal (beginning) portion of the urethra. The seminal vesicles drain into the urethra through the prostate. The vas deferens, that carries sperm from the testes, also drains into the prostate. When a man has an ejaculation, the semen produced from the prostate and seminal vesicles mixes with sperm from the testes and is emitted into the male urethra (urinary tube). The normal prostate is 15-25 ccs in volume for men under 40 years of age. The average prostate size increases as men age. Men with BPH can form very large prostates, some over 100 grams.

Assessment of Symptoms Due to BPH

The most common symptoms due to BPH are getting up at night to urinate, frequent urination, a slow urinary stream, difficulty getting started urinating, a feeling of incomplete emptying and urinary urgency. Not all symptoms are present in all patients and bother different patients to different degrees. We use a standardized questionnaire called the American Urological Association (AUA) symptom score of the International Prostate Symptom Score (IPSS) (see Figure 1). It consists of seven questions, each scored between 0 and 5, from mild to severe. The score of the entire questionnaire can range from 0-35. This has been shown to be a reproducible valid measurement of patient symptoms and helps physicians assess response to therapy and compare therapies.

Figure 1: International Prostate Symptom Score



Differential Diagnosis and Diagnostic Tests

There are many different diseases and conditions that can cause LUTS in men. Table 1 shown below contains a partial list. Your physician will differentiate the cause of your symptoms by taking a careful history of your current symptoms, their duration, your past medical problems, current medical problems, medications, previous surgeries and prior therapies for BPH. He or she will then do a physical examination and some basic laboratory tests. A urinalysis of serum electrolytes with creatinine is commonly done. Serum prostate specific antigen (PSA) is usually performed in men between the ages of 40 and 80 with new LUTS. PSA can help determine if prostate cancer is the cause of symptoms. PSA is somewhat controversial for screening purposes but in men with lower urinary symptoms it is usually recommended. Other tests may be ordered on case-by-case basis. These include a urinary flow rate (the patient urinates in a device that measures how much urine comes out per second), post void residual (a measurement of how much urine is left in the bladder after urinating), urodynamics (a test using small catheters in the urinary system to measure bladder pressure) or cystoscopy (using a lighted flexible telescope to examine the urinary tract).

Table 1: Diseases and conditions that can cause lower urinary tract symptoms (LUTS)

Neurological conditions

 Stroke

 Spinal compression

 Poor bladder function

Prostate cancer

Urethral scars or strictures

Urinary infection

Prostate infection

High water intake

Excessive diuretic use

Medical Therapy for LUTS and BPH

Medical therapy for BPH can be roughly divided into three groups; alternative therapies, alpha-blockers and 5 alpha-reductase inhibitors. This discussion will be fairly brief and not all-inclusive of potential risks and adverse events with the medications mentioned. The reader is referred to the Physicians Desk Reference or the medications package insert for detailed prescription information and potential adverse events.

Alternative Therapies

A number of different herbal therapies have been investigated for BPH including saw palmetto, pygeum africanum, hypoxis rooperi and Echinacea purpurea. Saw palmetto extracts are by far the most popular herbal therapies for BPH. A number of randomized clinical trails have been published with conflicting data as to whether saw palmetto is superior or inferior to placebo. At the Veterans Affairs Medical Center San Francisco a National Institutes of Health (NIH) sponsored clinical trial is currently underway. The trail is carefully evaluating the effectiveness of saw palmetto for BPH. UCSF urologists Christopher Kane, MD and Katsuto Shinohara, MD are investigators on this trial that is

now approximately 2/3 complete. The consensus of prior published data on saw palmetto is that it is likely safe and may be effective for some men with mild BPH symptoms. The mechanism of action is unknown.

Alpha-Blocker Therapy

The prostate capsule and bladder neck have alpha-adrenergic receptors. Alpha-blockers inhibit alpha-adrenergic receptors, causing relaxation of the prostate capsule, enhanced urethral opening and a stronger urinary stream with more complete bladder emptying. Alpha-blockers do not change the size of the prostate. The benefit of the medication is seen only as long as the patient takes the medication. Some of the medications in this class are also blood pressure medications, while others have minimal effects on blood pressure. Generally long acting alpha-blockers are preferable for BPH treatment and the most commonly prescribed are **Terazosin (Hytrin)**, **Doxazosin (Cardura)** and **Tamsulosin (Flomax)**.

Terazosin (Hytrin) comes in 1, 2, 5 and 10 mg pills. It can sometimes cause lightheadedness or dizziness, therefore the dose is usually titrated or gradually increased until a therapeutic dose is reached. It is inexpensive and effective. Multiple randomized prospective placebo controlled studies have documented improved symptoms and urinary flow rate. Hytrin can cause blood pressure changes so patients on blood pressure medication may need their medicines adjusted by their physician.

Doxazosin (Cardura) comes in 1, 2, 4 and 8 mg pills. It can sometimes cause lightheadedness or dizziness, therefore the dose is usually titrated or gradually increased until a therapeutic dose is reached. It is inexpensive and effective. Multiple randomized prospective placebo controlled studies have documented improved symptoms and urinary flow rate. Cardura can cause blood pressure changes so patients on blood pressure medication may need their medicines adjusted by their physician.

Tamsulosin (Flomax) comes in 0.4 and 0.8 mg pills. Its dose does not need titrating and most patients use the 0.4 mg dose unless they are very large. It is more expensive than the other alpha-blockers currently available. No adjustments to other blood pressure medications are required. Also, the therapeutic dose is reached more quickly, so he may have quicker symptom improvement. Flomax can cause dizziness and some patients notice less ejaculation (retrograde ejaculation) while taking the medication.

5 Alpha-Reductase Inhibitors

There are two medications in this class, **Finasteride (Proscar)** and **Dutasteride (Avodart)**. 5 alpha-reductase inhibitors block an important enzyme that converts the primary male hormone, testosterone, into the primary male hormone with prostate effects, dihydrotestosterone (DHT). As a result of this inhibition, a patient's overall testosterone level stays the same or increases up to 10%, but their intraprostatic DHT decrease by over 90%. This therapy causes the prostate to stop growing and shrink up to 15-20% over the first year of therapy. The process is fairly slow and most patients begin to notice an improvement in BPH symptoms 3-6 months after initiating therapy. 5 alpha-reductase

inhibitors appear most effective in men with larger prostates, at least 40 ccs in size. Also, the larger the prostate, the greater the relative benefits of 5 alpha-reductase inhibitors.

Finasteride (Proscar) comes in 5 mg tablets and is taken once daily. It is a very safe medicine. The most common side effect seen in 5-9% of patients is difficulty with erections. This tends to be less of a problem in patients who take the drug for over a year. One of the most important benefits of long term Proscar use is that it decreases the chance by over 50% that a patient with BPH will have urinary retention or need surgery. This was documented by the Proscar long-term efficacy and safety study (PLESS), a 4 year placebo controlled trial. Also, there is now evidence from the Prostate Cancer Prevention Trial (PCPT) that Proscar taken for 7 years may decrease prostate cancer risk by 25% in some patients. This is a new somewhat controversial finding, but it is exciting and will be studied in more randomized trials.

Dutasteride (Avodart) is a new drug in the 5 alpha-reductase inhibitors class that may be more potent and has a longer half-life than Proscar. It appears to cause similar symptom improvement and prostate size reduction. Avodart is expected to have similar risk reduction effects including less urinary retention and eliminating the need for surgery. It has a similar side effect profile to Proscar, although it may cause changes in thyroid stimulating hormone (TSH). Researchers at UCSF, Peter Carroll, MD, Christopher Kane, MD and Katsuto Shinohara, MD will soon offer a new randomized clinical trial examining the effectiveness of Avodart for patients with BPH symptoms.

Combination treatment with 5 alpha-reductase inhibitors and alpha-blockers is attractive since these therapies work through different mechanisms. A recent double blind, placebo controlled multicenter trial compared placebo, doxazocin, finasteride, and a combination of doxazocin and finasteride in over 3,000 patients. The patients were followed for over 5 years. The trial showed that combination therapy might be more effective than either therapy alone in decreasing symptom scores and improving urinary flow rate. The obvious drawback of combination therapy is the combined risk of adverse events, higher costs and the trouble of taking two medications. **All medical therapies are available at UCSF.**

Interventional Therapy

Surgical therapy, usually with TURP is recommended for patients with complications due to BPH such as urinary retention, bladder stones, kidney failure due to BPH or gross urinary tract bleeding. Most patients who come to require or desire interventional therapy have persistent symptoms in spite of medical therapy or side effects from medical therapy that are bothersome. There are now a number of different options for such patients with BPH. Each of the different procedures has its own nuances, risks benefits, expected outcomes and possible complications. Following is a brief review each of them, most of which are available through the urologists at UCSF.

Transurethral Needle Ablation (TUNA) of the prostate uses low-level radiofrequency energy to heat the prostate and cause shrinkage of the obstruction. At UCSF, we perform the procedure in the office under prostate local anesthesia or in the same day surgery

center. The procedure takes approximately an hour and most patients go home with a urethral catheter in place for 3-7 days. Katsuto Shinohara, MD has successfully performed the procedure on patients with small and large prostates, and those in urinary retention, achieving good improvements in urinary symptoms and flow rate. After the procedure some patients have blood in the urine and frequent urination, a few ultimately require a traditional TURP. Most patients find the procedure simple, painless and effective. **Available at UCSF**

Microwave Thermotherapy of the prostate uses microwave energy to heat the prostate tissue using a probe in the urethra. Some of the early reports of microwave therapy showed some improvement in urinary symptoms but no improvement in urinary flow rate. Newer microwave devices heat the prostate more effectively resulting in improvements in urinary symptoms and flow rate. The procedure is office based, usually under local anesthesia and/or sedation. It takes 30-60 minutes, most men require urethral catheterization for 3-7 days following the procedure. Immediately after the procedure, before ultimate improvement, most patients have worse urinary frequency and urgency. The re-operation rate or the chance of requiring a TURP is approximately 20%.

Interstitial Laser or the Indigo[®] laser system is an interstitial thermotherapy technique, designed for office-based use, which heats the prostate tissue causing shrinkage of obstructive tissue and improved urinary symptoms. It requires post-procedure catheterization and is associated with initial irritative voiding, followed by subsequent improvement in symptoms and flow rate.

Ethanol Injection Therapy is currently an investigational technique that involves the transurethral injection of absolute ethanol into the prostate under local or regional anesthesia. The ethanol causes necrosis and shrinkage of obstructive prostate tissue over a period of about a month. This technique requires catheterization for 2-7 days and patients have initial urinary frequency that improves over time. By one month after the procedure, patients have improved symptoms and urinary flow rate. There have been infrequent reports of bladder injury from alcohol injection and rare patients ultimately require TURP. Christopher Kane, MD and Katsuto Shinohara, MD are investigators on a multicenter trial at the Veterans Affairs Medical Center San Francisco, sponsored by American Medical Systems (AMS), evaluating alcohol injection therapy. **Available at UCSF.**

Surgery

The distinction between interventional therapies and surgery for BPH is now blurring. Some of the procedures typically classified as surgical therapy like transurethral resection of the prostate (**TURP**) and transurethral incision of the prostate (**TUIP**), are currently performed with brief hospitalizations, usually from 24-48 hours. Some interventional therapies such as TUNA, began as procedures done under general anesthesia in a hospital setting and are now safely performed in the clinic setting.

Transurethral Resection of the Prostate (TURP) has long been the “gold standard” for improvement of symptoms, urinary flow rate and complications due to BPH. It was

pioneered in the early 1900's but has evolved dramatically over the years. **TURP** is currently a less invasive procedure with less risk, a briefer hospitalization and better outcomes than 10 years ago. The procedure is usually performed under regional (spinal) anesthesia with the patient awake. A cystoscope, with video monitoring system, is passed into the patient's urethra and bladder and the obstructing prostate tissue is removed. Bleeding is carefully controlled with electrocautery. The procedure normally takes 30-60 minutes. A urethral catheter is placed at the end of the procedure and the patient is generally kept in the hospital overnight. The next day, if there is minimal urinary bleeding, the urethral catheter is removed and in most cases the patient is able to void. He then goes home and takes about a week off of work, depending on the type of work he does. After surgery, blood in the urine is common and normally clears in a period of days although it may persist for as long as 1-2 weeks. Urinary flow rate usually improves by about 100% and IPSS (symptom score) generally improves by about 75%. The chance of needing a blood transfusion, which used to be about 5-10% after a TURP, is now under 1%. The chance of needing an additional procedure or repeat TURP within 5 years is only about 5%. Retrograde ejaculation (less semen) is common. A decrease in erections occurs in about 10% of patients. TURP is still the most effective form of therapy for patients with LUTS due to BPH or complications from BPH. **Available at UCSF.**

Transurethral Incision of the Prostate (TUIP) is a similar procedure to TURP, however instead of removing the obstructing tissue, an incision is made in the prostate lumen that allows the prostate lumen to open. The outcomes are similar to TURP for patients with prostates under 40 cc. With the exception that retrograde ejaculation is less common, complications are similar to TURP. **Available at UCSF.**

Open Prostatectomy is an open surgical procedure, usually undertaken in men who have very large prostates, over 100 ccs. Open prostatectomy is sometimes necessary because there is a practical limitation to how much tissue can be removed with TURP. The procedure requires spinal or general anesthesia and takes place through a lower abdominal incision. Surgery typically takes about 60-120 minutes to complete and requires a 2-4 day hospitalization. The urethral catheter is removed on the 3 to 5 postoperative day. Postoperative blood in the urine and retrograde ejaculation are common. The symptom improvement and improvement in urinary flow is similar to TURP. **Available at UCSF.**