BENIGN PROSTATIC HYPERPLASIA

Nutritional and botanical therapeutic options

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Abstract

Benign prostatic hyperplasia (BPH, benign prostatic hypertrophy), a non-malignant abnormal growth of the prostate gland, affects almost all men in some degree as they age and can cause a significant disruption of lifestyle due to urinary outflow obstructive and irritative symptoms. An accumulation of estrogen in the aging prostate, along with increased conversion of testosterone to its more active metabolite dihydrotestosterone (DHT) seems to induce this aberrant hyperplasia. Fatty acid deficiencies, zinc deficiency, and amino acid deficiencies may also contribute to the disease process. Numerous studies confirm the mechanisms and efficacy of Serenoa repens, Pygeum africanum, and Urtica dioca in reducing DHT conversion and/or binding to nuclear receptors, and reducing or relieving BPH symptoms. Usage of the amino acids alanine, glycine, and glutamic acid, alone and in combination with the above botanicals, has been proven to be effective at reducing symptomatology and prostate size. Pollen preparations, antifungals, zinc, and essential fatty acid supplementation may also be helpful.

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Introduction

Benign prostatic hyperplasia (also known as benign prostatic hypertrophy or BPH) is one of the most common conditions in middle-aged and elderly males, with an incidence of approximately 50-60% of males age 40-60, and greater than 90% of men over 80. However, evidence from autopsy studies of young men reveal that this disease process may start as early as the late 20's, and may have an incidence rate of 10% at that age. It is rarely a fatal disease; more than anything else, it affects the patients' lifestyle and comfort .[1]

BPH is characterized by a non-malignant hypertrophy of the prostate which is caused by hormonal processes and/or imbalances within the glandular tissue. Hyperplasia begins in the periurethral region and includes the stromal, epithelial, and smooth muscle tissues of the gland. The fibrous capsule surrounding the gland forces most of the growth inward, compressing the urethra and causing the typical urinary symptoms characteristic of this disease. Decreased force and caliber of the urine stream, urinary hesitancy, urgency, frequency, post-void dribbling, a sensation as if the bladder is not completely emptying, dysuria, and nocturia are all common, and are related to a blockage of urinary outflow and inflammation of the urethra as it passes through the prostate. Incontinence and hydronephrosis are also possible complications of advanced BPH.

On digital rectal examination, a smooth, enlarged, non-nodular prostate is usually noted. It is important to note, however, that symptom severity has not been directly linked to the size of the prostate, the histology of the hyperplastic tissue, or the degree of urinary outlet obstruction. It is also noted that not everyone with BPH progresses with a worsening of symptoms. In addition, there is a variability of symptoms and course of the disease from patient to patient.

Diagnosis

It is recommended that a digital rectal examination be performed on all men presenting with symptoms suggestive of BPH. A urinalysis may also be necessary to rule out infection. A useful tool for the physician and the BPH patient is a "voiding diary." The patient assigns each symptom a number rating at baseline and at follow-up. This can help the doctor and patient recognize the severity of the symptomatology, and help the patient better understand the impact of the disease process on his lifestyle.

To objectively assess the extent of a decrease in urine flow rate, a device may be used to measure the amount of urine voided during a specific time period. Post-void residual urine, obtained via catheterization, may give useful information about the degree of obstruction. Transabdominal or transrectal ultrasound can help assess size of the prostate. In advanced cases, an intravenous pyelogram (IVP) may be useful to diagnose suspected hydronephrosis.[1]

THE TESTOSTERONE / DHT / ESTROGEN CONNECTION

DHT/Androgen receptors

Local conversion of testosterone to its metabolite dihydrotestosterone (DHT), catalyzed by the enzyme steroid 5-alpha-reductase (5-AR), is implicated as a causative factor in BPH. DHT exerts its effects by binding to androgen receptors in the nucleus of prostate cells, stimulating cellular growth and division.[1-3] It is interesting to note that DHT binds many times stronger than testosterone to these androgen receptors [2,3], and thus it is more likely that DHT is the preferred substrate for these receptors.

A genetic defect first discovered in 1974 which results in a rare condition of 5-alpha-reductase deficiency has illuminated the role of testosterone and DHT activity and the tissues each affects. In 5-AR deficiency, genetic males are born with phenotypically female external genitalia; a clitoris-like penis, labia-like scrotum, testes located in the labia or in the inguinal canals, and a blind vaginal pouch. At puberty, due to increased testosterone secretion, these males exhibit penile growth, testicular descent, a deepened voice, increased muscle mass, and show normal spermatogenesis and ejaculation. Because of their lack of conversion of testosterone to DHT, however, these individuals do not develop acne, temporal hair loss, or BPH.[2-5]

This genetic disease helps to elucidate the roles of testosterone and DHT from intra-uterine development to old age. The differentiation of genitalia in utero and the development of BPH, acne, and baldness all seem to be related to DHT production via 5-AR, while the normal male characteristics acquired at puberty are dependent on testosterone production. Therefore, both testosterone and DHT are required for normal development; however, an increased activity of 5-AR and the resultant increase in production of DHT in target tissues in the pubertal and adult male may result in the undesirable and/or unpleasant consequences of acne, male pattern baldness, and BPH.[2-5]

In BPH tissue, 5-AR activity has been found to be higher than in normals.[2,3] Increased 5-AR activity has also been found in polycystic ovary disease and in the hair follicles of men with frontal alopecia.[2,3,6] In rat studies it was found that the presence of DHT causes an up-regulation of 5-AR activity, resulting in a positive-feedback loop for DHT production, resulting in further increased levels of prostate DHT.[5]

Estrogen receptors are also abundant in the nuclei, and some researchers believe that estrogen itself, or a decreased DHT:estrogen ratio may be involved in this abnormal growth of the prostate. [7] Krieg et al noted in their 1993 study that there is an increase in levels of estradiol and estrone in prostate stromal tissue—but not epithelial tissue—as men age, as well as a stromal increase in DHT. This stromal estrogen increase is accentuated in BPH prostates. [7] It is not known whether this accumulation of estrogen occurs before the onset of BPH symptomatology or if it is caused by the disease itself.

ALLOPATHIC INTERVENTIONS

Watchful waiting

If the urinary outflow symptoms are not severe at presentation to the physician, the most common strategy is to wait and watch the symptoms and exam findings. If a worsening occurs, further drug and/or surgical intervention is performed.

5-alpha-reductase inhibiting drugs

Finasteride (Proscar- Merck, Sharp, & Dohme), a synthetic azasteroid compound, was the first 5-AR inhibitor approved by the FDA. It inhibits the 5-AR-mediated conversion of testosterone to DHT, resulting in a reduction of prostate size by up to 25%. However, even with this decrease in prostate size, less than 50% of patients experience an increase in urinary flow and lessening of symptoms. It may take six months to a year of constant use to achieve symptomatic relief in those who respond. Finasteride use also results in decreased serum DHT (up to 70%), decreased prostate tissue DHT (80%), and a 10% increase in serum luteinizing hormone (PH), follicle-stimulating hormone (FSH), and testosterone (while remaining in the normal range). However, prostate tissue levels of testosterone are increased up to ten times the pre-treatment levels. It is unknown what long-term effects this increased testosterone level might have.[1,8,9]

Finasteride also decreases serum prostate-specific antigen (PSA) by up to 50%, even in the presence of prostate cancer. This reduction must be taken into account if using PSA as a screening tool for prostate cancer and should not be used as an indicator of therapeutic effectiveness. As yet there are no long-term studies on whether finasteride decreases prostate cancer incidence.

Complications of finasteride use include a 3.7% incidence of impotence, 3.3% incidence of decreased libido, and 2.8% incidence of reduced ejaculatory volume.[10,11] Patients using finasteride are also warned to not allow women of childbearing potential to handle the tablets or come in contact with semen from a man being treated with finasteride. This is due to the concern that finasteride could interfere with the sexual differentiation of a male fetus and induce a pseudohermaphroditism in that child if the drug or its metabolites gets into the mother's bloodstream.[11] A one-month supply of Proscar (one 5 mg tablet per day) costs approximately $65-75.

Androgen-reducing drugs

Blocking the action of DHT by reducing overall testosterone or competition with androgen receptors is the therapeutic goal of the anti-androgen drugs. Unfortunately, side effects

of decreased libido, impotence, hot flashes, and gynecomastia are common with this class of drugs. These side effects are due to decreased testosterone binding/activity, which causes increased LH and FSH, increased serum testosterone, and increased conversion of testosterone in peripheral tissue (mainly fat) into estrogen, a reaction which is catalyzed by aromatase. [7] Aromatase inhibitors are currently being developed and tested as a possible treatment in BPH. [7] There are as yet no published studies regarding the efficacy or safety of this class of drugs.

Alpha-1 adrenergic blockers

This class of drugs has a relaxant effect on the smooth muscle of the prostate and urinary bladder, and may alleviate some urinary-retention symptoms. Common side effects include hypotension, dizziness, syncope, headache, and fatigue.[11,12]

Surgery

More than 300,000 prostate surgeries were performed in 1990, most being transurethral resections of the prostate (TURP). This surgery is the second most utilized surgical procedure (second to cataracts) in the U.S. Medicare population, with a cost of over $2 billion per year. The risks of TURP are infection, urinary retention, hemorrhage, and TURP Syndrome, a post-operative condition of hyponatremia and altered mental status.[1,13] Open prostatectomy is a surgical option usually reserved for advanced cases.[1]

Balloon Dilation

Similar to a cardiac balloon angioplasty, a catheter is inserted into the urethra up to the prostate, then is inflated, compressing the hypertrophied prostate tissue and lessening the urinary outflow blockage. Early studies of this procedure show an initial decrease in symptoms similar to TURP, followed by an increase in symptoms after three months.[1,14]

Other allopathic treatments under investigation are stents, lasers, coils, and thermal therapy.

NATURAL THERAPEUTICS

Alternative therapies aim to restore the hormonal imbalance(s) present in BPH, while providing symptomatic relief for the patient. Many alternative treatment regimens have a history of traditional use, and some of these have been studied in recent years to assess their biochemical mechanisms and clinical efficacy.

Diet/Lifestyle

In a study of 6,581 men in Hawaii over 17 years, it was noted that alcohol intake of at least 25 ounces per month was inversely correlated with the diagnosis of BPH. This association was significant for beer, wine, and sake, but not distilled spirits.[15]

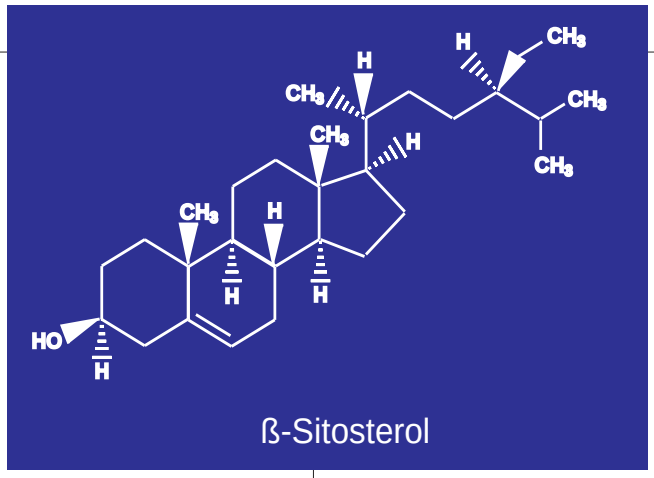
Zinc

Zinc is involved in numerous biochemical processes, including spermatogenesis, and is present in the greatest concentration in the prostate than in any other organ. Numerous studies have shown that zinc levels in prostate tissue are significantly increased in BPH and significantly decreased in prostatic cancer.[16-19] Elevated zinc levels in BPH may be explained by increased production and accumulation of citrate in the hyperplastic prostate. In BPH, zinc may be bound to cytoplasmic citrate; increased citrate equals increased zinc binding. In the presence of high levels of androgens, zinc is released from citrate and free zinc levels increase. Zinc may also act as a 5-AR inhibitor in the prostate,[20,21] which may explain the success of supplemental zinc usage in BPH.[22,23]

Serenoa repens (Saw Palmetto)

The fruit of Serenoa repens, a dwarf palm native to Florida, contains numerous fatty acids

and their ethyl esters, including ß-sitosterol and its glucoside, and ferulic acid.[24] ß-sitosterol (see figure 1) is a phytosterol (a plant substance with a steroidal structure) which is said to be estrogenic and hypocholesterolemic. Ferulic acid, a hydroxycinnamic acid, exhibits antibacterial, antifungal, and antimitotic properties.[25]



A liposterolic extract of the fruit has been found to be a potent inhibitor of 5-AR, resulting in decreased tissue DHT. Serenoa also competitively inhibits binding of DHT and testosterone to cytosolic and nuclear androgen receptors. [26,27] This extract was shown to reduce binding of testosterone and DHT 40.9% and 41.9%, respectively to in vitro tissue specimens.[28]

Serenoa seems to act only at the target tissue and enzyme level, and does not cause the compensatory increases in FSH, LH, and testosterone seen in anti-androgen drug therapy. At a dosage of 160 mg bid for 30 days, Serenoa extract did not increase plasma levels of testosterone, follicle-stimulating hormone, or luteinizing hormone. [29]

In a double-blind, placebo-controlled study of 110 patients with BPH, 160 mg bid of a Serenoa extract given for 30 days significantly improved nocturia, dysuria, post-voiding residual urine, flow rate, patient self-rating, and the physician's overall assessment.[30] Urinary symptoms and flow rates were significantly improved in 42.9% of patients taking a Serenoa extract, versus 15.4% of patients given placebo in another double-blind clinical study.[31] In an open trial, 67% of patients on Serenoa described their subjective symptom relief as "excellent," while 25% characterized their relief as "good."[32] No side effects or toxicity was noted. A one-month supply of Serenoa extract (160 mg bid) costs approximately $20.00.

Pygeum africanum

A tree native to southern Africa, Pygeum has been used traditionally for urinary tract symptoms.[33] Constituents of the bark include waxes, triterpenes, fatty acids and their esters, and ferulic acid. Among the triterpenes are ß-sitosterol, oleanolic acid, ursolic acid, and craetegolic acid, substances known to be anti-inflammatory and anti-edematous.

A multi-center, double-blind study of 263 patients utilizing Pygeum for the treatment of BPH at a dose of 50 mg bid of the extract for 60 days noted a significant improvement in residual urine, flow rate, and nocturia versus placebo. The patients' subjective rating of their symptoms was also significantly improved ($p<0.001$).[34] Another double-blind study of 120 patients given Pygeum extract showed a significant improvement in nocturia, post-voiding residual urine, and difficulty starting urination compared to placebo.[35] Similar improvements were seen with the use of ß-sitosterol alone,[36] and since this phytosterol is present in both Serenoa and Pygeum, it may be inferred that ß-sitosterol is one of the key active ingredients in these extracts.

Amino Acids

A combination of the amino acids glutamic acid, alanine, and glycine (390 mg capsules-2 caps three times a day for two weeks, then 1

cap three times a day thereafter) was found to be effective in BPH treatment, with significant improvement in nocturia (56% treated patients, 15% placebo), urgency (66% treated, 11% placebo), frequency (43% treated, 15% placebo), and delayed micturition (50% treated, 0% placebo) in a double-blind, placebo-controlled study of 45 men.[37] The mechanism for this improvement has not been elucidated.

In a study of 100 BPH patients, combination treatment using the above amino acid preparation and Pygeum extract was found to offer significantly better objective and subjective symptomatic relief than Pygeum alone or placebo.[38]

A comparison study of this amino acid combination versus Prazosin, an alpha-1 adrenoceptor blocker, showed equally significant improved obstructive and irritative symptoms in 156 men with BPH. Prazosin performed better than the above amino acids in improving urinary flow rates, but had a higher incidence of side effects.[12]

Pollen preparations

Cernilton, a commercial standardized pollen preparation, is another potentially beneficial alternative treatment for BPH. No mechanism is offered for the significant improvement in subjective complaints, residual urine, and prostate size in one study of 60 patients with urinary outflow symptoms secondary to BPH.[39] A head-to-head comparison of Cernilton versus the glutamic acid, alanine, and glycine combination showed significant improvements in residual urine, flow rates, and prostate size in both groups, with no significant difference between the treatments.[40]

Antifungals

Candicidin, an anti-fungal antibiotic with hypocholesterolemic properties has been shown in animal and human studies to significantly reduce the size of the prostate as well as overt symptomatology of BPH. The mechanism is unclear, but may be an inhibition of cholesterol synthesis or deposition in the prostate.[41-43] It has not been studied, but there is also a possibility that this drug may be treating an underlying fungal overgrowth causing inflammation of the prostate or otherwise altering the hormonal balance in prostate tissue.

Essential fatty acids

A deficiency of essential amino acids is postulated as a possible contributing factor in BPH. Essential omega-3 and omega-6 amino acids are necessary for normal prostaglandin synthesis, which may have an inhibitory effect on prostatic cellular growth.[44]

Urtica dioca (Stinging nettle)

A preparation from the root of Urtica dioca was found to be beneficial in reducing BPH symptomatology in a number of studies.[45-47] The mechanism may be an inhibitory action on binding of DHT to cytosolic receptors.[48]

CONCLUSION

Benign prostatic hyperplasia has become a ubiquitous disease in the aging male, causing a serious disruption of lifestyle and comfort. Drug and surgical therapies may provide relief, but almost always with a price—both monetarily and with side effects/complications. Nutritional and botanical treatments of this disease process offer a cost-effective, noninvasive form of therapy, and a potential for reversal of the disease process. Utilizing combinations of these clinically-proven substances—Serenoa, Pygeum, glycine-alanine-glutamic acid, zinc, and other botanicals—along with evaluation and treatment of underlying essential fatty acid deficiencies or fungal infections is a more rational and thought-

ful approach to this disease, and allows the patient to choose proven options for treatment not often mentioned in urologists' offices.

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