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On The COVER

BPH

The Other Side of the Coin

BPH isn't just a matter of testosterone...new research reveals the role of estrogen and what you can do about it.

A surprising new discovery explains why so many men now contract prostate disease. Most doctors think testosterone is the culprit, but scientists have exposed serious flaws in this theory. Now you can be the first to learn the most advanced method of preventing and treating prostate enlargement.

According to the conventional view, benign prostatic hyperplasia (BPH) develops when an active form of testosterone called dihydrotestosterone (DHT) stimulates cell growth. Testosterone is converted to DHT systemically as well as within the prostate by an enzyme known as 5-alpha-reductase. DHT is far more active than testosterone in binding to sites in prostate cells that regulate prostate growth. When DHT binds to these sites, it activates growth factors that stimulate cell proliferation. Commonly used medications for BPH, such as saw palmetto and the drug finasteride, inhibit 5-alpha-reductase in order to reduce DHT-stimulated growth in the prostate.

While it is hardly surprising that prostate growth is under hormonal control, the above view of BPH is difficult to explain when we consider the effects of aging. BPH is after all a disease of aging, and testosterone production declines with age. Moreover, levels of free, physiologically active testosterone decline more sharply due to increased testosterone binding by a protein called sex hormone binding globulin (SHBG). It is estimated that levels of free testosterone decline by about 1% per year from age forty to age seventy.

So, if testosterone production declines with age, could there be another mechanism contributing to prostate enlargement? The surprising answer may be the growing imbalance in aging men between their levels of estrogen and testosterone.

While levels estrogen appear to be relatively stable in the aging male, the level of free testosterone precipitously declines. Thus with age, an imbalance develops between estrogens and androgens (female and male hormones). Compared to younger men, the ratio of free estradiol (the most potent form of estrogen) to free testosterone is up to 40% higher in older men.

In the prostate itself, the contrast between rising estrogens and declining androgens is more sharply drawn. In the stroma of the prostate, the supporting tissue where BPH is thought to develop, estrogen levels increase significantly with age, while DHT levels remain stable. Estrogen levels in the stroma rise to even higher levels in BPH patients. In the epithelium of the prostate, DHT levels decline with age, while estrogen levels remain stable. German researchers who have been studying this for more than fifteen years describe "a tremendous increase with age of the estrogen/ androgen ratio in the human prostate." Their article in the *Journal of Clinical Endocrinology and Metabolism* concludes:

"Our results indicate that the prostatic accumulation of DHT, estradiol, and estrone is in part intimately correlated with aging, leading with increasing age to a dramatic increase of the estrogen/androgen ratio particularly in stroma of BPH."

A study published in the journal *Prostate* bears out the concept of an elevated serum estrogen/androgen ratio as a risk factor for BPH. Analyzing frozen blood samples collected in the course of a large-scale health study, the researchers found that BPH risk increased with higher estradiol levels, and that the risk was concentrated in men with relatively low androgen levels.

A Japanese study came to a similar conclusion, finding that prostate size correlates with estradiol level and with the ratio of estradiol to free testosterone. They suggest that "the endocrine environment tended to be estrogen-dominant with age, in particular, after middle-age, and that patients with large prostates have more estrogen-dominant environments," concluding "estrogens are key hormones for the induction and the development of BPH."

Experimental attempts to induce BPH with hormones would answer many questions, but obviously cannot be carried out in humans. The only animals known to develop BPH with age are dogs and lions. In experiments with dogs it has been established

than BPH cannot be induced without estrogen, however it should be noted that endocrine regulation and prostate structure are quite different in dog and man.

In men and postmenopausal women, most estrogens are produced from androgens; specifically, most estradiol is produced from testosterone. This conversion of androgens to estrogens is called aromatization, after the enzyme aromatase. In addition to receiving estrogen circulating through the bloodstream, the stroma of the prostate produces its own estrogen through aromatization.

It has long been suspected that estrogen - especially the estrogen/ androgen imbalance associated with aging - plays a role in BPH, but until recent years no direct effect of estrogen on the prostate could be demonstrated. A key piece of this puzzle has now been supplied by a group of researchers at Columbia University, St. Luke's/Roosevelt Hospital in New York, and the pharmaceutical company Merck. In a groundbreaking series of research papers culminating in articles published this past year in the journals *Endocrinology* and *Steroids*, they demonstrate the existence of a second hormonal pathway in the prostate whereby estrogens can mimic androgens.

It may help to understand this breakthrough by thinking of hormones as chemical messengers. When a hormone attaches to its special binding site in a cell, it sends a signal to that cell. In the case of BPH, androgens signal cells to proliferate, causing prostate growth. These researchers have shown that messages sent to prostate cells by androgens can also be sent, along an alternative signalling pathway, by estrogens. Even more surprisingly, the estrogens send this signal not by attaching to the usual cellular binding sites for estrogen, but instead to the sex hormone binding globulin (SHBG) that is already bound to the cell membrane. As the authors put it, they have shown that in the prostate, estradiol is "capable of activating pathways normally considered androgen responsive."

In a review article published in the journal *Prostate* in 1996, a pioneer of modern prostate research proposed a new model of prostate physiology and pathogenesis based in part upon this research. Wells Farnsworth, Professor of Urology at the Northwestern University Medical School, discovered the conversion of testosterone to DHT in the prostate in the early 60s. In his article in *Prostate*, Professor Farnsworth proposes that "estrogen, mediated by SHBG, participates with androgen in setting the pace of prostate growth and function."

Farnsworth notes that, as explained above, SHBG increases with age and "can act like an additional androgen receptor [binding site for androgen]" in the prostate cell. He suggests that, when estrogen binds to SHBG in the cell membrane, a growth factor called IGF-I (insulin-like growth factor I) is synthesized, causing proliferation of epithelial cells in the prostate. This sets the stage for further proliferation when androgens activate binding sites for growth factors. In Farnsworth's language, "estrogen not only directs stromal proliferation and secretion, but also, through IGF-I, conditions the response of epithelium to androgen." Subsequent research suggests that IGF-II, which is less well understood than IGF-I, may also be involved. In addition to its possible role in BPH, recent research indicates that elevated IGF-I levels may be a key predictor of prostate cancer risk. IGF-I may also contribute to the age-related increase in SHBG.

Farnsworth likens the protein SHBG to a hormone, concluding: [SHBG's] newfound capability to evoke BPH and its possible involvement in the transformation of normal to cancer cells by oncogenes calls for increased efforts to understand and manage SHBG and estrogen secretion.

The researchers who discovered the alternative signalling pathway concur: "...antagonism [inhibition] of the pathway by which SHBG leads to the induction of androgen-responsive genes may be a valuable therapeutic target for the treatment or prevention of BPH or prostate cancer."

Accordingly, these researchers studied an agent thought to inhibit the binding of SHBG to the prostate cell membrane, an extract of the root of the stinging nettle plant, *Urtica dioica*. In a paper published in 1995 in *Planta Medica*, they demonstrated that nettle root does indeed inhibit the binding of SHBG to the cell membrane.

In a subsequent series of articles, German researchers have identified a constituent of nettle root known as (-)-3,4-divanillyltetrahydrofuran whose very high binding affinity to SHBG they describe as "remarkable." These researchers suggest that the beneficial effects of plant lignans (such as found in flaxseed oil) on hormone-dependent cancers may be linked to their binding affinity to SHBG. The most potent known lignans in this respect are constituents of nettle root.

Studies show that the ethanolic extract of nettle root is not inhibiting SHBG binding, while the aqueous and methanolic extracts are.

In addition to inhibiting SHBG binding, at least six constituents of nettle root inhibit aromatase, reducing conversion of androgens to estrogens. Combining nettle root with pygeum results in a stronger, synergistic inhibition. The studies on aromatase inhibition by nettle root used methanolic extracts.

A recent experimental study provides a dramatic demonstration of nettle root's effect on BPH tissue. This experiment was based

upon the hypothesis that BPH is comparable to a reawakening of embryonic growth potential in the prostate. A fetal urogenital sinus was implanted into a lobe of the prostate gland in adult mice. After 28 days, the implanted lobes of mice fed a nettle root methanolic extract similar to an extract on the German pharmaceutical market showed 51.3% less growth than the lobes of mice in the control group.

Nettle root is widely used as a first-line therapy for BPH in Germany, where there are 15 pharmaceutical drugs consisting solely of nettle root. Nettle root has been extensively studied in European clinical trials over the past twenty years. Good study design is essential in evaluating BPH therapies, since sizable placebo effects are normal in BPH studies.

A well designed double-blind, placebo-controlled trial of nettle root was published in the German urological journal *Urologe* in 1996. This three month study involved 41 BPH patients with maximum urinary flow under 15 ml/sec. and an average score of 18.2 on the IPSS (International Prostate Symptom Score) scale. An IPSS score of 0-7 is considered as slightly symptomatic, 8-19 as moderately symptomatic, and 20-35 as highly symptomatic.

By the end of the trial, maximum urinary flow increased by an average of 66.1% (from 10.9 to 18.1 ml/sec.) in the group treated with nettle root, compared to 36.6% (from 12.3 to 16.8 ml/sec.) in the placebo group. Average IPSS scores dropped twice as much in the nettle root group (from 18.2 to 8.7) as in the placebo group (from 17.7 to 12.9). By comparison, trials of the standard BPH drug finasteride (Proscar) show more modest improvements relative to placebo. Again, this study used the methanolic nettle extract.

Eight previous trials of nettle root showed beneficial effects on a total of approximately 15,000 BPH patients. These trials used daily doses of nettle extract ranging from 600-1200 mg and lasted from 3 weeks to 180 days.

In Europe nettle root is also used in combination with saw palmetto. This combination is a logical one since nettle root acts through the alternative signalling pathway in the prostate cell, while saw palmetto acts on the primary signalling pathway by limiting DHT activity. In effect, nettle root addresses the estrogen side of BPH, while saw palmetto addresses the androgen side. Additionally, both herbs have anti-inflammatory actions.

Since 1995, three clinical studies of a standard saw palmetto/nettle combination have been published in German medical journals. The studies used two capsules per day of 160 mg saw palmetto extract plus 120 mg nettle root extract.

A randomized double-blind study compared the saw palmetto/nettle combination to the standard BPH drug finasteride in 543 patients suffering from BPH stages I to II. The herbal therapy and drug therapy proved similarly effective in all measures: urinary flow rate, urination time, IPSS scores, and patients' quality of life assessments. Both therapies increased in effectiveness over a period of months. For example, the average IPSS score in the herbal therapy group declined from 11.3 to 8.2 after 24 weeks and 6.5 after 48 weeks; in the finasteride group it declined from 11.8 to 8.0 after 24 weeks and 6.2 after 48 weeks. Patients tolerated herbal therapy better than finasteride which causes diminished libido and sexual dysfunctions including impotence in some patients.

Another placebo-controlled study used a crossover design. Forty patients with BPH stage I or II and urinary flow below 20 ml/sec. received either saw palmetto/nettle or placebo for 24 weeks. Patients receiving the herbal combination showed significant improvement in maximum urine flow rate (3.3 ml/sec.) compared to placebo, and there were similar improvements in average flow rate, total urination volume, urination time, and flow increase time. There was also a significant improvement on the American Urological Association symptom score compared to placebo. In the crossover phase of the trial, patients who had been on placebo for 24 weeks were switched to the herbal combination for another 24 weeks. These patients showed similar positive results.

A large observational study involving 419 urology practices followed 2,030 patients with mild to moderate BPH. All patients received saw palmetto/nettle for 12 weeks. This study found the following average improvements: maximum urinary flow increased 25.8%, average urinary flow increased 29.0%, residual urine decreased 44.7%, nocturia declined 50.4%, dysuria declined 62.5%, and post-urination dribbling declined 53.6%. 86% of patients reported symptom improvement. Fewer than 1% of the patients reported side effects, and these were mild.

Thus far, there have been no clinical trials of a saw palmetto/nettle/ pygeum combination. As mentioned above, nettle root and pygeum synergize in inhibiting aromatase. In addition, these three herbs affect growth factors in ways that appear to be beneficial in the prevention and treatment of BPH. According to a 1997 article in the *Journal of Urology*, pygeum inhibits cell proliferation induced by the growth factors EGF (epidermal growth factor), bFGF (basic fibroblast growth factor), and IGF-I (insulin-like growth factor I) in stromal cells from rat prostate. A 1998 study in *European Urology* found that saw palmetto inhibits bFGF-stimulated cell proliferation in human prostate cell cultures. Preliminary research suggests that a constituent of nettle root inhibits the binding of EGF to human prostate cells.

As is the case for many medicinal herbs, the clinical efficacy of nettle root was demonstrated at a time when medical science had not yet made the basic advances needed to understand its mechanism of action. This may be one reason that nettle root is relatively unknown in America whereas saw palmetto, with its relatively clearcut mechanism of action based upon testosterone, is in common use. As was the case for saw palmetto, it will probably take years for the pharmaceutical companies to develop a

synthetic drug to effectively address the mechanism of action of nettle root. Both of these extraordinarily well tolerated herbal extracts are available now to BPH sufferers.

The Life Extension Foundation has expended significant resources to develop a better understanding of prostate cell proliferation and how to control it. The immediate benefit to members is that all of the prostate products offered by the Life Extension Buyers Club have been re-formulated to reflect these new findings.

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