

## Health Condition: Men's Health

"Henry has now been on testosterone for about five years. He's about 85. We started him when he was 79 or 80. I put pellets in him. He had stable cardiovascular disease and immediately had a positive response, which I write about in the book. He went down and kicked all the seniors on the golf circuit in Florida over the winter. He was 80 and playing the guys who were 60. I know from playing with Henry and being beaten by him when he was 80, that he's a good player.

When his testosterone was down, however, his cardiovascular disease symptoms (shortness of breath, mild angina) resulted in his not being able to finish 18 holes with his usual level of play. When we would replace his hormone, he would immediately improve in all those factors. As he's gotten older, now when his testosterone declines, he starts to get congestive heart failure. So, he's one in whom we maintain the level very carefully. When he's out of gas, he's in trouble and you have to replace it carefully. I've got him on a balanced regimen with a topical preparation with which we can now vary the dose. The pellets are a little too strong for him. Henry has a delicate balance. Too much and he gets into fluid retention; too little and he gets cardiac weakness and gets into cardiac decompensation. He's now 85. I played golf with him last week and darned if he didn't take a dollar out of my wallet. But thank God for Henry because he's my hero."

—Eugene Shippen, MD

Author, *The Testosterone Syndrome: The Critical Factor for Energy, Health, & Sexuality--Reversing the Male Menopause*

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## Hormone Balance in Men: Understanding Testosterone

Testosterone is a molecule that has received mixed reviews in the literature. As an important part of male vitality and female libido, it has positive benefit. On the other hand, the suggestion has been made that men's high testosterone levels may increase risk of heart disease and prostate cancer and may explain why many men live shorter lives than women. Anti-testosterone drugs, such as estrogen, have been used without success in an attempt to help prevent heart disease in men. The testosterone issue has been a growing area of confusion and controversy.

As men age, their levels of testosterone go down and their levels of estrogen go up. Of course, the level of estrogen in men is a lot lower than in women, but it's always present, and it does go up as men age. The fingerprint of hormones is different for each person. Clinically, a measurement of total testosterone can be misleading. It is important to measure free testosterone levels, which is done by measuring sex binding globulin. Symptoms of low testosterone in men include:

- Fatigue
- Depression
- Lack of initiative
- Sexual changes
- Decrease in libido

- Loss of muscle
- Prostate symptoms (BPH)

Low testosterone—beyond the decline that generally occurs with natural aging—can be caused by a variety of factors, including use of drugs, high estrogen levels, and a range of pituitary problems. When symptoms are present and low testosterone is confirmed by laboratory testing, some clinicians may recommend testosterone replacement treatment. This therapy can have side effects, and the effects of long-term treatment are not fully understood. Testosterone replacement therapy is available in several formulations, including transdermal (skin patch), gel, mouth patch, injections, and implants (pellets). Oral testosterone has been found to not be well absorbed and may have effects on the liver.

### **Benign Prostate Hyperplasia (BPH)**

Benign prostatic hyperplasia (BPH) is a condition present in 80% of men over 40 years of age in which benign (non-malignant) growths cause swelling of the prostate gland. Due to the enlargement of the gland, there are typically problems associated with urine output and bladder obstruction.

Some of the symptoms experienced by men with BPH include:

- Increased urinary frequency (especially at night)
- Having the sudden urge to urinate
- Feeling a sensitivity to the need to empty the bladder
- Decreased urinary stream
- Blood in the urine or urine of abnormal color
- Impotence
- Incontinence
- Difficult, burning or painful urination
- Straining or delayed start of the urinary stream

Diagnosing BPH involves a physical exam complete with a prostate gland evaluation and/or an ultrasound test together with a blood test for prostate-specific antigen (PSA), a protein produced in the prostate. High levels of PSA, above 4 ng/mL, can be associated with BPH, while much higher levels above 10 ng/mL may signal prostate cancer. It is worthwhile to note that, in some cases, prostate cancer can be present without elevations in PSA, which is why having a digital prostate examination together with the blood test is recommended.

The cause of BPH is unknown, however, there are a number of factors that are associated with increased

risk, including the following: genetic predisposition, age, the presence of testicles, inadequate zinc intake (due to its role in testosterone metabolism), excess testosterone or dihydrotestosterone (DHT), alcohol (especially beer) consumption, essential fatty acid deficiency, and smoking/exposure to cigarette smoke.

Therefore, there are numerous lifestyle medicine measures to assist with prevention and/or treatment of BPH including:

- Eating a high-protein diet to help reduce levels of DHT along with increasing intake of fish, flaxseed oil, and walnuts to provide good amounts of essential fatty acids in addition to moderate amounts of organic whole soy products which may help with relieving BPH due to the isoflavones they contain (resulting in lower DHT).
- Eating foods high in zinc or taking a zinc supplement to reduce 5-alpha-reductase activity, and, thus DHT levels.
- Any number of botanical medicines prescribed by a healthcare professional who is knowledgeable about these therapies. One well-studied botanical for BPH is *Serenoa repens* (saw palmetto). Although the data is inconsistent and contradictory, there are some studies indicating some degree of efficacy for BPH, especially in reducing urinary frequency at night, most probably due to its inhibitory effect on 5-alpha reductase and lowering DHT levels, in addition to its anti-inflammatory properties. Interestingly, it does not appear to reduce the size of the prostate or the levels of PSA like pharmaceuticals used for BPH.

### Abstracts on Benign Prostate Hyperplasia (BPH)

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#### **Observational database serenoa repens (DOSSER): overview, analysis and results. A multicentric SIUrO (Italian Society of Oncological Urology) project.**

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#### Abstract

**OBJECTIVE:** Men affected with Benign Prostate Hyperplasia (BPH) and Lower Urinary Tract Symptoms (LUTS) are demonstrating to require an increasing amount of attention from Urologists and Primary-care Physicians. Over the years, common urological medications were based on either alpha-blockers and/or 5alpha-reductase inhibitors. During the last decade the phytotherapeutic drugs are gaining a more often central role in the BPH and LUTS managements. In particular, clinical usage of the extract of the dried ripe fruit of serenoa repens with a dosage of 320 mg per day, has shown its clinical efficacy and its superiority. Purpose of this multicentric observational retrospective study was to evaluate all the

urological aspects (clinical, biochemical, instrumental and pathological) of patients affected by BPH and LUTS, with a PSA < 10 ng/ml, a previous negative prostatic biopsy and in therapy with a daily dose of 320/640 mg of serenoa repens.

**PATIENTS AND METHODS:** The study was conducted in 8 different centers throughout Italy from September 2010 to November 2011. Data and information of 298 men with an average of 63 years (mean PSA of 5.4 ng/ml and mean prostate gland volume of 57 cc), affected by non-acute urinary symptoms caused by BPH, a dosed PSA level inferior to 10 ng/ml, a previous negative prostate biopsy and in therapy with serenoa repens alone or associated to an alpha-blocker, were retrospectively inserted in an extensive on-line SIUrO Database. Comprehensive questionnaires were filled in for each patient at 3 and 6 months of follow-up. Each questionnaire contained various sections, each of them composed by several items: dosed PSA levels, uroflowmetry, International Prostate Symptoms Score (IPSS), International Index of Erectile Function (IIEF-5), trans-rectal ultrasound (TRUS) patterns, digital rectal examinations (DRE) aspects, previous prostate bioptical results (histology) and side effects.

**RESULTS:** PSA levels weren't subjected to an increase, revealing a stabilizing or downward trend. Percentage of patients with PSA below the level of 4 ng/mL was lower at the end of the study. The overall changes in the uroflowmetry were similar and parallel both in the group with only serenoa repens intake and in the group with serenoa repens plus alpha-blocker. The mean medium flow and the mean maximum flow had a slightly increase along the observation time. There was a substantial decreasing in the amount of patients presenting severe prostatic symptoms. Patients reported through the IIEF-5 score a sexual activity substantially unchanged after 6 months of follow-up. The serenoa repens intake resulted in an improvement of the "inflammatory-like reports", in terms of ultrasound patterns, DRE and bioptical features.

**CONCLUSIONS:** serenoa repens demonstrated its efficacy reducing dysuria with minimal side effects. Further prospective studies might confirm its stabilization or lowering role on PSA levels in this cohort of patients and its possible clinical anti-inflammatory action.

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### **Nutrition and benign prostatic hyperplasia.**

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#### Abstract

**PURPOSE OF REVIEW:** Nutrition seems to modify the pathogenesis of benign prostatic hyperplasia (BPH) effect symptomology in men suffering from lower urinary tract symptoms (LUTS). Although there are numerous pharmaceuticals and procedures for these conditions, nutrition may improve outcomes as a

primary approach or in tandem with BPH medications or procedures. The purpose of this review is to highlight the benefits of nutrition and dietary supplements in men with BPH and LUTS.

**RECENT FINDINGS:** Dietary factors have an impact on metabolic disorders that lead to diabetes and obesity - both of which inversely effect BPH and LUTS. Dietary patterns associated with increased risks include starches and red meats, whereas moderate alcohol intake and polyunsaturated fat and vegetable consumption decrease risks. Dietary supplements of zinc, saw palmetto, and beta-sitosterol in relieving BPH symptoms have had mixed results. Randomized clinical trials of nutritional practices and other lifestyle alterations such as exercise for the prevention or treatment of BPH and LUTS have yet to be performed.

**SUMMARY:** Nutritional practices may provide for the prevention and treatment of BPH and LUTS while positively affecting other systemic parameters. Whereas there are a few clinical randomized trials for the prevention and treatment of BPH and LUTS, nutritional modifications may have a healthy lifestyle alternative with minimal to no adverse effects.

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## **Serenoa repens for benign prostatic hyperplasia.**

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### **Source**

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### **Abstract**

#### **BACKGROUND:**

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate, which can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH is common. The extract of the berry of the American saw palmetto, or dwarf palm plant, *Serenoa repens* (SR), which is also known by its botanical name of *Sabal serrulatum*, is one of several phytotherapeutic agents available for the treatment of BPH.

#### **OBJECTIVES:**

This systematic review aimed to assess the effects and harms of *Serenoa repens* in the treatment of men

with LUTS consistent with BPH.

### **SEARCH METHODS:**

We searched for trials in general and in specialized databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE®, EMBASE, CINAHL®, Web of Science, SCOPUS, BIOSIS Previews®, LILACS, ClinicalTrials.gov, Controlled-Trials.com, World Health Organization (WHO), and Google Scholar. We also handsearched systematic reviews, references, and clinical practice guidelines. There were no language restrictions.

### **SELECTION CRITERIA:**

Trials were eligible if they randomized men with symptomatic BPH to receive preparations of SR (alone or in combination) for at least four weeks in comparison with placebo or other interventions, and included clinical outcomes, such as urologic symptom scales, symptoms, and urodynamic measurements. Eligibility was assessed by at least two independent observers (JT, RM).

### **DATA COLLECTION AND ANALYSIS:**

One review author (JT) extracted information on patients, interventions, and outcomes which was then checked by another review author (RM). The main outcome measure for comparing the effectiveness of SR with active or inert controls was change in urologic symptom-scale scores, with validated scores taking precedence over non validated ones. Secondary outcomes included changes in nocturia and urodynamic measures. The main outcome measure for harms was the number of men reporting side effects.

### **MAIN RESULTS:**

In a meta-analysis of two high quality long-term trials (n = 582), *Serenoa repens* therapy was not superior to placebo in reducing LUTS based on the AUA (mean difference (MD) 0.25 points, 95% confidence interval (CI) -0.58 to 1.07). A 72 week trial with high quality evidence, using the American Urological Association Symptom Score Index, reported that SR was not superior to placebo at double and triple doses. In the same trial the proportions of clinical responders ( $\geq$  three-point improvement) were nearly identical (42.6% and 44.2% for SR and placebo, respectively), and not significant (RR 0.96, 95% CI 0.76 to 1.22). This update, which did not change our previous conclusions, included two new trials with 444 additional men, an 8.5% (5666/5222) increase from our 2009 updated review, and a 28.8% (1988/1544) increase for our main comparison, SR monotherapy versus placebo control (17 trials). Overall, 5666 men were assessed from 32 randomized, controlled trials, with trial lengths from four to 72 weeks. Twenty-seven trials were double blinded and treatment allocation concealment was adequate in 14. In a trial of high quality evidence (N = 369), versus placebo, SR did not significantly decrease nightly urination on the AUA Nocturia scale (range zero to five) at 72 weeks follow-up (one-sided P = 0.19). The three high quality, moderate-to-long term trials found peak urine flow was not improved with *Serenoa repens* compared with placebo (MD 0.40 mL/s, 95% CI -0.30 to 1.09). Comparing prostate size (mean change from baseline), one high quality 12-month trial (N = 225) reported no significant difference between SR and placebo (MD -1.22 cc, 95% CI -3.91 to 1.47).

### **AUTHORS' CONCLUSIONS:**

Serenoa repens, at double and triple doses, did not improve urinary flow measures or prostate size in men with lower urinary tract symptoms consistent with BPH.

### **Endothelial Dysfunction and Erectile Dysfunction**

“ED equals ED. One of the key questions to male patients when they come in your office is you ask him about erectile dysfunction, and if they have it, you’re almost guaranteed they are going to have endothelial dysfunction as well.”

—Mark Houston, MD

Author, *What Your Doctor May Not Tell You About Heart Disease*

June 2012

Endothelial dysfunction is a condition in which the endothelium (inner lining) of blood vessels does not function normally. It is thought to play a major role in the development of atherosclerosis, and has been shown to be a significant marker for predicting myocardial infarction and stroke due to the inability of the arteries to fully dilate.

Endothelial dysfunction relates to erectile dysfunction because both depend on the availability of nitric oxide (NO) in the body. Nitric oxide is a powerful vasodilator and functional biological regulator. Dr. Mark Houston, a well-known expert cardiologist and founder of the Hypertension Institute of Nashville, explained the relevance of nitric oxide balance in a 2012 interview with Dr. Jeffrey Bland:

“Nitric oxide is really the key to understanding endothelial function and vascular health. It has numerous functions. It’s not just a vasodilator, but it’s an anti-inflammatory, an anti-atherosclerotic, it reduces cell adhesion molecules, it reduces growth hypertrophy, oxidative stress, and even autoimmune dysfunction. So if you have a normal nitric oxide level (or bioavailability, I should say—that’s a much better term), if your NO bioavailability is good then that’s a good signal that you’re going to have good endothelial function. There are so many things that decrease nitric oxide in your system.”

Nitric oxide levels in the body cannot be directly measured, but one method that can be used clinically is measurement of asymmetric dimethylarginine (ADMA). High ADMA is considered to be an inhibitor for eNOS, which is the enzyme that forms nitric oxide, so it is a way to analyze whether someone might have low NO bioavailability.

Exercise has been determined to be an excellent way of naturally increasing nitric oxide in the body. Dietary choices can also affect the level of nitric oxide in the body. For example, foods high in the amino acid, L-arginine, that converts to NO, such as nuts (Brazilian nuts are one of the highest), meat, seeds, and other rich protein sources such as soy protein. Additionally, there are certain vegetables such as beets and spinach that contain naturally-occurring nitrates, that when eaten, convert into nitrites and eventually NO.

## Prostate Cancer

In 2003, *The New England Journal of Medicine* published an editorial titled “The Prevention of Prostate Cancer—The Dilemma Continues.”<sup>1</sup> Ten years later, we still do not have a handle on the question of how important the suppression of dihydrotestosterone (DHT) is in the prevention of prostate cancer, or what role androgens directly play in prostate cancer.

### Finasteride and Prostate Cancer

Prevention of prostate cancer may be related to giving a DHT testosterone inhibitor, such as finasteride, which is the classic drug. A report in *The New England Journal of Medicine* concluded, “Finasteride prevents or delays the appearance of prostate cancer, but this possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer.”<sup>2</sup>

Finasteride may subdue the risk of early-grade prostate cancer only to have it appear later as a fulminant form of cancer. The most significant problem has not been treated, only the early warning signs of the problem. In other words, you may have put a veil over what is going on until it is much more significant and of clinical concern. That is why the editorial that followed this study talks about the continuing dilemma.

### PSA Testing

It is very important for men to be screened with routine Prostate-Specific Antigen (PSA) testing when they reach age 50, but anyone with prostate-related symptoms should be screened even earlier. Screening should be done serially on a routine basis because the change in relative PSA levels over time seems to be more important than the absolute number. Some numbers that are considered borderline-high stay high and do not change. Other numbers that are initially low may, while still in the normal range when next measured, be double or triple what they were. A change from .5 to 1.5, for example, is still within the range of normal, but that relative change appears to be a greater indication of risk than the absolute value. The important consideration is a combination of the absolute value (in other words, how high the number is) and the relative change.

Two articles that discuss prostate examination appeared in the *Journal of the National Cancer Institute* in 2003. One is an editorial titled “Prostate Cancer and Prostate-Specific Antigen: The More We Know, the Less We Understand.”<sup>3</sup> An associated article is titled “Association between Genetic Polymorphisms in the Prostate-Specific Antigen Gene Promoter and Serum Prostate-Specific Antigen Levels.”<sup>4</sup> We do not know the whole story. PSA may not be the only measurement, but at present, it is the best clinical



marker we have, and it should be used on a routine basis to get a history of the PSA levels in a specific patient.

Prostate cancer prevention trials are still showing some positive value in suppressing DHT, but we need to pay attention to a few precautions.<sup>5</sup> The story is more than DHT alone.

### **Vitamin D and Prostate Cancer**

We might also be looking at cell signaling in the prostate cell. What controls genomic signaling? What might control suppression of the expression of oncogenes in the prostate gland? Vitamin D, with its cell signaling capability, plays a role in this process. Research related to pathways that mediate the growth actions of vitamin D is ongoing. Vitamin D and its metabolites inhibit prostate cancer growth and prostate cell proliferation. Through 1,25 dihydroxyvitamin D3, vitamin D may play a role in preventing cell replication or keeping it at low levels in prostate cancer.<sup>6</sup>

### **Hydroxylated Estrogens and Prostate Cancer**

Estrogen metabolites, the so-called 4-hydroxycatecholestrogens may be stimulators for cell proliferation in the prostate gland. They may trigger oncogenesis and relate to further amplification of cell growth with dihydrotestosterones. There may be an association between estrogen metabolites in the prostate and androgens. A study in *Carcinogenesis*, titled "Catechol Estrogen Metabolites and Conjugates in Different Regions of the Prostate of Noble Rats Treated with 4-Hydroxyestradiol: Implications for Estrogen-Induced Initiation of Prostate Cancer," discusses this topic.<sup>7</sup>

The topic of hydroxylated estrogens and prostate cancer has been around for some time and goes back to the research of Dr. Martin Bosland at New York University. We should look not only at androgens such as DHT in prostate cancer, but also at the estrogen component.

### **Resveratrol and Prostate Cancer**

Scientists have identified a number of natural products that favorably modify production of the 4-hydroxycatecholestrogens that may initiate prostate cancer. One compound is resveratrol, one source of which is the skin of grapes. A candidate for prostate cancer prevention, resveratrol has a significant effect on modifying hydroxylation patterns of estrogen and it also inhibits aromatase somewhat, preventing excessive estrogen production. The discussion of resveratrol as a candidate nutritional substance for prostate cancer prevention appeared in a recent paper in the *Journal of Nutrition*.<sup>8</sup>

Resveratrol is present in red wine. Amounts vary from wine to wine, from 2 to 40 mmol, or from grape skins, in which it represents 5 to 10 percent of the biomass once the grape skins have been dried. It has a variety of effects related to reduction of prostate cancer risk. In fact, it may be just the tip of the iceberg of a broad class of phytonutrients with a polyphenolic structure that are valuable for inhibiting each of the many stages of carcinogenesis found in prostate cancer.

Polyphenols scavenge incipient populations of androgen-dependent prostate cancer cells through androgen receptor antagonism, and they scavenge incipient populations of androgen-independent

prostate cancer cells by short-circuiting the epidermal growth factor-dependent autocrine loops. Finally, they influence the metabolism of androgens to estrogens and influence estrogen metabolism into the hydroxylated estrogens. These substances may be involved in the initiation of prostate cancer.

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