

ORIGINAL ARTICLE

# Benign prostatic hypertrophy: Pycnogenol® supplementation improves prostate symptoms and residual bladder volume

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## ABSTRACT

**BACKGROUND:** The aim of this study was to evaluate the efficacy of Pycnogenol® supplementation in terms of safety and tolerability in the setting of preclinical or borderline, initial symptoms of benign prostatic hyperthrophy (BPH), in otherwise healthy subjects, using Pycnogenol® over a period of 60 days.

**METHODS:** Seventy-five healthy men with symptoms and signs of initial BPH were included. The subjects were divided into three groups: 1) control group using only the standard management (SM); 2) a group using SM plus Pycnogenol® 150 mg/day; 3) a group using standard pharmacological management.

**RESULTS:** BPH symptoms like emptying, frequency, intermittency, urgency, weak flow, straining, nocturia, were all significantly improved with Pycnogenol® ( $P<0.05$ ) and the difference with both control groups was statistically significant ( $P<0.05$ ).

**CONCLUSIONS:** Pycnogenol® may be an important option for self-management of BPH in otherwise healthy men.

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**KEY WORDS:** Prostatic hyperthrophy - Dietary supplements - Prostate - Pycnogenol® - Nocturia.

**B**enign prostatic hypertrophy (BPH) is a non-malignant growth of the prostate associated with signs and symptoms of bladder outflow obstruction, weak urinary stream, hesitancy, urinary frequency and urgency, nocturia, and feeling of incomplete emptying. Altogether these symptoms significantly affect the quality of life of otherwise healthy individuals.

The diagnosis of BPH is generally made by rectal examination and ultrasound evaluation following the patients' complaints for symptoms. Additionally, other diagnostic techniques such as cystoscopy, ultrasound and urodynamics may be

useful to quantify prostate enlargement, as well as to exclude other concomitant disease, including cancer. The prevalence of BPH in males of 55-74 years, without known prostate cancer, is established in the presence of a prostate volume  $>30$  mL and a high *American Urological Association Symptom Score*, and it is approximately 19%. Additional criteria such as voiding parameters (maximum urinary flow rate  $<10$  mL/s and a postvoid residual urine volume  $>50$  mL) may be added to the diagnostic workflow in order to reduce the prevalence of BPH, which decreases to about 4% when considering these additional

elements. Distribution by age is important, with a higher prevalence in older men (40-50% in men between 51 and 60 years of age, and up to >80% in men in their eighties) as compared to the younger generations (8% in subjects between 31 and 40 years).<sup>1, 2</sup> At the moment, there is no specific or definitive treatment,<sup>1</sup> and this is generally symptomatic only; 5-alpha reductase inhibitors, alpha blockers are possible treatments. The surgical option is reserved for more severe cases, not responding to medical treatment.

Signs and symptoms of BPH may affect a large number of individuals; therefore, costs and safety are important medical and social issues. Initial mild symptoms may benefit from mild treatment with supplement or low-dose drugs.<sup>1-4</sup> In most preparations of Saw Palmetto (SP), fatty acids elements inhibit 5-alpha-reductase opposing the conversion of testosterone to dihydrotestosterone.<sup>3</sup> Most SP formulations tested in clinical studies are extracts of SP berries (containing 80-90% essential fatty acids and phytosterols).<sup>3, 4</sup> Clinical evidence supports the use of SP to manage signs/symptoms of BPH.<sup>1</sup> Several other standardized supplements have also been successfully used in recent studies in preclinical situations and in borderline symptomatic BPH. Polyphenols have documented effects on prostatic tissue.<sup>5-7</sup> The French maritime pine bark extract, Pycnogenol® has shown to be effective in reducing signs and symptoms of prostatic origin in uncomplicated patients.<sup>8</sup>

The aim of this registry study was to evaluate the efficacy of Pycnogenol® supplementation in terms of safety and tolerability in the setting of preclinical or borderline, initial symptoms of BPH, in otherwise healthy subjects, using Pycnogenol® over a period of 60 days.

## Materials and methods

### Population

Healthy men with symptoms and signs of initial BPH were included. Additional inclusion criteria were absence of concomitant pharmacological treatment, no history of previous surgical procedures or urinary retention, and no significant infections in the previous three years before enrollment. The presence of prostatic cancer was

also excluded prior to study participation.<sup>2, 3</sup> PSA values indicated that subjects in the study were all at low-risk for cancer, defined as: PSA <10, a Gleason score ≤6; no masses were detectable at ultrasound assessment.<sup>3</sup>

All subjects were below 80 kg with a BMI <26. Clinical conditions had been stable over the previous 3 months before inclusion in the registry, and remained basically stable, apart from the target symptoms, throughout the study period. PSA always remained lower than ten.

The evaluation forms for these patients were modified International Prostate Symptom Score (IPSS) forms, including signs and symptoms evaluation, adapted to the need of self-management and self-evaluation.<sup>3</sup>

### Study design

The subjects were divided into three groups:

1. A control group using only standard management (SM) according to the Merck Manual;<sup>1</sup>

2. A group using SM associated with the supplementation of Pycnogenol®

3. A group using standard pharmacological management, including dutasteride (one capsule, 0.5 mg/day) and/or finasteride 5 mg/day. This treatment may modify PSA values up to 50%, and up to six months may be needed to see results on symptoms. These dosages were considered appropriate by the urologist in charge of the patients considering their borderline BPH and symptoms.

### Standard management

Standard management of subjects with initial BPH without surgical indications is based on the avoidance of anticholinergic, sympathomimetics, opioids drugs. Patients were instructed to void regularly, avoid long seating periods, exercise regularly, hydrate appropriately preferably avoiding caffeine and spices, follow a low-sugar and low-salt diet.<sup>3</sup>

In more advanced stages of BPH, alpha-adrenergic blockers such as terazosin, doxazosin, tamsulosin, and alfuzosin, may help to improve voiding, whereas 5-alpha-reductase inhibitors (finasteride, dutasteride) tend to reduce prostate size. In the treatment of symptomatic BPH a combination of drugs is generally more effective than single treatments.

### Pycnogenol® supplementation

Pycnogenol® (Horphag Research) is a natural, standardized extract from the bark of the French maritime Pine, containing anti-inflammatory and antioxidant compounds. It was used as a supplement at the dosage of 50 mg 3 times daily (total of 150 mg/day). Pycnogenol is a very safe product with a good tolerability profile.<sup>9-19</sup> Its metabolites have been detected in blood and urine<sup>11, 12, 20-22</sup> of treated subjects.

### Statistical analysis

All results regarding signs and symptoms as well as ultrasound measurements were considered non-parametric. A numerosity of 20 subjects in each group was derived statistically to be the minimum needed to evaluate differences in treatments strategy over a period of at least 4 to 8 weeks of treatment.

Observational items were measured with a visual analogue scale. After voiding, the residual urinary volume in the bladder was measured by ultrasound, as well as prostate volume (high-resolution transrectal ultrasound).

A high resolution ultrasound scanner (Preirus, Hitachi, Japan) was used to evaluate residual urinary volumes and prostate morphology; PSA and routine blood tests (hematocrit, liver and kidney functions, electrolytes) were performed at inclusion and at end of the study period: they had to be normal as per inclusion criteria.

The evaluation of plasma free radicals using a FRAS analyzer (Langhirano, Parma, Italy) was made using a single drop of blood according to methods described in previous studies.<sup>13, 14</sup>

Safety was the most important endpoint of the study. Several studies in the form of registries have already defined the field of activity of standardized supplements and possible preventive, preclinical applications.<sup>4, 15-17</sup>

## Results

A total of 75 men completed the registry study. Three groups were formed, which were comparable for age, symptoms distribution, ultrasound findings (both considering prostate volume and residual urinary volume), and days of follow-up (Table I).

No significant safety concerns were raised; no side effects or tolerability problems with the supplementary management were observed, and compliance with the supplement was optimal: more than 98% of the capsules correctly used.

There were several drop-outs in groups 1 and 2 due to logistic problems, whereas 3 out of 8 patients dropped out from group 3 (dutasteride, finasteride) due to mild nausea or minor gastrointestinal disturbances caused by the pharmacological treatment during the initial two weeks of therapy.

BPH symptoms like emptying, frequency, intermittency, urgency, weak flow, straining, nocturia were all significantly improved with Pycnogenol® ( $P < 0.05$ ) and the difference with both control groups was statistically significant (Table II).

The improvement produced by Pycnogenol® for any single item was significantly higher in comparison with the improvements observed in both control groups ( $P < 0.05$ ).

Urinary bacterial contamination was absent at inclusion and at the end of the study in all subjects. Prostatic volume at ultrasound showed minimal changes after eight weeks in all groups. Conversely, the most important target measurement, postvoid residual urine volume, was significantly lower in the Pycnogenol® supplement group after 8 weeks in comparison with both control groups ( $P < 0.05$ ), thus indicating a better improvement. PSA values remained basically stable during the entire study period.

Other physiological variables such as heart rate and blood pressure, as well as all routine blood tests (including hematocrit, liver and renal functions, and coagulation) were unchanged in all groups during the entire study period.

TABLE I.—*The three registry groups.*

Group	1) Pycnogenol	2) Control 1 Best standard managment	3) Control 2 Dutasteride, finasteride
Number completing	22	27	26
Drop outs	4	4	8
Days of follow-up	61	60	62
Age; SD	65.5;2.2	65.7;2.8	66.2;3.1
PSA ng/mL; SD	3.27;0.7	3.32;1	3.29;0.76
Prostatic volume; SD (normal <30 mL)	42.3;1.3	40.9;1.6	41.3;1-6

TABLE II.—*The main observation items measured in a visual analogue scale line.*

Symptoms	Pycnogenol® Score range (0-5)		Control 1 Best/standard management		Control 2 AVODART (dutasteride) FINASTID (finasteride)	
	Inclusion	8 W	Inclusion	8 W	Inclusion	8 W
Emptying; SD	3.3; 0.2	1.9; 0.3*#	3.2; 0.4	2.9; 0.4*	3.3; 0.2	3.1; 0.7*
Frequency; SD	3.5; 0.7	2.2; 0.3*#	3.4; 0.5	3; 0.3*	3.5; 0.2	3; 0.3*
Intermittency; SD	3.6; 0.2	2.5; 0.1*#	3.5; 0.4	3.1; 0.12*	3.5; 0.1	2.84; 1.1*
Urgency; SD	3.3; 0.4	2.5; 0.3*#	3.4; 0.3	3.1; 0.3*	3.3; 0.3	3.1; 0.2*
Weak flow; SD	3.3; 0.2	2.5; 0.3*#	3.4; 0.1	3.1; 0.2*	3.5; 0.2	2.9; 0.3*
Straining; SD	3.6; 0.3	2.5; 0.2*#	3.5; 0.3	2.8; 0.3*	3.5; 0.3	3.3; 0.6*
Nocturia; SD	3.5; 0.3	2.4; 0.3*#	3.3; 0.3	2.7; 0.2*	3.3; 0.1	3; 0.4*
Postvoid residual urine volume (mL); SD	99.4; 8.8	48.3; 2*#	94.4; 4.1	61.2; 6.2*	95.1; 4.4	56; 6*
Oxidative stress [Carr units]; SD	376; 22	311; 14*	386; 21	388; 22	378; 25	396; 24

\*P variations before-after (P<0.05); # difference between the supplement group and the other 2 groups (P<0.05).

Volume formula:  $(4/3) \cdot (\pi) \cdot (r1) \cdot (r2) \cdot (r3)$  where r1= radius 1, r2= radius 2, r3= radius 3 are the radii of the three dimensions. In 3 dimensions, the inside a sphere/spheroid (ball-shape) is derived to be  $V = 4/3 \pi r^3$  where r is the radius of the sphere and  $\pi$  is the constant pi. The formula is also derived using integral calculus, i.e. disk integration to sum the volumes of an infinite number of circular disks centered side by side along the x axis from x=0 where the disk has radius r (i.e. y=r) to x=r where the disk has radius 0 (i.e. y=0).

## Discussion

Recently it has been postulated that symptoms of initial BPH may be managed with self-assessment by patients using Pycnogenol® and other similar supplements before starting a targeted pharmacological treatment.

Several standardized supplements may be considered: they are all recognized for long-term management, and share an effective and safe profile.<sup>1-4</sup> This is opposed to the possible side effects of pharmacological treatments, which may also interfere and interact with other drugs.<sup>3</sup> This is true for 5-alpha reductase inhibitors and for alpha blockers as well. To note, with these therapeutic strategies symptoms may need months to improve, and PSA values may be altered.

For example, men treated with finasteride experience a worsening of their ejaculatory function; both doxazosin and finasteride may cause significant worsening of erectile function and other sexual problem, including decreased libido.<sup>3</sup> In addition, high rates of depression and anxiety have been observed.<sup>3</sup> Other relatively rare side effects include breast tenderness and enlargement (gynecomastia) and allergic reaction. Finasteride is also associated with intraoperative floppy iris syndrome and cataract formation.<sup>3-6</sup>

Currently, medical treatment of BPH is limited, and it is considered a “poor” option by most patients and specialists, since most prostatic studies have been focusing on interventional and surgical possibilities, that generate higher profits. Studies on drug interactions (i.e. with other drugs such as anticoagulants) are also limited and unsatisfactory.

Most urologists are not interested in the pharmacological treatment of BPH, and therefore they have a minimal interest in supplements, although they may present a very significant individual option, particularly in countries where the medical services are limited or when there is no medical coverage.

As demonstrated by our registry, Pycnogenol® may represent an important tool in the management of initial BPH in asymptomatic patients, as it has a favorable tolerability profile. Moreover, it improves all the main items usually affected by BPH, both in terms of patients' symptoms, and in terms of diagnostic measures.

## Conclusions

In conclusion, Pycnogenol® may be an important option for self-management of BPH in otherwise healthy men. They may individually judge the effects of this supplement on their most common symptoms and decide, in accordance with their

specialist, to continue with the supplementary treatment or to shift to more expensive and side-effects-prone pharmaceutical treatments.

Possibly, combination with other safe standardized supplements may improve the long-term efficacy of Pycnogenol®.

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