

PROSTATIC FIBROSIS; IMPROVEMENT IN TISSUE MORPHOLOGY AND SYMPTOMS OF ENLARGED PROSTATE WITH THE COMBINATION PYCNOGENOL® AND CENTELLICUM®

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SUPPLEMENTS*

INTRODUCTION

Benign prostatic hypertrophy (BPH) is associated with symptoms of partial, temporary bladder outflow obstruction, weaker urinary stream, increased frequency and urgency, nocturia with an incomplete vesical emptying. BPH is diagnosed with rectal examination, an ultrasound and by evaluating the patients' symptoms.

Other diagnostic techniques such as cystoscopy, ultrasound and urodynamics are used to quantify BPH and to exclude other diseases and cancer or to plan a surgical procedure. The diagnosis of BPH in males of 55-74 years, without known prostate cancer, is established in the presence of a prostatic volume greater than 30 mL and a high *American Urological Association Symptom Score* (its prevalence is around 19%). Additional criteria (voiding parameters, maximum urinary flow, post-void residual urine volume >50 mL may be added to the diagnostic process of BPH^(1,2).

At the moment, there is no specific or definitive treatment⁽¹⁾; 5-alpha reductase inhibitors or alpha adrenoreceptor blockers are possible medical treatments to control some symptoms. Surgical options are reserved for more severe cases, not responding to medical treatment.

Signs and symptoms of PBH affect a large number of individuals; costs and safety are therefore important medical issues.

Initial mild symptoms may benefit from mild management with supplements or low-dose drugs⁽¹⁻⁴⁾. In saw palmetto (SP), also called *Serenoa repens*, fatty acids elements inhibit 5-alpha reductase opposing the conversion of testosterone

to dihydrotestosterone⁽³⁾. SP formulations tested in clinical studies are hexane extracts of SP berries (containing 80-90% essential fatty acids and phytosterols)^(3,4). Clinical studies support the use of SP to manage symptoms of BPH^(1,2). Other standardized supplements (Pygeum, Pycnogenol®), have been successfully used in preclinical situations and in borderline symptomatic BPH. Polyphenols have documented effects on prostatic tissue⁽⁵⁻⁷⁾. Recently, a new highly standardized extract of *Centella asiatica* (CA), Centellicum® (Horphag Research Ltd.), has been produced. The components in CA extracts have been shown in several in-vitro studies and in human studies to modulate collagen production into lesions and wounds, either increasing or blocking collagen production with the result of preventing or reducing fibrosis.

Pycnogenol®, French maritime pine bark extract, has been shown to be effective in reducing prostatic signs and symptoms in uncomplicated patients^(8,9). This registry *study* evaluates the efficacy of Pycnogenol®/Centellicum® supplementation on the structure of the prostate in BPH, in otherwise healthy subjects. *This preliminary, concept' study was an extension of the recent registry study: Benign Prostatic Hypertrophy: Pycnogenol® Supplementation improves Prostate Volume and Residual Bladder Volume*⁽¹⁾.

PATIENTS, METHODS

Only 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^(2,3). 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⁽³⁾.

All subjects were below 80 kg and a BMI lower than 26.

The clinical conditions were 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 remained lower than 10 ng/mL⁽⁴⁾. The assessment forms for these patients were the modified International Prostate Symptom Score (IPSS) forms, including assessment of signs and symptoms, tailored to the need for self-management and self-evaluation⁽³⁾.

Method of density measurements.

The primary endpoint of this registry was the evaluation of the grey scale median, (GSM) of an ultrasound image of the prostate (GSM: as a percentage of white parts in the total image area under evaluation, prostate sections). Grayscale median analysis quantifies, with a specific software (Adobe), prostate echodensity as a percentage of white parts in the total image area under evaluation) and is used to define the density of the tissues.

The test is made with ultrasound, elastosonography (an ultrasound method to evaluate density differences in tissue). Subjects' ultrasound images showed the white, stromal, component of the structure of the prostate in defined, transperineal, mid-section images. A more dense, fibrotic tissue (white on ultrasound, due to the presence of collagen) produces a higher GSM.

In this initial condition, therapy is not always indicated as symptoms may be minimal.

The registry study was conducted as a supplement study. The open registry was constituted by 3 groups of comparable subjects that were followed-up for a period of 6 months; A. subjects managed with standard management (SM) of saw palmetto extract supplement at the dose of 600 mg/day; B. subjects using oral centella asiatica as Centellicum[®], 3 cps (225 mg) per day; C. subjects using Pycnogenol[®] 50 mg 3 times daily + Centellicum[®] (3 cps).

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 the end of the study period (6 months): they had to be normal as per inclusion criteria.

Pycnogenol[®] supplementation

Pycnogenol[®] (Horphag Research Ltd), French maritime pine bark extract, contains anti-inflammatory and antioxidant compounds. It was used as a supplement. Pycnogenol[®] is a very safe product with a good tolerability profile. Its metabolites have been detected in blood and urine⁽¹⁰⁾.

Centellicum[®], centella asiatica, produces a progressive modulation of collagen increasing the level of collagen when the tissue has minimal quantities and improving its regular deposition and controlling the deposition of an excess of collagen in areas where there is too much fibrosis (i.e. cheloids)^(11,12).

Method of density measurements.

The ultrasound areas under evaluation were identified and a gray scale median – GSM – with a specific software (Adobe) was used to define (as for arterial plaques) the density of the tissues. *Standard management* of subjects with initial BPH without surgical indications is based on the intake of 600 mg/day of saw palmetto extract and 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 ⁽³⁾.

Generally, in more advanced stages of BPH, alfa-adrenergic blockers such as terazosin, doxazosin, tamsulosin, and alfuzosin, may help to improve voiding, whereas 5-alfa-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.

Statistical analysis

All results (symptoms and ultrasound measurements) were considered non-parametric. A number of 15 subjects in each group was derived statistically to be the minimum needed to evaluate differences in treatments strategy over a period of at least 3 to 6 months of treatment. Observational items were measured with a visual analogue scale. After voiding, the residual bladder urinary volume was measured by ultrasound, as well as prostate volume (high-resolution transrectal ultrasound) ⁽⁹⁾.

RESULTS

Table I shows the details of the patients evaluated with this method. In total, 69 patients with BPH completed the 6-month study. 22 were managed with saw palmetto, 21 with Centellicum[®] and 26 with the combination Pycnogenol[®]- Centellicum[®].

The groups were comparable for age and distribution of demographic and clinical parameters at inclusion.

Images of prostatic section with the areas with a more fibrotic component are shown in figure 1. Samples of the ultrasound method are shown in figure 2.

The main results, shown in Table I, show that Centellicum[®] and the combination Pycnogenol[®]- Centellicum[®] significantly decreased the level of GSM, the combination being significantly more effective than Centellicum[®] alone ($p < 0.05$) indicating a decrease in prostatic fibrosis (Figure 3).

Table 1. Assessment parameters.*= $p < 0.05$ vs the two other groups. #= $p < 0.05$ vs SM.

	SM	CEN	PYCN CEN
SUBJECTS	22	21	26
AGE; SD	57.1;2	56.6;2.6	6.8;3.1
Prostatic fibrosis			
Initial BPH with limited symptoms			
GSM[%];range	Inclusion	19.9;5-29	20.1;6-28
	3 months	19.2;6-28	14.3;3-19#
	6 months	21.3;6-32	14.8;3-18#
			12.2;2-22*#
			13.2;3-21*#
SIDE EFFECTS	minimal 6/22	none	none
PSA <4 Incl	3.1;0.2	3.3;0.7	3.31;0.6
[ng/mL]; SD	3.02;0.3	3;0.3	3.2;0.2
PROSTATIC VOLUME [mL];SD			
(normal < 30 mL)	Incl	43.2;1.4	42.3;1.2
	6 months	41.2;1	39.2;1.1#
			36.4;1.6*#
Global symptoms assessment			
Scale [0-4];SD	Incl	3.2;0.5	3.3;0.4
	6 months	2.9;0.2	2.6;0.3#
			2.1;0.4*#
Residual Urinary Volume			
[mL]; SD	incl	68.4;3	69.3;3
	6 months	48.3;4.3	44.5;2#
			67.6;4.4
			40.4;3.6*#

Volume formula: $(4/3) * (\pi) * (r1)^3 + (r2)^3 + (r3)^3$ where $r1 = \text{radius } 1$, $r2 = \text{radius } 2$, $r3 = \text{radius } 3$ are the radii of the three dimensions. In 3 dimensions, the volume inside a sphere/spheroid (ball-shape) is derived to be $V = \frac{4}{3} * \pi * r^3$ where r is the radius of the sphere and π 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. $y = 0$).

In addition, the total volume of the prostate decreased significantly in the Centellicum® group and especially more in the combination Pycnogenol®-Centellicum® group in comparison with group saw palmetto (SP) ($p < 0.05$).

Finally, it was shown that the combination Pycnogenol®-Centellicum® relieved the BPH symptoms as shown by the significant decrease of the symptoms scores ($p < 0.05$) in comparison with the SP management as well as significantly decreased the residual bladder volume ($p < 0.05$).

No side effects were observed,

Results: comments

In this 'CONCEPT STUDY' the fibrosis in BPH, prostatic volume and global symptoms were linked and visualized in a mathematical model (Figure 4).