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Short communication

Effects of a supplement combining Pycnogenol® and L-arginine aspartate on lower urinary dysfunction compared with saw palmetto extract

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ABSTRACT

Objectives: Lower urinary tract symptoms (LUTS) and sexual dysfunction (SDys) are common problems that affect quality of life (QOL) in elderly men. In addition to prescribed drugs, many over-the-counter medications including supplements are used to treat QOL diseases. Phosphodiesterase inhibitors are reported to be effective for both LUTS and SDys by increasing nitric oxide levels. French maritime pine bark extract Pycnogenol®, which is a potent nitric oxide donor, is reported to be effective for SDys. However, no reports have been published on whether it ameliorates LUTS.

Design: Open-labeled, randomized study. The effects of two supplements, Nokogiriyashi EX® containing 160 mg saw palmetto (SP) extract per tablet and Edicare® containing 10 mg of Pycnogenol®, 115 mg of L-arginine and 92 mg of aspartate (PAA) per tablet on International Prostate Symptom Score (IPSS), IPSS–QOL, Overactive Bladder Symptom Score (OABSS), International Index of Erectile Function 5 (IIEF5), Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), urinary 8-OHdG and uroflowmetry (UFM) of total 40 men with LUTS and SDys were examined.

Results: 19 subjects were instructed to take two tablets of SP, on the other 20 were on four tablets of PAA for 16 weeks. IPSS and IPSS–QOL showed statistically significant improvements in both groups. OABSS and IIEF5 were significantly improved in the PAA group. Conversely, ICIQ-SF, 8-OHdG and UFM did not change in either group.

Conclusions: PAA might be an effective therapeutic alternative for elderly patients with LUTS and SDys.

1. Introduction

The incidence of benign prostatic hyperplasia (BPH) gradually increases with age, and the disease results in both lower urinary tract syndromes (LUTS) and sexual dysfunction (SDys).[1] The treatment options for LUTS range from behavioral modifications, such as bladder training, to medical treatment. Alpha-1 blockers and 5-alpha-reductase (5AR) inhibitors are the most frequently prescribed drugs, but they can also cause SDys.[2]

Preparations made from the berries of saw palmetto (SP) (*Serenoa repens*) have a long history of use in the treatment of LUTS and SDys.[3–7] Reported modes of action include inhibition of 5AR and anti-inflammatory activities, as well as inhibition of autonomous receptors in the lower urinary tract.[7] On the other hand, clinical studies have reported that the proprietary, patented combination of L-arginine aspartate and French maritime pine (*Pinus pinaster*) bark extract Pycnogenol® might improve mild to moderate SDys.[8] Pycnogenol® consists of a concentrate of polyphenols and acts to improve SDys by increasing nitric oxide production and promoting vasodilation.[8–11] However, there is no reports on the clinical assessment of supplements containing of Pycnogenol®, L-arginine, aspartic acid (PAA) for LUTS accompanied by SDys.

In the present study, we attempted to determine the efficacy and safety of a supplement containing PAA for elderly patients with

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both LUTS and SDys compared with a supplement containing SP extract.

2. Materials and methods

This study was conducted in compliance with the Helsinki Declaration after approval was granted by the Ethics Committee of Dokkyo Medical University Koshigaya Hospital. We obtained written informed consent from all participants after thoroughly explaining the efficacy and possible adverse reactions of SP and PAA.

Patients who consulted our hospital with LUTS and SDys between June 2013 and May 2014 were considered for enrollment. The inclusion criteria were 1) male patients between 55–80 years of age; 2) an International Prostate Symptom Score (IPSS) of 8 or more; 3) the presence of LUTS for at least 2 months; and 4) the presence of SDys (erectile dysfunction and/or decreased libido). Exclusion criteria were 1) habitual consumption of a supplement that is intended for the treatment of LUTS or SDys; 2) allergy to the substances under investigation; 3) any complications that could affect voiding function such as neurogenic bladder, urethral stricture, and active urinary tract infection; 4) the existence of diabetes mellitus, heart disease, renal disease, or hepatic disease. And all participants were required to visit the outpatient clinic at the first visit, and after 4, 8 and 16 weeks.

The study was designed as an open, randomized, two-arm study comparing the commercialized food supplement Nokogiriyashi EX® (manufactured by Kobayashi Pharmaceutical Co., Ltd., and containing 160 mg SP extract per tablet) and Edicare® (manufactured by Kobayashi Pharmaceutical Co., Ltd., and containing 10 mg of Pycnogenol®, 115 mg of L-arginine, and 92 mg of aspartic acid per tablet).

Subjects had blood and urine samples collected, were asked about their general health condition and examined by a physician before the start of the study, and again at 8 and 16 weeks after the study. In combination with the questioning by the physician: IPSS, IPSS-Quality of Life (QOL), the 5-item version of the International Index of Erectile Function (IIEF5), Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), Overactive Bladder Symptom Score (OABSS), height, body weight, BMI, uroflowmetry (UFM) and prostate estimated weight measured by abdominal ultrasonography were also recorded. Blood test parameters consisted of red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, total protein, albumin, lactate dyhydrogenase (LDH), alkaline phosphatase (ALP), aspartate amino transferase (AST), alanine transaminase (ALT), total bilirubin, creatinine, urea nitrogen, hemoglobin Alc, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, sodium, potassium chlorine, and serum prostaglandins. The pH, qualitative protein, qualitative glucose and occult blood were investigated by urinalysis. As a marker of oxidative stress, we evaluated urinary 8-OHdG levels using an ICR-001 device (Techno Medica, Yokohama, Japan) according to the manufacturer's recommendations.

Data are reported as means ± SD and were analyzed using SPSS software version 12.0 (IBM, Chicago, IL). Wilcoxon signed-rank test was used to evaluate the effects of treatment, and $P < 0.05$ was considered significant.

3. Results

3.1. Patients

Forty subjects were instructed to take two tablets of Nokogiriyashi EX® (SP 320 mg/day) or 6 tablets of Edicare® (Pycnogenol® 60 mg/day) for 16 weeks. One subject in the SP group was unable to continue the study because of an adverse reaction (loose stool) and was excluded from the analysis. Thus, 19 subjects (age range 68–80 years, mean 76.7 ± 6.9) in the SP group and 20 subjects (age range 67–80 years, mean 76.1 ± 4.7) in the PAA group (Table 1) were examined. There were no significant differences in clinical parameters between the two groups.

3.2. Efficancy

We found the following results in the SP group: 1) subjective outcomes assessed by IPSS total, subscore (storage and voiding score) and QOL were significantly improved; 2) no significant improvements were observed in the other parameters (OABSS, IIEF5, ICIQ-SF, UFM and 8-OHdG). On the other hand, the PAA group showed the following results: 1) subjective outcomes assessed by IPSS total, subscore (storage and voiding score), QOL, OABSS and IIEF5 were significantly improved; 2) no significant improvements were observed in the other parameters (ICIQ-SF, UFM and 8-OHdG) (Table 2). Comparing PAA to SP group showed a significant difference regarding change from baseline of IIEF5 (Table 3). The other parameters (IPSS total, subscore, QOL, OABSS, ICIQ-SF, UFM and 8-OHdG) did not show a significant difference between the two groups.

3.3. Blood and urine test

The baseline mean red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count were all within normal limits in both groups. At the end of the 16 weeks study period, the difference of haematology results were not statistically different (data not shown). Results of biochemistry markers indicated a slight decrease in AST and HbA1c in the PAA group (data not shown), but these changes were all within normal limits. Urinalysis remained unchanged in both group at 8 and 16 weeks.

3.4. Safty

Three patients reported 4 adverse events, including nausea, loose stool and pruritus, all of which were mild in nature and seen as related to the study medication. From the total of 40 patients,

Table 1
Backgrounds of participants.

	SP	PAA	p-value
Age (years)	76.7 ± 6.9	76.1 ± 4.7	0.142
Height (cm)	168.3 ± 3.6	167.2 ± 4.9	0.177
Body weight (kg)	69.1 ± 8.9	68.3 ± 6.9	0.467
BMI (kg/m^2)	23.8 ± 2.7	24.9 ± 2.3	0.267
P-EW (cc)	29.2 ± 8.4	31.1 ± 9.8	0.423
IPSS			
Total	13.4 ± 5.5	14.5 ± 6.2	0.182
Storage	6.2 ± 2.5	8.1 ± 2.9	0.114
Voiding	7.3 ± 4.3	8.4 ± 4.3	0.974
QOL	4.0 ± 1.1	4.0 ± 0.9	0.228
OABSS	4.9 ± 2.5	6.8 ± 3.3	0.706
IIEF5	1.2 ± 0.5	1.4 ± 0.5	0.453
ICIQ-SF	1.9 ± 3.2	5.3 ± 4.9	0.197
UFM			
RV (ml)	30.8 ± 22.3	36.4 ± 21.5	0.655
Qmax (ml/s)	13.3 ± 6.8	12.6 ± 6.7	0.187
8-OHdG (ng/mlCRE)	18.4 ± 8.2	17.4 ± 5.4	0.725

*p-value, estimated probability of rejecting the null hypothesis.
Notes: P-EW, prostate estimate weight; QOL, quality of life; OABSS, Overactive Bladder Symptom Score; IPSS, International Prostate Symptom Score; IIEF5, 5-item version of the International Index of Erectile Function; ICIQ-SF, Consultation on Incontinence Questionnaire e-short Form; UFM, uroflowmetry; RV, residual urine volume; Qmax, maximum flow rate; 8OHdG, 8-hydroxy-2'-deoxyguanosine.

Table 2
Effects of SP and PAA.

	SP baseline	After 16 weeks	PAA baseline	After 16 weeks
IPSS				
Total	13.4 ± 5.5	9.6 ± 5.3	14.5 ± 6.2	10.4 ± 5.6
Storage	6.2 ± 2.5	4.4 ± 2.6	8.1 ± 2.9	4.4 ± 2.6
Voiding	7.3 ± 4.3	5.2 ± 4.1	8.4 ± 4.3	5.2 ± 4.1
QOL	4.0 ± 1.1	2.9 ± 1.3	4.0 ± 0.9	2.9 ± 1.3
OABSS	4.9 ± 2.5	3.9 ± 2.9	6.8 ± 3.3	3.9 ± 2.9
IIEF5	1.2 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	2.3 ± 1.4
ICIQ-SF	1.9 ± 3.2	1.6 ± 2.7	5.3 ± 4.9	2.9 ± 3.8
UFM				
RV (ml)	30.8 ± 22.3	41.9 ± 43.2	36.4 ± 21.5	41.9 ± 43.2
Qmax (ml/s)	13.3 ± 6.8	12.3 ± 5.3	12.6 ± 6.7	12.3 ± 5.3
8-OHdG (ng/mlCRE)	18.4 ± 8.2	22.5 ± 20.8	17.4 ± 5.4	18.9 ± 5.4

Notes: IPSS, International prostate symptom score; QOL, quality of life; OABSS, Overactive Bladder Symptom Score; IIEF5, 5-item version of the International Index of Erectile Function; ICIQ-SF, Consultation on Incontinence Questionnaire e-short Form; UFM, uroflowmetry; RV, residual urine volume; Qmax, maximum flow rate; 8OHdG, 8-hydroxy-2′-deoxyguanosine.

Table 3
Change from baseline.

	SP	PAA	p-value
IPSS			
Total	−3.8 ± 5.3	−6.1 ± 4.8	0.536
Storage	−1.7 ± 2.6	−3.1 ± 2.6	0.414
Voiding	−2.1 ± 3.8	−2.7 ± 3.0	0.804
QOL	−0.8 ± 1.4	−0.9 ± 1.6	0.805
OABSS	−1.2 ± 2.6	−1.9 ± 2.8	0.724
IIEF5	0.2 ± 0.5	0.9 ± 1.1	0.047
ICIQ-SF	−0.9 ± 3.8	−2.4 ± 4.7	0.564
UFM			
RV (ml)	0.5 ± 44.0	−1.4 ± 31.1	0.892
Qmax (ml/s)	−1.0 ± 5.3	−0.3 ± 7.0	0.703
8-OHdG (ng/mlCRE)	−1.0 ± 5.4	2.3 ± 5.7	0.232

Notes: IPSS, International prostate symptom score; QOL, quality of life; OABSS, Overactive Bladder Symptom Score; IIEF5, 5-item version of the International Index of Erectile Function; ICIQ-SF, Consultation on Incontinence Questionnaire e-short Form; UFM, uroflowmetry; RV, residual urine volume; Qmax, maximum flow rate; 8OHdG, 8-hydroxy-2′-deoxyguanosine.

one from the SP group was unable to continue the study because of loose stool and was excluded from the analysis.

4. Discussion

In the present study, we demonstrated that consumption of a supplement of PAA combination taken for 16 weeks improved both LUTS and SDys. Pycnogenol® reportedly improves erectile dysfunction (ED) by activating endothelial nitric oxide synthase (eNOS).[8] Increases of nitric oxide are achieved when Pycnogenol® is administered in combination with L-arginine, the substrate for eNOS, which is suggested to be a physiological response secondary to increased sexual activity.[9] The rationale for Pycnogenol® dosage was inferred from a similar study of Aoki et al (2012) that used a similar PAA, we refered similar study of report of similar PAA combination with Pycnogenol® 60 mg, which demonstrated a significant improvement of ED.[11] However, results of improvement in IIEF5 was smaller in comparison with other reports on the effects of Pycnogenol®.[10–12] This could be partially attributed to the smaller dose of Pycnogenol® used in this study compared with other studies. The clinical trial that reported successful treatment with PAA involved 40 men between 25 and 45 years of age suffering from mild ED.[10] After treatment with 1.7 g L-arginine per day for one month, only 5% of all patients experienced normal erections. During a second month of treatment, 80 mg Pycnogenol® per day was added to the arginine regimen and yielded a significant improvement, with 80% of patients showing normal erections. A third month's treatment with L-arginine, together with an increased amount of Pycnogenol® (120 mg per day), further increased the number of patients with restored normal erectile function. At the end of the trial, 37 patients, equivalent to 92.5% of all participants, achieved normal erectile function. Moreover, the other reason for the smaller improvement in IIEF5 was because of the mean age of patients in that study. Patients were in their fifties compared to the mean age of 76.1 years in the present study.[13]

The results of this study showed that consumption of a supplement of SP significantly improved IPSS total, subscore of storage and voiding, IPSS-QOL. SP have a long standing use in the treatment of mild to moderate LUTS and ED.[3–7] More than 30 controlled clinical trials evaluating treatments for LUTS and SDys have demonstrated long-term efficacy.[5–7] The plant, which is indigenous to Florida, was first used by white settlers in the United States not only for treatment of LUTS but also a treatment for ED, to improve testicular atrophy and sperm production.[3,4] Regarding the mode of action, a variety of mechanisms for SP have been proposed including anti-androgenic effects (prevention against the body's natural response to testosterone by inhibition of the 5AR), anti-inflammatory and anti-proliferative effects, but none have been conclusively proven.[7] In a 2002 Cochrane meta-analysis of the efficiency of SP extracts for men with LUTS attributed to BPH, 21 clinical trials were identified. Compared to placebo, SP significantly reduced nocturia, increased self-rated improvement, and improved peak uroflow.[14] Adverse effects were infrequent. However, results comparing PAA to SP group in this study demonstrated that change from baseline of IIEF5 was significantly improved in the PAA group.

Oxidative stress is reported to result in pathophysiological conditions of the urinary bladder by damaging the urothelium and sensitizing bladder afferent signaling.[15] Previous studies have shown that oxidative stress mediates capsaicin-sensitive c-fibers to induce bladder hyperactivity.[16] Several investigators have shown that Pycnogenol® enhances antioxidant systems and scavenges free radicals.[17,18] Therefore, we hypothesized that Pycnogenol® might ameliorate pathophysiological conditions in the urinary bladder and could be a possible therapy for cases of LUTS that are unresponsive to α1-blockers or antimuscarinic drugs[19,20] However, we did not demonstrate the anti-oxidative effects of either supplement in this study.

The major limitations of this study were the small number of patients, lack of a placebo group, and the omission of urodynamic data. The improvement of LUTS and SDys has a strong placebo component, so the possibility of a placebo effect might be high. It remains unclear whether a supplement containing PAA might be a potential therapeutic alternative for elderly patients with LUTS and SDys; therefore, a prospective placebo-controlled study should be conducted in the near future.

5. Conclusions

Edicare®, a supplement containing PAA might be an effective potential therapeutic alternative for elderly patients with LUTS and SDys. However, further clinical investigations by placebo control studies are required to elucidate the precise mechanisms of this supplement.

Conflict of interest

None declared.

Author disclosure statement

No competing financial interests exist.

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