SAW PALMETTO (*Serenoa repens*) IN MEN WITH LOWER URINARY TRACT SYMPTOMS: EFFECTS ON URODYNAMIC PARAMETERS AND VOIDING SYMPTOMS

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ABSTRACT

Objectives. To assess the effects of saw palmetto on voiding symptoms and urodynamic parameters in men with lower urinary tract symptoms (LUTS) presumed secondary to benign prostatic hyperplasia (BPH).

Methods. Fifty men with previously untreated LUTS and a minimum International Prostate Symptom Score (IPSS) of 10 or greater were treated with a commercially available form of saw palmetto (160 mg twice per day) for 6 months. The initial evaluation included measurement of peak urinary flow rate, postvoid residual urine volume, pressure-flow study, and serum prostate-specific antigen (PSA) level. Patients completed an IPSS, serum PSA was determined, and flow rate was measured every 2 months during the course of the study. A urodynamic evaluation was repeated at the completion of the 6-month trial.

Results. The mean IPSS (±SD) improved from 19.5 ± 5.5 to 12.5 ± 7.0 ($P < 0.001$) among the 46 men who completed the study. Significant improvement in the symptom score was noted after treatment with saw palmetto for 2 months. An improvement in symptom score of 50% or greater after treatment with saw palmetto for 2, 4, and 6 months was noted in 21% (10 of 48), 30% (14 of 47), and 46% (21 of 46) of patients, respectively. There was no significant change in peak urinary flow rate, postvoid residual urine volume, or detrusor pressure at peak flow among patients completing the study. No significant change in mean serum PSA level was noted.

Conclusions. Saw palmetto is a well-tolerated agent that may significantly improve lower urinary tract symptoms in men with BPH. However, we were unable to demonstrate any significant improvement in objective measures of bladder outlet obstruction. Placebo-controlled trials of saw palmetto are needed to evaluate the true effectiveness of this compound. UROLOGY **51:** 1003–1007, 1998.

The use of phytotherapeutic agents, also known as plants or plant extracts, in the treatment of men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) varies widely in different parts of the world.[1] In some European countries, plant extracts are the most commonly recommended initial treatment for men with voiding symptoms, and patients are reimbursed for the cost of these agents by health insurance companies.[1] By contrast, few American physicians recommend natural compounds in the treatment of men with LUTS, although many Americans use these agents because they are available without a prescription.[2] *Serenoa repens,* or saw palmetto, is the most commonly used natural compound in the treatment of men with voiding symptoms secondary to BPH.[1] This agent is derived from the berry of the American dwarf palm tree and has not been associated with any significant toxicity.[3] In a variety of European clinical trials, the use of saw palmetto in men with LUTS has led to significant subjective and objective improvement.[4–7] In general, however, these studies are flawed by the inclusion of limited numbers of men, brief study periods of 30 days or less, inadequate assessment of objective changes in bladder outlet obstruction, and/or failure to use standardized symptom ques-

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TABLE I. *Changes in serum prostate-specific antigen, peak urinary flow rate, and symptom score in 50 men treated with saw palmetto for 6 months*

	Initial	2 Months	4 Months	6 Months	*P* Value*
Serum PSA level (ng/mL)					
Mean (±SD)	3.1 ± 5.7	2.7 ± 3.7	2.9 ± 5.0	2.8 ± 3.9	0.80
Range	0.4–36.3	0.3–19.2	0.2–31.0	0.2–19.4	
Peak urinary flow rate (mL/s)					
Mean (±SD)	13.7 ± 5.8	14.9 ± 9.6	14.1 ± 7.4	13.0 ± 6.1	0.60
Range	4–26	5–34	5–33	4–28	
International Prostate Symptom Score					
Mean (±SD)	19.5 ± 5.5	13.7 ± 5.5	13.6 ± 6.8	12.5 ± 7.0	<0.001
Range	10–31	4–27	2–25	1–28	

KEY: PSA = prostate-specific antigen.
** Initial and 6-month results were compared.*

tionnaires in the evaluation of treatment efficacy. Therefore, despite the widespread use of saw palmetto, both in the United States and Europe, clear evidence of its benefits is lacking.

In an effort to better evaluate the efficacy of saw palmetto, a prospective, open-label study was undertaken to investigate the changes in voiding symptoms, urodynamic parameters, and serum prostate-specific antigen (PSA) levels in men treated with this agent for 6 months. Because limited information is available concerning these effects, the present study was performed to acquire such data. This information is necessary to properly design randomized, placebo-controlled studies concerning the effectiveness of saw palmetto in men with LUTS and BPH.

MATERIAL AND METHODS

Fifty men with LUTS suggestive of bladder outlet obstruction secondary to BPH were treated with saw palmetto. Patients were excluded if they had previously undergone prostate surgery, had a history of prostate cancer or urethral stricture disease, or had been treated with finasteride or saw palmetto (within 6 months) or terazosin or doxazosin (within 1 month). The initial evaluation included completion of an International Prostate Symptom Score (IPSS) questionnaire, measurement of urinary flow rate using a standard flowmeter, determination of the postvoid residual volume by catheterization, digital rectal examination (DRE), and measurement of serum PSA level and routine serum chemistries (electrolytes, renal and hepatic function studies). A minimum initial symptom score of 10 was required for entry into the study. Patients with an elevated serum PSA level and/or an abnormal DRE were allowed to participate if a prostate biopsy demonstrated no evidence of malignancy.

Urodynamic evaluation was performed before treatment with saw palmetto using an 8F transurethral catheter. Abdominal pressure was recorded with a 14F transrectal catheter. The bladder was filled with room temperature water at a rate of 50 mL/min. Bladder pressure, volume infused, and rectal pressure were recorded. Patients were then asked to void in a standing position. Urinary flow rate, bladder pressure, rectal pressure, volume voided, and subtracted detrusor pressure were simultaneously recorded. Unless technical difficulties were encountered, a single urodynamic study was performed using one filling and voiding cycle.

All patients were treated with a commercially available preparation of saw palmetto that did not contain any other active components (160 mg twice per day, Nutraceutical Corp, Ogden, Utah) for 6 months. Patients returned 2, 4, and 6 months after initiating therapy with saw palmetto, at which time an IPSS questionnaire was completed, the presence of side effects was determined, and the urine flow rate and serum PSA level were measured. In addition, at the completion of the 6-month trial, the postvoid residual volume and urodynamic evaluation were repeated.

Objective evaluation of the degree of bladder outlet obstruction initially and after 6 months of treatment with saw palmetto was performed in two ways: (1) using the Abrams-Griffiths nomogram, all patients were categorized as obstructed, equivocal, or unobstructed[8]; and (2) the Abrams-Griffiths number (AG number) was determined: detrusor pressure at maximum urine flow rate (PdetQmax) minus 2 × maximum urine flow rate (Qmax).[9] Using this calculation, all patients with an AG number of 40 or greater were considered to be obstructed.[9,10] Statistical comparisons were made using Student's *t* test.

RESULTS

The mean age (±SD) of the 50 patients treated with saw palmetto was 61.8 ± 9.4 years (range 46 to 84). Four men discontinued the use of saw palmetto before completion of the study because of severe voiding symptoms that did not improve during the course of treatment. Therefore, 46 (92%) men completed the 6-month study, including the initial and follow-up urodynamic evaluations. No significant side effects were reported by patients receiving saw palmetto and there were no significant changes in serum chemistries noted. A significant improvement in the IPSS was noted when comparing the mean initial symptom score with the mean value at 2, 4, and 6 months ($P < 0.001$) (Table I). However, there was no significant change in peak urinary flow rate, serum PSA level, or in any of the measured urodynamic parameters (Tables I and II).

The mean percentage improvement in symptom score (±SD) in the 46 men who completed the 6-month study was 34.1% ± 35.3%. Overall,

TABLE II. *Changes in urodynamic parameters in men treated with saw palmetto for 6 months*

	Initial	6 Months*	*P* Value
Postvoid residual (mL)			
Mean (±SD)	72.0 ± 64.0	62.7 ± 59.8	0.47
Range	5–217	2–240	
Bladder capacity (mL)			
Mean (±SD)	298 ± 88	301 ± 89	0.88
Range	128–565	139–595	
Detrusor pressure at peak urinary flow (cm H_2O)			
Mean (±SD)	64.8 ± 26.8	68.1 ± 31.1	0.58
Range	18–135	10–137	
Abrams-Griffiths number			
Mean (±SD)	37.8 ± 31.3	42.3 ± 36.3	0.53
Range	−44–115	−46–127	

** 46 patients underwent urodynamic evaluation at 6 months.*

TABLE III. *Results of objective evaluation of bladder outlet obstruction in 50 men treated with saw palmetto for 6 months*

	Initial	6 Months*
Abrams-Griffiths number†		
No. obstructed	21	19
No. unobstructed	29	27
Abrams-Griffiths nomogram		
No. obstructed	20	19
No. equivocal	25	24
No. unobstructed	5	3

** 46 patients underwent urodynamic evaluation at 6 months.*
† Obstructed = AG number > 40; unobstructed = AG number < 40.

85% (39 of 46) of patients had an improvement in the IPSS of any magnitude, 13% (6 of 46) had a higher symptom score at 6 months than was recorded initially, and 2% (1 of 46) had no change in the IPSS. An improvement in symptom score of 50% or greater after treatment with saw palmetto for 2, 4, and 6 months was noted in 21% (10 of 48), 30% (14 of 47), and 46% (21 of 46) of patients, respectively. On the basis of the AG number, 58% (29 of 50) of the patients were not obstructed at the outset of the study (Table III). The mean percentage improvement in symptom score after 6 months among men who were or were not obstructed initially was 24.9% and 40.0%, respectively ($P = 0.16$).

COMMENT

The role of phytotherapeutic agents in the treatment of patients with voiding symptoms and BPH remains poorly defined. In the present, nonrandomized, open-label investigation of the use of saw palmetto, there was a significant improvement in LUTS, as assessed by the mean decrease in the IPSS, among the 46 men who completed the 6-month trial. In addition, 21 (46%) of 46 patients had at least a 50% improvement in their symptom score when comparing initial and 6-month results. Saw palmetto was also very well tolerated with no significant adverse effects and no change in serum chemistries noted. However, we were unable to demonstrate any significant improvement in the mean peak urinary flow rate, postvoid residual urine volume, or bladder pressure in patients treated with saw palmetto for 6 months.

The results of our study may be interpreted in several ways. First, it is possible that the changes in symptom score that we noted may be largely due to placebo effect. In an open-label study of medical therapy for men with symptomatic BPH, the placebo effect may be substantial. Nickel *et al.*[11] have demonstrated that patients with LUTS who are treated with placebo may have marked, long-term improvement in their symptoms. However, the magnitude of the decrease in the IPSS seen in the present study greatly exceeds that which has been reported in the placebo arms of randomized, controlled studies of pharmacologic therapy in men with LUTS, which average approximately 3 points.[12,13] The mean improvement of 7 points that we found in men treated for 6 months with saw palmetto closely approximates the reported improvement in symptom score among patients receiving alpha-blockers, such as terazosin or doxazosin, or 5-alpha reductase inhibitors, such as finasteride.[7,12,13] This comparison may not be valid, however, because the men receiving saw palmetto in the present study knew that they were being treated with an "active" agent, and patients in a randomized trial are aware that they may be receiving a placebo. Because the relative placebo effect may vary greatly in these different clinical sit-

uations, the efficacy of saw palmetto can only be reliably established by a randomized, controlled trial. The data generated in the present study are being used to help design and properly power such a placebo-controlled study.

Alternative explanations for our findings include the size of our patient population or the method of patient selection in our study, which may have prevented us from detecting small but significant improvements in urinary flow rates or urodynamic measures. Among patients entered into this trial, 58% (29 of 50) had no urodynamic evidence of bladder outlet obstruction, compared with most other studies of men with voiding symptoms and BPH in which only 20% to 30% of patients are unobstructed.[10,14,15] Our ability to detect urodynamic changes in men treated with saw palmetto may have been limited because most patients in this study were not obstructed. Finally, the improvement in voiding symptoms seen in patients receiving saw palmetto may not be dependent on direct relief of bladder outlet obstruction. A variety of alternative mechanisms by which saw palmetto may alleviate urinary symptoms in men with BPH have been proposed and investigated to varying degrees.[16–18]

The most commonly suggested mechanism of action of saw palmetto in relieving voiding symptoms is inhibition of the 5-alpha reductase-mediated conversion of testosterone to dihydrotestosterone (DHT).[3,16,19] Although this action has been demonstrated using in vitro studies,[16,19] evidence of clinically significant 5-alpha reductase activity associated with saw palmetto has not been presented. Carraro *et al.*[7] performed a 6-month, randomized comparison of the effects of finasteride and saw palmetto (Permixon) in 1098 men with LUTS. Although similar improvements in symptom scores and flow rates were noted in the two groups, men treated with finasteride had an 18% decrease in prostate volume as compared with only 6% in those receiving saw palmetto ($P < 0.001$). In addition, unlike finasteride, saw palmetto appears to have no significant effect on serum PSA or DHT levels.[7,20] Finally, Rhodes *et al.*[21] directly compared the 5-alpha reductase inhibitory effects of finasteride and saw palmetto using in vitro and in vivo techniques and found that saw palmetto had no effect on DHT-stimulated prostate growth. Other proposed mechanisms by which saw palmetto may relieve voiding symptoms include inhibition of cytosolic androgen receptor binding,[16,22] antiestrogenic activity in prostatic tissue,[18] and relief of edema and inflammation within the prostate.[23,24] However, the clinical significance and importance of these effects remains unproved.

CONCLUSIONS

Among 50 men with LUTS presumed secondary to BPH who were treated with saw palmetto for 6 months, the mean IPSS improved from 19.5 ± 5.5 to 12.5 ± 7.0 ($P < 0.001$). There were no significant changes in serum chemistries or PSA levels and no patient discontinued participation because of perceived adverse effects. No significant improvement was noted in peak urinary flow rate, postvoid residual urine volume, bladder capacity, or detrusor pressure at peak flow after treatment with saw palmetto for 6 months.

The subjective improvement in voiding symptoms that occurred in our patients without demonstrable objective change in any of the measured urodynamic parameters may be largely attributable to the placebo effect. Alternative explanations include patient selection factors, the limited size of our patient population, and/or improvements in urinary symptoms secondary to mechanisms other than direct relief of bladder outlet obstruction. Overall, saw palmetto is a well-tolerated agent that may significantly improve LUTS in men with BPH. Further study of saw palmetto, including placebo-controlled trials, is warranted.

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EDITORIAL COMMENT

This is simply another of the numerous phytotherapy articles that fails to address the basic issue of whether plant extracts are effective and useful in the treatment of men with symptomatic BPH. It is unfortunate that a placebo control arm was not included in this nonrandomized, open-label study of saw palmetto berry extract because the authors studied their patients well with up-to-date urodynamics.

This study can be used by both proponents and detractors of herbal medications to support their underlying beliefs about plant extract therapy for BPH.

The believers/herbalists will emphasize the significant (compared with baseline) improvement in symptom scores from 19.5 to 12.5 units on the IPSS and that 46% (21 of 46 evaluable patients) had at least a 50% improvement in their IPSS. Additionally, the magnitude of the improvement is greater that the usual 3 to 4-unit improvement seen in the placebo control arms of other drug studies.

The nonbelievers will emphasize the lack of improvement in any of the objective parameters (peak urinary flow rate, postvoid residual, and bladder capacity) and the failure to demonstrate any improvement in terms of urodynamic signs obstruction—either Abrams-Griffiths number or Abrams-Griffiths nomogram (see Table III). The magnitude of the symptom improvement could be simply attributed to an enhanced placebo effect that occurred because all patients knew that they were receiving an "active" and "efficacious" medication.

The authors concluded that the subjective improvement in voiding symptoms that occurred in their patients without any demonstratable objective changes in any of the measured urodynamic parameters "may be largely attributable to the placebo effect." Without an appropriate control arm, the attributable drug effect of these agents cannot be demonstrated. Hopefully, the appropriate placebo-controlled studies with phytotherapies will be undertaken.

This study clearly demonstrated that there was no correlation between relief of urodynamic signs of obstruction and improvement in symptoms. Thus, relief of bladder outlet obstruction is not necessary to improve LUTS. Possibly the effect is mediated through a central effect, bladder desensitization, "the power of positive thinking," or some other mechanism. Whatever the cause or mechanism, 46% (21 of 46) of the patients had a greater than 50% improvement in their voiding symptoms without any notable side effects. Maybe a "placebo" for BPH is not so terrible?

Perhaps if we "knew" the cause(s) of LUTS, which occurs in both men and women (who do not have obstructing prostates), we might have a better understanding of the role and the mechanisms of actions of the phytotherapeutic agents, alpha-blockers, alpha-reductase inhibitors, and other agents/methods that we use to improve the quality of life of our patients. Further research in the etiology of BPH/LUTS is clearly needed. The efficacy of phytotherapeutic agents is still to be determined.

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REPLY BY THE AUTHORS

We agree that the efficacy of agents used in the treatment of LUTS, including plant extracts, can only be reliably determined by randomized, placebo-controlled trials. Significant resources are generally needed to perform such trials properly. Unfortunately, these resources are limited in the United States because phytotherapeutic agents are most often categorized as food additives and are generally not eligible for patent protection. We believe that the present study provides useful information concerning the safety and tolerability of saw palmetto, the lack of its effect on serum PSA levels, and what may be the "best case scenario" when men with voiding symptoms use this agent. Because LUTS is a benign condition with an improvement in quality of life as the primary goal of treatment in most cases, the use of a safe, well-tolerated agent, such as saw palmetto, may be reasonable for some patients even if further study were to demonstrate that its primary mechanism of action is a placebo effect.

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