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TISSUE EFFECTS OF SAW PALMETTO AND FINASTERIDE: USE OF BIOPSY CORES FOR IN SITU QUANTIFICATION OF PROSTATIC ANDROGENS

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ABSTRACT

Objectives. To determine the effects of a saw palmetto herbal blend (SPHB) compared with finasteride on prostatic tissue androgen levels and to evaluate needle biopsies as a source of tissue for such determinations.

Methods. Prostate levels of testosterone and dihydrotestosterone (DHT) were measured on 5 to 10-mg biopsy specimens (18-gauge needle cores) in three groups of men with symptomatic benign prostatic hyperplasia: 15 men receiving chronic finasteride therapy versus 7 untreated controls; 4 men undergoing prostate adenomectomy to determine sampling variability (10 specimens each); and 40 men participating in a 6-month randomized trial of SPHB versus placebo, before and after treatment.

Results. Prostatic tissue DHT levels were found to be several times higher than the levels of testosterone (5.01 versus 1.51 ng/g), that ratio becoming reversed (1.05 versus 3.63 ng/g) with chronic finasteride therapy. The finasteride effect was statistically significant for both androgens ($P < 0.01$), and little overlap of individual values between finasteride-treated and control patients was seen. In the randomized trial, tissue DHT levels were reduced by 32% from 6.49 to 4.40 ng/g in the SPHB group ($P < 0.005$), with no significant change in the placebo group.

Conclusions. For control versus finasteride-treated men, the tissue androgen values obtained with needle biopsy specimens were similar—both for absolute values and the percentage of change—to those previously reported using surgically excised volumes of prostatic tissue. The quantification of prostatic androgens by assay of needle biopsies is thus feasible and offers the possibility of serial studies in individual patients. The SPHB-induced suppression of prostatic DHT levels, modest but significant in a randomized trial, lends an element of support to the hypothesis that inhibition of the enzyme 5-alpha reductase is a mechanism of action of this substance. UROLOGY **57:** 999–1005, 2001. © 2001, Elsevier Science Inc.

Saw palmetto extract is a widely used "natural remedy" for men with symptomatic benign prostatic hyperplasia (BPH),[1–3] but the mechanism of action is unknown. In a prior study, we found that the epithelial tissue in the prostate transition zone appears to undergo involution after 6 months of treatment with a saw palmetto herbal blend (SPHB).[4] Qualitatively, the epithelial effect of saw palmetto appears similar to that seen after finasteride administration,[5] connoting a common mechanism of action.

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Inhibition of the enzyme 5-alpha reductase is the pathway by which finasteride deprives the prostate of the trophic androgen dihydrotestosterone (DHT).[6] This mechanism has also been suggested for saw palmetto extracts[7–9]; however, contrary evidence exists.[10,11] Suppression of prostatic DHT, which underlies finasteride-induced epithelial involution, could explain the epithelial involution seen after saw palmetto administration. DHT suppression in vivo would be powerful evidence that saw palmetto functions as a 5-alpha reductase inhibitor when administered therapeutically. However, an evaluation of the effects of saw palmetto in a randomized trial quantifying tissue androgens is not yet available.

Thus, the possible hormonal effects of an SPHB were studied in the prostatic tissues of men with symptomatic BPH during a placebo-controlled trial, comparing them with the effects seen in similar patients taking finasteride. We focused on the quantification of tissue androgens, since theoretically, tissue changes should be more sensitive than serum changes in discerning a hormonal mechanism of action within the prostate. In contrast to other studies using large volumes of surgically excised prostate, in the present study, 18-gauge biopsy cores averaging 5 to 10 mg in weight were used to quantify the tissue androgen levels in situ before and after treatment.

MATERIAL AND METHODS

Patients

Three groups of men with symptomatic BPH were studied, two groups in preliminary studies and one group in a randomized trial of an SPHB.[4] No patient was taking any medication that could affect their androgen status (eg, gonadotropic-releasing hormone agonists, testosterone antagonists, or anabolic steroids), except for finasteride where indicated. The full inclusion and exclusion criteria, which were similar to those used in major BPH drug trials, for the men in the randomized trial have been previously published.[4] A customized consent form approved by the Western Institutional Review Board (Seattle, Wash) was used.

Preliminary Studies

Finasteride Effect. Twenty-two men (mean age 67.5 ± 10.1 years SD) with symptomatic BPH were the subjects in this study. These men underwent biopsy to rule out cancer (n = 18) or transurethral resection of the prostate (TURP) for the relief of obstruction (n = 4). They furnished serum and prostatic tissue to determine the differences between men receiving no treatment (n = 15) and men receiving chronic (3 months or longer) finasteride therapy (n = 7). During the routine sextant biopsy, an additional 18-gauge mid-gland core was taken for the study from the right and left prostatic lobe of each patient. In this and all subsequent studies, the tissues were removed from the patient, quick frozen on dry ice, and then transferred within 30 minutes into a −70°C freezer, where they were stored for batch analysis at the end of each study. Each storage vial contained 0.1 mL of normal saline to prevent desiccation. Carcinoma was excluded in all patients by conventional pathologic examination of the other tissues. For the TURP patients, chips from the right and left lobes were cut into pieces approximating the size of a needle biopsy (1 × 15 mm) with fine scissors, washing the instruments with methanol between each sample. The specimens were frozen in buffer in 12 × 75-mm extraction tubes as described below.

Sampling Effect. Four other men with symptomatic BPH (age 66, 72, 84, and 92 years) who underwent TURP (n = 3) or open prostatectomy (n = 1) for the relief of obstruction had 10 biopsies taken from each specimen to examine the effect sampling variability might have on the determination of the tissue hormone levels. The specimens were obtained randomly by repeated needle biopsy of the adenoma (both lobes) or by cutting biopsy-size tissue (approximately 1 × 15 mm) from the TURP chips from the right and left lobes. All tissues were collected immediately on removal from the patients before fixation. Carcinoma was excluded in all patients by routine pathologic examination of the tissues.

Randomized Trial

Forty-four men with symptomatic BPH were entered into a 6-month randomized trial of an SPHB (n = 21) versus a placebo (n = 23). The SPHB supplied 320 mg/day of a standardized saw palmetto extract and has been described in detail elsewhere.[4] Standardization of the compound (ie, assurance that the product uniformly contained at least 85% total fatty acids and sterols) was confirmed by an independent testing laboratory (http://www.consumerlab.com) using gas chromatography. Moreover, the same product lot number was used throughout. The clinical and immunohistochemical results of the trial have been previously reported.[4] In brief, the men had a mean age of 64 years, International Prostate Symptom Score of 17, peak urinary flow rate of 10.5 mL/s, prostate volume of 56 mL, and serum prostate-specific antigen level of 3.3 ng/mL.[4] At baseline and again after 6 months of randomization, right and left mid-sagittal biopsy cores were taken from each patient for quantitative hormone studies in the same manner as for the biopsy cores taken from the men in the finasteride study.

Tissue Handling

At the time of assay, each prostate sample was individually thawed, blotted on laboratory tissue, weighed using a Cahn 29 Electrobalance, and immediately transferred to a 12 × 75-mm glass tube containing 1 mL phosphate-buffered saline (pH 7.0) and flash frozen on dry ice. The total number of biopsy specimens assayed was 244 (mean weight 5.99 ± 2.76 mg SD, range 1.58 to 16.25).

Steroid Determinations

After all the samples were weighed, each was individually thawed and homogenized with 3 × 1-second pulses using a Janke and Kunkel Ultra Turrax T25 homogenizer with an 8-mm probe. The sample was maintained at 4°C throughout the process. The homogenate was transferred to a 13 × 100-mm glass extraction tube at 4°C and the probe and homogenization tube were washed with 3 × 1 mL diethyl ether, pulsing 3 × 1 second for each wash. The individual ether washes were transferred to the extraction tube, an additional 3 mL ether was added, the tubes were capped, and the sample was swirled vigorously for 15 seconds and then returned to 4°C until all the samples had been processed. All samples were further extracted by repeated inversion of the tubes for 3 minutes, and the organic and aqueous phases were separated by centrifugation at 4°C for 5 minutes at 2500 rpm in a Sorval RC3 centrifuge.

The aqueous phase was flash frozen in a dry ice-ethanol bath and the organic phase decanted to a new set of 13 × 100-mL glass tubes. The ether was evaporated under room air

at 37°C, and the residue concentrated to the tip of the tube with two ether washes (1.0 and 0.5 mL), drying between each wash. The concentrated residue was stored in 300 μL redistilled ethanol until chromatographed on Sephadex LH-20 microcolumns to isolate estradiol, testosterone, and DHT. The ether extract from each sample was applied to individual 1.0-g Sephadex LH-20 columns and neutral and estradiol fractions collected using hexane:benzene:methanol (62:20:13 vol/vol/vol) as the eluting solvent.[12] The estradiol fraction was assayed by a nonequilibrium radioimmunoassay.[13] The neutral fraction was chromatographed on individual 2.5-g Sephadex LH-20 columns, and testosterone and DHT fractions were collected using hexane:benzene:methanol (85:15:5 vol/vol/vol) as the application and eluting solvent.[14] Testosterone and DHT concentrations of the appropriate fractions were estimated by radioimmunoassay.[14]

Independent estimates of method blanks were done by extracting and chromatographing 1 mL phosphate-buffered saline buffer without tissue present. The estimates of the method recoveries were made by adding ^{3}H-estradiol, ^{3}H-testosterone, or ^{14}C-DHT to similar-size samples of either human or banked macaque prostate and serum and collecting appropriate fractions for scintillation counting after extraction and chromatography. Multiple independent recoveries with equivalent tissue/serum samples were used in this study to assess the extraction and chromatography losses, rather than adding labeled steroids to each assay tube, because the quantities of testosterone and DHT anticipated to be in the tissues studied was very small, and we sought to avoid adding extra mass in the form of labeled hormone. Quality control samples of male macaque serum were processed at three levels to monitor assay performance. For estradiol (n = 3), testosterone (n = 9), and DHT (n = 9) assays, the average solvent blank was 0.6 pg, 3.5 pg, and 2.4 pg, respectively, and the average percentage of recovery was 81.1%, 71.7%, and 82.4%, respectively. The intra-assay coefficient of variation for the three assays was 12.4%, 7.3%, and 12.9%. The interassay coefficient of variation was 31.1%, 4.2%, and 15.0%.

The serum samples were similarly extracted with ether, subjected to chromatography, and assayed for estradiol, testosterone, and DHT using the same assay as for the tissue samples. The prostatic tissue levels of estradiol were undetectable in the present study.

Statistical Analysis

All data were entered into a personal computer using Excel spreadsheets (Microsoft, Redmond, Wash) and analyzed using the Stata statistical package (Stata, College Station, Tex). Because the distribution of the assay values was not normal, nonparametric rank-sum statistical analysis was used to compare the groups. The comparison of the baseline with the 6-month values was made using nonparametric signed-rank testing. Intraperson assay variability was assessed using the coefficient of variation. Correlations between assay values were made using the nonparametric Spearman rank correlation. Statistical significance was defined a priori as $P < 0.05$.

RESULTS

Tissue Analysis

A total of 244 prostate biopsies were analyzed: 40 from the sampling variability study (4 patients), 44 from the finasteride study (22 patients), and 160 from the SPHB trial (40 patients; 4 other patients were enrolled but excluded because of incomplete data).

In the saw palmetto study,[4] the histologic evaluation revealed microfocal adenocarcinoma in 4 men at baseline and in another 4 men (3 in the placebo group and 1 in the saw palmetto group) at the second biopsy; invasive cancer was detected in 1 man from each group at the second biopsy. No adenocarcinoma was detected in the other groups. Examples of the analyzed tissues are shown in Figure 1.

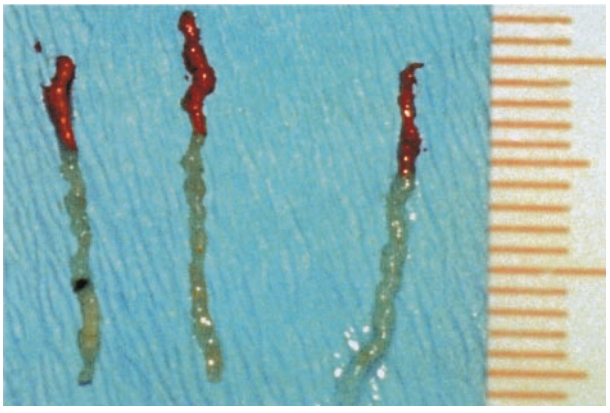

FIGURE 1. *Examples of tissues analyzed; 244 prostate biopsy cores were subjected to quick freezing at −70°C, subsequent thawing, homogenization, and quantification of tissue androgen levels (see Methods section). Average weight of biopsies analyzed was 5.99 ± 2.76 mg SD. Red India ink, clearly visible histologically, denotes the transition zone.[5] A millimeter rule is at right.*

Sampling Variability

To evaluate the effect of sampling variability on tissue hormone levels, 4 patients who underwent adenomectomy had 10 biopsies taken randomly from various areas of the excised prostate specimen. Each biopsy was assayed separately. The tissue androgen levels were expressed in nanograms of testosterone or DHT per gram of wet weight of prostatic tissue; estradiol levels were undetectable in all the specimens. The first 3 patients in Table I were untreated and the fourth was receiving chronic finasteride therapy. The tissue weights in this study (range 2.7 to 9.5 mg) were similar to the weights recorded in the other two studies.

The results of the 10 testosterone and DHT assays are shown in Table I for each of the 4 patients. Despite considerable sampling variability, no overlap of any value was found for testosterone or DHT between the three untreated men and the man receiving chronic finasteride therapy. For example, the tissue DHT levels ranged from 2.66 to 24.45 ng/g in the 3 untreated men; in the man receiving chronic finasteride therapy, the 10 assays yielded results ranging from 0.09 to 0.73 ng/g. Thus, the sizable coefficients of variation (0.23 to 0.61) did not prevent complete separation of all DHT assays

TABLE I. *Sampling variability of hormone levels in prostatic tissue*

Patient Age (yr)	Biopsy Weight* (mg)	Testosterone (ng/g)	Dihydrotestosterone (ng/g)
66	4.6 ± 1.0 (3.0–6.2)	0.67 ± 0.47 (0.15–1.63; 0.71)	9.12 ± 5.61 (5.17–24.45; 0.61)
84	3.6 ± 0.8 (2.7–5.0)	0.64 ± 0.31 (0.17–1.15; 0.48)	5.99 ± 1.38 (3.79–7.61; 0.23)
92	6.7 ± 1.4 (5.1–8.8)	0.26 ± 0.21 (0.02–0.72; 0.81)	4.53 ± 1.58 (2.66–7.26; 0.34)
72	6.9 ± 1.2 (6.0–9.5)	2.54 ± 0.49 (1.69–3.17; 0.19)	0.42 ± 0.19 (0.09–0.73; 0.45)

Data presented as the mean ± SD, with the range and coefficient of variation (SD/mean) in parentheses.
** 10 biopsies analyzed for each patient.*

from the three untreated men versus the man receiving chronic finasteride therapy. Similar results were found for the tissue testosterone levels.

Finasteride Effect

In Figure 2A, the serum testosterone and DHT levels are shown for the control patients versus the men receiving chronic finasteride therapy. The median levels of serum testosterone were not significantly different between the groups. However, the median DHT levels were markedly suppressed in the men taking finasteride (0.14 ng/mL) compared with the untreated men (0.43 ng/mL) ($P < 0.01$).

In Figure 2B, the prostatic tissue levels of testosterone and DHT are shown for the control patients versus the men receiving chronic finasteride therapy. In the untreated men, the tissue levels of DHT were three to four times higher than the tissue levels of testosterone. In the finasteride-treated patients, the median levels of DHT were markedly decreased, from 4.9 ng/g in the control patients to 1.0 ng/g in the finasteride-treated patients ($P < 0.01$). The median levels of tissue testosterone were markedly increased, from 1.5 ng/g in the control patients to 3.6 ng/g in the finasteride-treated patients ($P < 0.01$).

When comparing the DHT levels in the control and finasteride-treated groups, the median differences for the tissue levels (approximately five times) were greater than the differences in the serum levels (approximately three times).

Saw Palmetto Effect

In the SPHB trial at baseline, the median tissue DHT levels in the two groups were similar: 6.49 ng/g in the SPHB group and 5.43 ng/g in the placebo group. The difference was not significant. The median tissue testosterone level was 1.62 ng/g and 1.38 ng/g for the SPHB group and placebo group, respectively. Again, the difference was not significant. Only the DHT levels are shown in Table II and Figure 3, since the testosterone levels exhibited no significant change after treatment. Also, only the tissue levels are shown, since in an earlier report,[4] the serum levels of both testosterone and DHT did not change significantly after treatment.

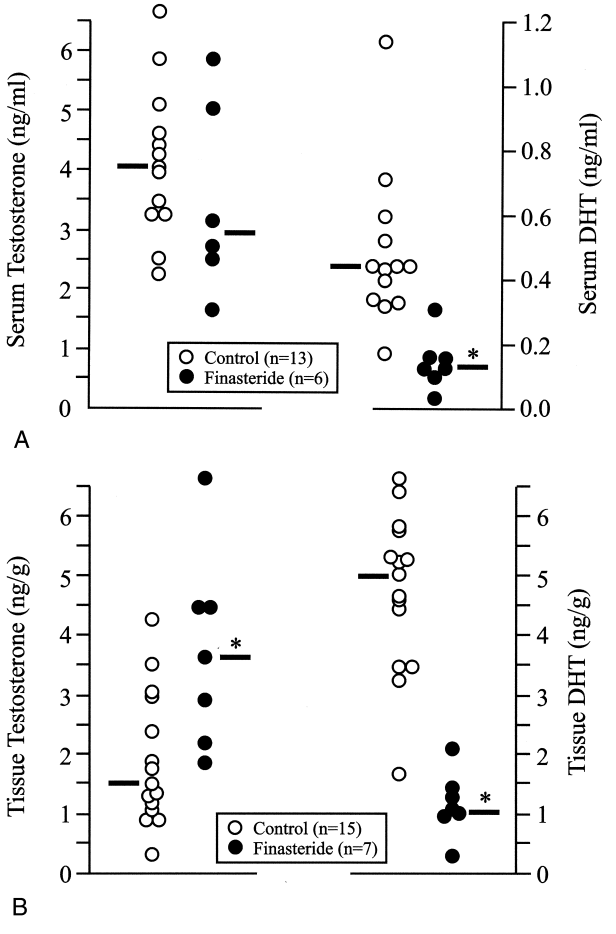

FIGURE 2. *Finasteride effect. Testosterone and DHT levels in (A) serum and (B) prostate biopsies in control and treated patients. Finasteride treatment results in marked suppression of DHT levels in serum and prostatic tissue and marked elevation in tissue testosterone levels. Dark lines indicate median values and asterisks indicate statistically significant difference (*$P < 0.05$*).*

In Figure 3, the change from baseline in the DHT tissue levels is shown for each patient; absolute values are shown in Table II. For the placebo group, no significant change was seen between the baseline (5.43 ng/g) and 6-month (4.87 ng/g) levels. However, for the SPHB group, a significant decrease in tissue DHT levels from baseline (6.49 ng/g) to 6 months (4.40 ng/g) was observed ($P =$

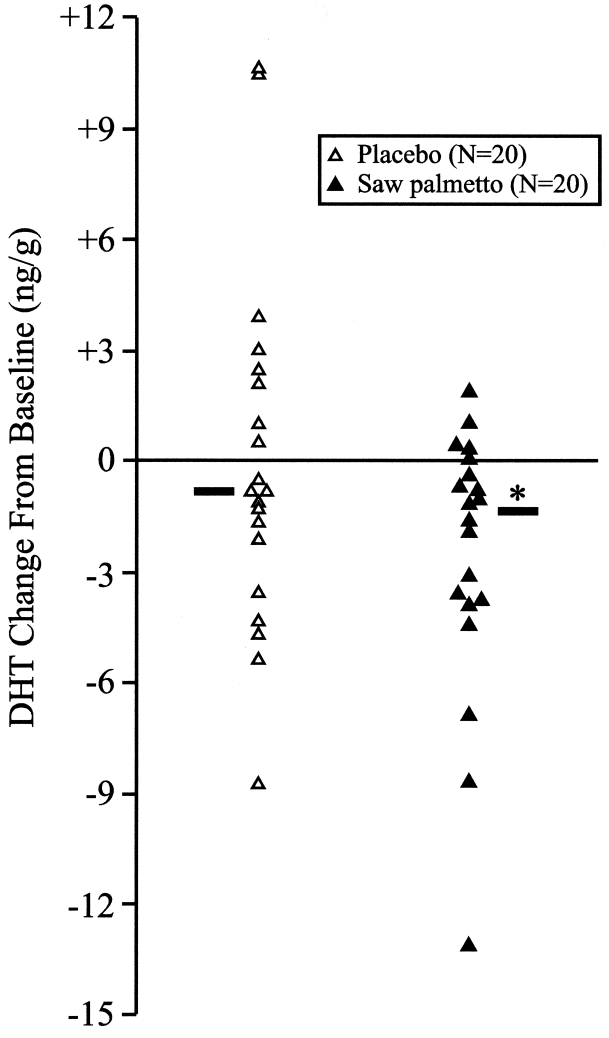

FIGURE 3. *Saw palmetto effect. Change from baseline in tissue DHT levels in placebo and SPHB groups after 6 months of treatment. Median baseline values were 6.49 ng/g for the SPHB group and 5.43 ng/g for the placebo group. SPHB treatment resulted in a 32% median decline in DHT levels in prostatic tissue (see text). Dark lines indicate median value and asterisk indicates statistically significant change from baseline (P = 0.005).*

0.005, signed-rank test). In a separate analysis, the median change in the tissue DHT values for the SPHB group (1.38 ng/g) did not differ significantly from the corresponding change in the placebo group (0.87 ng/g) (*P* value not significant by the rank-sum test). The correction of the tissue DHT levels for the epithelial content of each prostate[4] did not clarify the results further, and no correlation was found between epithelial involution and DHT suppression. Overall, 12 patients in the placebo group and 16 in the SPHB group exhibited a treatment-related decline in tissue DHT levels.

At baseline, the coefficient of correlation between the serum and tissue DHT levels for all 40 men was $r = 0.23$ (*P* value not significant).

COMMENT

DHT is the major androgen in the human prostate and is required throughout life for the growth and maintenance of the gland.[6] Within the prostate, DHT is derived from testosterone, the conversion catalyzed by the enzyme 5-alpha reductase (type 2). Inhibition of 5-alpha reductase by drugs such as finasteride effectively ablates this pathway. The drug-induced decline in serum DHT levels follows the primary event (ie, decreased production of DHT within the prostate and, to a lesser extent, other end organs).[15] In adult men, prostatic tissue levels of DHT are reduced and testosterone levels are increased within a few days of oral administration of 5-alpha reductase inhibitors; both changes are profound, yielding tissue androgen levels readily differentiable from those seen in untreated men.[16]

Direct measurement of DHT deprivation within the prostate has, with rare exception,[17] been accomplished by the study of relatively large masses of tissue (0.2 to 1.0 g or more) surgically excised from treated subjects.[16] Of necessity, controls for such studies have been separate patients who were not treated. In the present study, we demonstrated that target-organ assay may be accomplished using biopsy specimens weighing only 5 to 10 mg. A biopsy approach offers the advantage of serial in situ sampling within the same patients, before and after treatment. The safety of transrectal ultrasound-guided prostate needle biopsy has been previously demonstrated.[4]

Although sampling variability is a concern with such small specimens (Table I), the results obtained here (Figs. 2 and 3) were similar to the results obtained in studies using large surgical specimens.[16] The similarity holds true for both absolute tissue levels and treatment-induced differences. Using biopsy material, the difference in the median tissue DHT levels from finasteride-treated versus untreated men was statistically significant ($P < 0.01$), and little overlap was found among the individual patient values (Fig. 2B). Thus, the magnitude of the finasteride effect far exceeds that of the sampling variability.

To evaluate the possibility that saw palmetto extract functions in vivo as a mild inhibitor of 5-alpha reductase, we measured the tissue DHT levels in men with symptomatic BPH before and after 6 months of treatment with an SPHB or placebo. In this randomized clinical trial,[4] administration of SPHB caused tissue DHT levels to decrease after 6 months to 4.40 ng/g, a 32% decline from the baseline value ($P < 0.005$) (Fig. 3). Since epithelial contraction is known to occur after saw palmetto treatment,[4] the possibility also existed that the DHT change was secondary to the loss of functional epithelium, which could be the result of some mech-

TABLE II. *Prostatic tissue levels of dihydrotestosterone (ng/g)*

Saw Palmetto Group			Placebo Group		
Pt. No.	Baseline	6 Mo	Pt. No.	Baseline	6 Mo
1	7.63	6.83	7	8.73	4.04
2	8.45	4.64	9	4.29	4.78
3	14.36	13.27	10	3.16	7.12
4	12.72	4.02	11	13.68	4.96
8	6.07	4.12	13	11.85	6.51
12	8.29	4.38	15	3.92	3.07
14	9.70	6.13	19	7.46	3.90
16	6.02	4.42	22	3.48	5.97
17	4.87	5.01	27	2.35	5.36
18	3.41	3.03	28	5.54	3.89
20	8.26	3.82	29	4.32	6.40
21	3.96	4.32	31	7.49	18.18
23	19.69	6.55	34	4.62	4.12
24	3.67	5.55	35	8.99	4.64
26	3.54	4.54	36	6.48	5.29
30	11.07	4.15	37	5.32	15.78
33	6.72	7.13	39	6.23	4.10
38	4.49	3.76	40	5.69	6.65
41	6.25	3.11	42	4.51	3.64
44	4.25	3.08	43	5.27	4.09
Median	6.49	4.40	Median	5.43	4.87

KEY: Pt. No. = patient number.

TABLE III. *In vivo effects of finasteride vs. saw palmetto extract**

	Finasteride	Saw Palmetto
Serum		
PSA	50% decrease[5,18,19]	No change[4,10,22]
DHT	70% decrease[5,18]	No change[4,10]
Testosterone	Slight increase[18]	No change[4,10]
Prostate gland		
Volume	20% decrease[5,18]	No change[3,4,22]
Epithelium (%)	55% decrease[5]	40% decrease[4]
DHT	80% decrease[5]	32%, 50% decrease[†,7]
Testosterone	5–10× increase[5]	No change, 125% increase[†,7]
Apoptosis	Increase[19]	No change[4]
Cell proliferation	No change[21]	No change[4]
Androgen receptors	Unknown	No change[4]

KEY: PSA = prostate-specific antigen; DHT = dihydrotestosterone.
** Approximate change from baseline during treatment of men with symptomatic BPH; where a percentage of change is given, $P < 0.05$.*
† Data from present study.

anism other than 5-alpha reductase inhibition (eg, androgen receptor blockade). However, we observed no correlation in these patients between epithelial contraction and tissue DHT levels. Thus, the present data must be regarded as compatible with, but not proof of, the 5-alpha reductase hypothesis. Another possible explanation for these differences could be a "regression to the mean" phenomenon; this study was exploratory and not powered specifically to test the tissue DHT levels. On the basis of the present data, the first of its kind available, a study with a larger sample size (or different sampling technique) could be designed.

In comparison with the finasteride effect on prostatic DHT levels (80% reduction from levels seen in untreated men, Fig. 2B), the saw palmetto effect—although statistically significant—appears to be modest, both in terms of the nadir value and the percentage of reduction from control. Furthermore, the tissue testosterone levels, which were markedly elevated in the finasteride-treated men (Fig. 2), were unchanged by treatment with SPHB. Serum DHT levels, which characteristically decline

by approximately 70% with finasteride treatment,[18] were unchanged during the 6 months of saw palmetto treatment.[4] Also, the prostate-specific antigen levels and prostate volume, which after finasteride treatment decreased by approximately 50% and 20%, respectively, did not decrease with saw palmetto treatment.[4,18,19] The other tissue effects examined in the SPHB trial included apoptosis, cell proliferation, and androgen receptor expression.[4] None of these was affected by SPHB. Finasteride is believed to increase apoptosis,[20] but not to change the rate of cell proliferation,[21] and it is without known effect on androgen receptors.

In Table III, the in vivo effects of finasteride versus saw palmetto extract demonstrated by us and other investigators are listed. The present DHT data lend qualitative support to the work of Di Silverio and associates,[7] who found a 50% decrease in prostate DHT levels after saw palmetto treatment.[7] However, the present testosterone results (ie, no change after saw palmetto treatment), were at variance with that same report, which showed a 125% increase ($P < 0.01$) in tissue testosterone levels.[7] These findings deserve additional study, since, if confirmed, they would strengthen the hypothesis that saw palmetto functions in vivo as an inhibitor of 5-alpha reductase. A trial comparing the clinical effects of finasteride and a saw palmetto extract was conducted recently in Europe, but the absence of a placebo control group makes interpretation of the results problematic.[22]

Since inhibition of 5-alpha reductase is an initiating event, and the other changes follow, the above data are compatible with the possibility that saw palmetto extract functions in vivo as a mild inhibitor of 5-alpha reductase. However, any stronger statement is prevented by the possibility that the observed differences seen in the present study (Fig. 3) might have been caused by the sampling error inherent in the method (Table I). Conclusive proof of this action must await larger studies, longer patient follow-up, and more interval determinations of androgen levels than available in this pilot project. The use of 18-gauge needle biopsy specimens for quantitative serial evaluation of tissue androgen status in situ appears to be valid and may have application to the study of future prostate therapies.

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