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Effects of the 5α-reductase inhibitor finasteride on serum levels of gonadal, adrenal, and hypophyseal hormones and its clinical significance: A prospective clinical study

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In the present study, we investigated the effects of a steroid 5α-reductase inhibitor, finasteride, when given orally (5 mg/day), on the serum levels of gonadal, hypophyseal, and adrenal hormones and the clinical significance of these effects. Forty-eight patients with a mean age of 63 (range 49–81) were included in the study. All patients had symptoms of benign prostatic hyperplasia. Serum levels of testosterone, dihydrotestosterone, follicle-stimulating hormone (FSH) luteinizing hormone (LH), prolactin, aldosterone, cortisol, and dehydroepiandrosterone were determined before the study. The degree of symptoms in each patient and serum prostate specific antigen levels were determined together with uroflowmetric studies. Sexual status of the patients was also assessed with a self-administered questionnaire. All patients received finasteride, 5 mg/day, for 6 weeks. All of the above mentioned studies were repeated at month 3 and month 6. All of the patients had baseline hormonal values within the normal range. At month 3, the dihydrotestosterone level decreased by 60%, while the testosterone level increased by 15%. FSH and LH levels decreased by 24% and 16%, respectively. The changes in the serum levels of these hormones were further evident at month 6. No significant changes were noted in the serum levels of prolactin, aldosterone, cortisol, and dehydroepiandrosterone. Thirty-six patients (75%) were judged to be potent before the treatment. Finasteride caused erectile dysfunction in 8 patients (22%) by month 3 and in 12 (33%) by month 6. A substantial improvement was noted in symptoms of benign prostatic hyperplasia in all patients. The serum prostate specific antigen level decreased by 42% and 50% at month 3 and at month 6, respectively. Continued administration of finasteride, 5 mg/day alters the serum levels of testosterone, dihydrotestosterone, FSH, and LH significantly. Finasteride also causes sexual dysfunction in a substantial number of patients and should be offered with caution to patients who have an active sexual life. (*Steroids* **63**:208–213, 1998) *© 1998 by Elsevier Science Inc.*

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Introduction

Benign prostatic hyperplasia (BPH), a condition characterized by a proliferation of prostatic tissue, occurs in most men over 40 years of age.[1,2] At age sixty, approximately half of all men have histologic evidence of BPH, and by age eighty, it is evident histologically in almost all men.[3] Enlargement of the prostate gland often results in anatomic obstruction of the urethra and leads to obstructive and irritative symptoms.[4]

Although the etiology of BPH is still incompletely understood, it is evident that the presence of androgens is necessary for its development. Males castrated before puberty or males with congenital 5α-reductase deficiency do not develop BPH.[5] It is also known that enlarged prostates regress after orchiectomy. This suggests that androgens, especially the 5α-reduced testosterone (T) metabolite dihydrotestosterone (DHT), play a prominent role in the pathogenesis of BPH. The major androgen in the plasma is testosterone. However, in most target tissues, including the prostate gland, DHT is quantitatively the major androgen as well as the active form of testosterone.

Finasteride is a novel 4-azasteroid that inhibits intracellular conversion of testosterone to DHT by inhibiting the steroid 5α-reductase selectively.[6] Finasteride treatment results in a decrease in the prostatic DHT level which is reported to be associated with a decrease in prostatic size.[7] After it was approved for the treatment of BPH, several

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clinical studies documented that finasteride not only decreased prostatic size but also improved symptoms in men with BPH.[8,9]

Although efficacy and safety of finasteride therapy for BPH have been studied extensively,[10–12] few studies deal with its effects on circulating levels of certain hormones[13] and on sexual functions of men.[14] The main objective of the present study was to investigate the effects of finasteride on serum levels of gonadal, adrenal, and hypophyseal hormones and to determine the clinical significance of these effects.

Experimental

The population studied consisted of 48 consecutive men 49 to 81 years old (mean 63 years) presenting with symptoms of benign prostatic hyperplasia. All patients were ambulatory and in good general physical and mental health. All patients with a suspicious digital rectal examination (DRE) and/or serum prostate specific antigen (PSA) level above 4 ng/mL (Hybritech, Tandem-R) underwent transrectal ultrasonography (TRUS) guided, sextant biopsies of the prostate gland. Patients whose biopsy documented prostate cancer were not included in the study. Patients with other diseases causing bladder outlet obstruction, (more than 150 mL residual urine, serum creatinine level greater than 1.5 mg/dL, or liver function tests out of the normal range) as well as those who had an indwelling urethral catheter for chronic urinary retention were also excluded from the study. Intravenous urograms were obtained from all patients to evaluate the urinary system. Patients receiving concurrent barbiturates, heparin, warfarin, theophylline, antiarrhythmic agents and drugs with androgenic or antiandrogenic properties were excluded from the study as well. Informed consent was obtained in advance from the participating patients.

Hormonal evaluation for the present study included determination of serum levels of T, DHT, dehydroepiandrosterone (DHEA), cortisol (C), aldosterone (A), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). No dietary restrictions were applied to the patients. All blood samples for endocrine studies were obtained at 8:00 a.m. after overnight fasting.

Sexual functions of the patients were evaluated also. The brief sexual inventory developed by O'Leary et al. was translated to Turkish, and the patients were asked to answer this questionnaire.[15] The questionnaire included a total of 11 self-administered questions about sexual drive, erections, ejaculation, problem assessment, and overall satisfaction (Table 1). Each question was scored from 0 to 4, providing a total score ranging from 0 to 44. Partner satisfaction was not considered in this context. The patients were defined as potent if they had the ability to achieve erection sufficient for penetration and had intercourse at least once in the past 30 days.

Symptoms of BPH were defined and quantified using a self-administered urinary symptom questionnaire described by Boyarsky et al.[16] and modified and validated by Bolognese et al.[17] This

Table 1 Brief Sexual Function Questionnaire Used in the Present Study[15]

Sexual drive					
1. During the past 30 days, on how many days have you felt sexual drive?	no days	only a few days	some days	most days	almost every day
	0	1	2	3	4
2. During the past 30 days, how would you rate your level of sexual drive?	none at all	low	medium	medium high	high
	0	1	2	3	4
Erections					
3. Over the past 30 days, how often have you had partial or full erections when you were sexually stimulated in any way?	not at all	a few times	fairly often	usually	always
	0	1	2	3	4
4. Over the past 30 days, when you had erections, how often were they firm enough to have sexual intercourse?	0	1	2	3	4
5. How much difficulty did you have getting an erection during the past 30 days?	no erections	a lot of difficulty	some difficulty	little difficulty	no difficulty
	0	1	2	3	4
Ejaculation					
6. In the past 30 days, how much difficulty have you had ejaculating when you have been sexually stimulated?	no sexual stimulation	a lot of difficulty	some difficulty	little difficulty	no difficulty
	0	1	2	3	4
7. In the past 30 days, how much did you consider the amount of semen you ejaculate to be a problem for you?	did not climax	big problem	medium problem	small problem	no problem
	0	1	2	3	4
Problem assessment					
8. In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?	big problem	medium problem	small problem	very small problem	no problem
	0	1	2	3	4
9. In the past 30 days, to what extent was your ability to get and keep erections considered a problem?	0	1	2	3	4
10. In the past 30 days, to what extent have you considered your ejaculation to be a problem?	0	1	2	3	4
Overall satisfaction					
11. Overall, during the past 30 days, how satisfied have you been with your sex life?	very dissatisfied	mostly dissatisfied	equally satisfied and dissatisfied	mostly satisfied	very satisfied
	0	1	2	3	4

symptom scoring questionnaire was translated and adapted to Turkish as well. The total symptom score was computed as the sum of the following nine symptoms: impairment in size and force of urinary stream, hesitancy or delay in initiating urination, dribbling, interruption in urinary stream, feeling that the bladder is incompletely emptied, straining to start urine flow, urgency, wetting clothes, and dysuria. The obstructive symptom score was computed as the sum of the scores of the first five of these symptoms. Each question was scored from 0 (never) to 6 (always), providing a range for the total symptom score between 0 and 54, and for the obstructive symptom score between 0 and 30. Maximum and mean urinary flow rates were also obtained. Uroflowmetric studies were repeated if the voided urine volume from which urinary flow rates were obtained was less than 150 mL.

All patients received finasteride, 5 mg daily, for 6 months. Five mg is the approved therapeutic dosage of finasteride for the treatment of BPH. Patient compliance was evaluated by tablet count.

All of these baseline studies, together with complete physical examination including digital rectal examination, complete blood count (CBC), serum multiple analysis (SMA), including kidney and liver function tests, and serum PSA determinations, were repeated at month 3 and month 6.

Data are presented as the mean ± SD. The statistical analyses were performed by one-way analysis of variance, the Mann-Whitney 2-sample test, and the Wilcoxon nonparametric test for pairs. The SPSS (Statistical Programme for Social Sciences) for Windows software was used for the calculations.

Results

Baseline and three months' evaluations were available for all patients. The sixth month evaluation was not available for 4 patients who gave up finasteride use after 3 months of medication and underwent surgery. We did not encounter any changes in the CBC and SMA parameters at both month 3 and month 6.

All 48 patients had baseline hormonal values within the normal range accepted for adult males (Table 2). After 3 months of finasteride use a 15% increase was noted in T levels ($p < 0.05$) and this increase reached 26% at month 6 ($p < 0.01$). However, all patients still had T values within the normal range both at month 3 and month 6. DHT levels decreased by more than 60% in all patients at month 3, and the difference from baseline was statistically significant ($p < 0.001$). At month 6 however, the decrease in DHT levels reached 75% ($p < 0.001$). It must be noted that the decrease in DHT level was uniformly observed in all patients, and both month 3 and month 6 values of all patients were below the normal range, unlike the T levels.

A slight but statistically insignificant decrease was noted in DHEA levels at both month 3 and month 6 ($p > 0.05$). It appeared that C and A levels were not affected by finasteride use since no significant change was noted in serum levels of these two hormones throughout the study period ($p > 0.05$ for all comparisons).

Although apparent decreases were noted in PRL levels both at month 3 and month 6, neither reached statistical significance ($p > 0.05$ for both). A steady decrease was noted in both FSH and LH levels also. While at month 3 the decrease in FSH level was 24% ($p < 0.01$), it was 40% at month 6 ($p = 0.001$). At month 3 and month 6, 16% ($p < 0.05$) and 25% ($p < 0.01$) decreases were noted in LH levels, respectively. However, the levels of these two hor-

Table 2 Baseline, Month 3, and Month 6 Mean Serum Levels ± SD of the Hormones Investigated in this Study

Hormone (range)	T (3–10 ng/mL)	DHT (30–88 ng/dL)	DHEA (0.5–5.5 ng/mL)	C (7–21 μg/mL)	A (10–160 pg/mL)	FSH (0.9–9.8 mLU/mL)	LH (2.2–12 mLU/mL)	PRL (2–15 ng/mL)
Baseline	3.82 ± 1.24	43.20 ± 8.71	3.21 ± 1.78	20.01 ± 9.19	140.09 ± 57.48	9.74 ± 6.19	9.13 ± 4.42	10.42 ± 7.41
Month 3	4.44 ± 1.40	26.78 ± 5.19	3.01 ± 1.54	19.52 ± 9.76	150.57 ± 54.58	7.45 ± 5.18	7.65 ± 3.71	8.20 ± 3.56
Month 6	4.82 ± 1.38	10.8 ± 2.8	2.86 ± 1.61	18.39 ± 8.37	122.85 ± 55.94	5.80 ± 2.61	6.80 ± 3.47	7.57 ± 3.86
p value (baseline–month 3)	**0.015**	0.0001	0.426	0.852	0.232	**0.0017**	**0.0105**	0.111
p value (baseline–month 6)	**0.005**	**0.0001**	0.137	0.364	0.151	**0.0010**	**0.0070**	0.055

Confidence interval: 95%.

mones also remained within the normal range throughout the study.

The mean baseline PSA level of 48 patients was 1.99 ± 1.61 ng/mL. With finasteride use, PSA levels decreased to 1.15 ± 1.09 ng/mL at month 3 and to 0.79 ± 0.98 ng/mL at month 6. The decreases in PSA levels at month 3 and month 6 were equivalent to 42% and 50%, respectively, and both changes from baseline were statistically significant ($p < 0.001$ for both).

Baseline, month 3, and month 6 mean ± SD of the sexual function scores of the patients are presented in Table 3. After analyzing the baseline data of the sexual function questionnaire, 36 patients (75%) were judged to be potent. After 3 months of treatment, a decrease by 10.3% in total score was observed and finasteride caused loss of erectile function in 8 of 36 potent patients (22%). Four of these patients (11% of potent patients receiving finasteride) gave up medication and underwent surgery (TURP) after 3 months of finasteride use because of its side effects on sexual desire and erections. By month 6, the decrease in total sexual function score reached to 14.3% and 4 more patients suffered from loss of erectile function. Overall, the number of patients who lost their erectile function after finasteride use at month 6 reached 12 (33%). Both at month 3 and at month 6 the decrease in the sore of sexual drive was most significant followed by the decrease in the scores of erections. Additionally, gynecomastia developed in 2 (4%) of these patients by month 6. The changes in total sexual function scores from baseline scores after 3 months and 6 months of finasteride use were both significant ($p < 0.01$ for both comparisons).

The total symptom score improved significantly over the course of the study (Table 4). At month 3, a mean decrease of 5.4 points was noted from the baseline of 13.3 points ($p < 0.001$). With an additional 1.5 points decrease during the next 3 months, the total symptom score reached 6.4 points at month 6 ($p < 0.001$). A similar improvement was evident in the obstructive symptom score as well. At month 3, it decreased to 5.1 points from a baseline of 7.8 points ($p < 0.001$) and at month 6, to 3.9 points ($p < 0.001$).

Maximum urinary flow rate increased from the baseline mean of 10.0 mL/s to 12.7 mL/s at month 3 and to 14.5 mL/s at month 6. These changes were statistically significant ($p < 0.01$ for both). Mean urinary flow rate also increased from the baseline mean of 4.9 mL/s to 6.4 mL/s at month 3 and to 7.0 mL/s at month 6. Both changes from baseline were significant ($p < 0.01$).

Discussion

The hypothalamic-pituitary-gonadal axis plays an important role in prostatic growth.[18] Gonadotrophin releasing hormone secreted from hypothalamic neurones in the preoptic area, passes to the anterior pituitary through hypophyseal portal veins. Gonadotrophin releasing hormone stimulates the release of LH, FSH, and ACTH. LH, in turn, causes testicular Leydig cells to produce T. Other androgens are also secreted, but at much lower levels. In males, the principal mechanism of controlling LH release is feedback inhibition by T on the hypothalamus and anterior pituitary. Testosterone is metabolized to dihydrotestosterone by tissues possessing 5α-reductase, and 90% of prostatic androgens consist of DHT, which is mainly derived from testicular androgens. However, a small proportion may be derived from adrenal androgens.[19] Both T and DHT bind to the same androgen receptor.[13] Finasteride is a pure and competitive inhibitor of 5α-reductase and has no affinity for the androgen receptor.[13]

Early studies in healthy volunteers showed that finasteride (0.5 or 1.5 mg at a single oral dose) reduced plasma DHT levels by 50% within 24 h.[19] The lowest dose of finasteride, which reduced plasma DHT levels marginally was, 0.2 mg. Recovery of DHT levels to baseline was slow and took up to 7 days.[19] Administration of finasteride (5 to 100 mg) resulted in a reduction of plasma DHT levels by about 75% to 80%.[13] Plasma DHT levels were reduced by a mean of 61 to 63% following continued oral administration of finasteride, 1 or 10 mg/day for 7 days.[20] In single-dose studies on healthy volunteers, no clear changes in circulating testosterone levels were observed 24 h after oral administration of 10 to 100 mg of finasteride[21] and 4 to 72 h after oral finasteride, 5 to 100 mg.[20] It was reported that finasteride 5 mg/day for 28 days did not affect circulating T levels either.[19] In these studies, no changes in circulating LH, FSH, C, and DHEA levels were observed after single oral finasteride doses of 5 to 100 mg.[20] However, in a recent study, it was shown that finasteride reduced the circulating levels of both DHEA and DHEA sulfate.[22] In the present study, continued administration of 5 mg finasteride for 3 months resulted in a 60% decrease in plasma levels of DHT. Unlike previous studies, we observed a 15% increase in T levels as well as a 24% decrease in FSH levels and a 16% decrease in LH levels. All of these changes were statistically significant. After 6 months, the effects of finasteride on DHT, T, FSH, and LH levels were further evident. How-

Table 3 Mean ± SD of Baseline, Month 3, and Month 6 Sexual Function Questionnaire Scores

	Baseline (48 patients)	Month 3 (48 patients)	*p* Value (baseline–month 3)	Month 6 (44 patients)	*p* Value (baseline–month 6)
Sexual drive (0–8)	4.9 ± 2.4	4.1 ± 1.8	<0.001	3.8 ± 2.2	<0.001
Erections (0–12)	7.2 ± 3.9	6.2 ± 3.1	<0.01	5.9 ± 2.7	<0.01
Ejaculation (0–8)	4.9 ± 1.7	4.4 ± 2.1	>0.05	4.2 ± 1.6	<0.05
Problem assessment (0–12)	8.4 ± 3.3	6.8 ± 2.7	<0.01	6.5 ± 3.1	<0.01
Overall satisfaction (0–8)	4.1 ± 2.9	3.7 ± 2.3	<0.05	3.4 ± 1.9	<0.01
Total (0–44)	26.6 ± 9.8	24.8 ± 7.2	<0.01	22.3 ± 8.7	<0.01

Confidence interval: 95%.

Table 4 Mean ± SD of Baseline, Month 3, and Month 6 Symptom Scores and Urine Flow Rates

	Baseline	Month 3	*p* Value (baseline–month 3)	Month 6	*p* Value (baseline–month 6)
Total symptom score (units)	13.3 ± 5.5	7.9 ± 4.8	<0.001	6.4 ± 4.7	<0.001
Obstructive symptom score (units)	7.8 ± 4.7	5.1 ± 3.9	<0.001	3.9 ± 3.6	<0.001
Maximum urinary flow rate (mL/s)	10.0 ± 4.8	12.7 ± 6.4	=0.002	14.5 ± 7.2	<0.001
Mean urinary flow rate (mL/s)	4.9 ± 2.4	6.4 ± 3.3	=0.003	7.0 ± 3.5	<0.001

Confidence intervals: 95%.

ever, it must be noted that T, FSH, and LH levels remained within the normal range, even after 6 months of finasteride use. PRL levels were also affected by finasteride use, but only marginally, and this effect did not reach statistical significance. We did not observe any significant changes in plasma levels of adrenal steroids: C, DHEA, and aldosterone, after 6 months of 5 mg finasteride use. Neither present nor previous studies used pooled analysis for hormone studies. We obtained the blood samples uniformly at 8:00 a.m. from all patients after overnight fasting. However, pooled analysis of several samples taken in a day may better reflect circulating levels of these hormones especially those of LH and FSH since it is known that there occur more than 8 secretory pulses of gonodotropins in adult men in a day. Nevertheless, the results of the present study confirm the potency of finasteride in inhibiting 5α-reductase and lowering plasma levels of DHT. However, the changes in the plasma levels of FSH, LH, and PRL also suggest that finasteride may have a central effect in the brain, which is possibly at the hypothalamic level.

Many studies have shown that decreased sexual function commonly occurs with aging and BPH is a benign condition which effects aging men.[22,23] Quality of life was shown to be an important outcome in BPH, and sexual function appears to be of major importance for these patients.[24] It is known that T deficiency decreases libido and impairs erectile function in men, and replacement therapy can restore sexual desire and potency.[25] Most evidence indicates central nervous system mediation of these effects. Since the human brain possesses 5α-reductase also, the involvement of either T or its metabolite DHT in the maintenance of libido and potency cannot be excluded.

Molecular genetics experiments suggest that there exist at least two isoenzymes of 5α-reductase in man.[26,27] Finasteride is now known to primarily inhibit the type 2 isoenzyme.[26] It is possible that finasteride can cross the blood–brain barrier, as it is a lipid soluble 4-aza steroid. However, Thigpen et al.[28] showed that the dominant isoenzyme in the brain was type-1, and Cunningham and Hirshkowitz[14] reported that finasteride did not inhibit 5α-reductase in the brain enough to impair sleep related erections. Finasteride may have local effects in erectile tissues of the penis as well. Recently, Seyam et al.[29] demonstrated that, at high doses, finasteride impaired erection through altering the nitric oxide synthetase activity in the penis.

In the present study finasteride caused decrease in the scores of sexual drive, erections, ejaculation, problem assessment, overall satisfaction, and total score as well. The decrease in sexual drive and erections were most significant. Considering the hormonal effects of finasteride the decrease in libido can be explained by its effects in the central nervous system. However, loss of erections can either be mediated via central effects of finasteride or its local effects in the penis may also contribute.

Sexual dysfunction after finasteride use was reported to be between 2.1% and 15.8% in different series.[7,10–12] In the present study, sexual dysfunction following finasteride, 5 mg/day, was found to be 22% at month 3 and 33% at month 6. This is higher than in any previous report.

Like many previous placebo controlled studies, the present study also confirms the effectiveness of finasteride in improving symptoms of BPH.[8–12] The decreases in serum PSA values that paralleled the improvement in BPH symptoms indicates that finasteride decreases prostatic size. Unfortunately, the present study did not document the decrease in prostatic size objectively, as the follow-up TRUS was not available for all patients. However, many other studies have confirmed the effect of finasteride on prostatic size by TRUS. In those studies, the reduction in prostatic size reached 15 to 30% at 6 months and was sustained for up to 5 years, as long as the treatment continued.[8,11,12]

In conclusion, finasteride, an effective medical treatment option for BPH, alters the serum levels of T, DHT, FSH, LH, and to some degree, that of PRL. The effect of finasteride on the sexual functions of men with BPH is not negligible. Although the present study suggests that hormonal effects of finasteride may cause sexual dysfunction, its local effects on the erectile tissues of penis may also be a contributing factor, as proposed by others.[29] We strongly recommend that physicians dealing with BPH should evaluate the sexual functions of their patients thoroughly before instituting finasteride therapy. Those patients with an active sexual life should either not receive finasteride treatment or should be followed closely for any side effects on sexual function.

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