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The Effect of 5 α -Reductase Inhibition With Dutasteride and Finasteride on Bone Mineral Density, Serum Lipoproteins, Hemoglobin, Prostate Specific Antigen and Sexual Function in Healthy Young Men

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Abstract

Purpose—Dutasteride and finasteride are 5 α -reductase inhibitors that dramatically decrease serum levels of dihydrotestosterone. Because androgens affect bone, lipids, hematopoiesis, prostate and sexual function, we determined the impact of 5 α -reductase inhibitors on these end points.

Materials and Methods—We conducted a randomized, double-blinded, placebo controlled trial of 99 men 18 to 55 years old randomly assigned to receive 0.5 mg dutasteride (33), 5 mg finasteride (34) or placebo (32) daily for 1 year. Bone mineral density was measured at baseline, after 1 year of treatment and 6 months after drug discontinuation. In addition, markers of bone turnover, fasting serum lipoprotein concentrations, hemoglobin and prostate specific antigen were measured at baseline, after 26 and 52 weeks of treatment, and again 24 weeks after drug discontinuation. Sexual function was assessed at these points by a validated questionnaire.

Results—Significant suppression of circulating dihydrotestosterone levels with the administration of dutasteride or finasteride did not significantly affect bone mineral density or markers of bone metabolism. Similarly serum lipoproteins and hemoglobin were unaffected. Serum prostate specific antigen and self-assessed sexual function decreased slightly during treatment with both 5 α -reductase inhibitors but returned to baseline during followup.

Conclusions—Profound suppression of circulating serum dihydrotestosterone induced by 5 α -reductase inhibitors during 1 year does not adversely impact bone, serum lipoproteins or hemoglobin, and has a minimal, reversible effect on serum prostate specific antigen and sexual function in normal

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Study received approval from the investigational review boards for human subjects at all sites.

men. Circulating dihydrotestosterone does not appear to have a clinically significant role in modulating bone mass, hematopoiesis or lipid metabolism in normal men.

Keywords

dutasteride; finasteride; bone density; dihydrotestosterone; sexual behavior

Approximately 5% of serum testosterone produced in men undergoes 5α -reduction to form the more potent androgen, dihydrotestosterone.¹ During embryogenesis DHT has an essential role in the formation of the male external genitalia, and in the adult DHT acts as the primary androgen in the prostate and hair follicles.²

Two isozymes of 5α -reductase have been identified in humans.³ The type 2 5α -reductase found primarily in the prostate is effectively inhibited by finasteride, which decreases circulating serum concentrations of DHT by approximately 70%.⁴ Long-term administration of finasteride is not associated with harmful effects on androgen responsive end points such as bone mineral density, lipoprotein concentrations or general health.^{5,6} As a result finasteride has been used successfully in large numbers of men for several years for the treatment of benign prostatic hyperplasia,⁷ and in the treatment of male pattern baldness in younger and older men.⁸

Dutasteride inhibits type 1 5α -reductase (found in the skin, gut, liver and other tissues) and type 2 5α -reductase, leading to a 95% decrease in serum DHT concentrations.⁹ In men with BPH a marked decrease in DHT production leads to a 25% reduction in prostate volume, improvement in symptoms associated with BPH, and a significant reduction in the risk of acute urinary retention and the need for surgical intervention with finasteride or dutasteride administration.^{10–12} It is less clear whether the greater DHT suppression resulting from inhibition of both isozymes of 5α -reductase by dutasteride has important effects on other androgen responsive tissues such as bone, lipoprotein metabolism, hemoglobin, PSA and sexual function. Because low serum concentrations of androgens are associated with an increased risk of osteoporosis and fracture, therapy that decreases DHT has the potential to decrease BMD and increase fracture risk.¹³ In addition, the effect of near complete inhibition of DHT production observed with dutasteride might have effects on lipoprotein metabolism, hematopoiesis, PSA and/or sexual function that were not observed with finasteride treatment since these end points are also androgen responsive and finasteride does not completely inhibit DHT synthesis. Therefore, to ascertain the effect of the marked DHT suppression mediated by dutasteride on bone density, lipid metabolism, hematopoiesis, PSA and sexual function, we conducted a randomized, double-blinded, placebo controlled study of the effect of dutasteride, relative to finasteride and placebo, on these outcomes.

SUBJECTS AND METHODS

Subjects

A total of 99 healthy male subjects 18 to 55 years old (mean age 34 ± 8), were enrolled at 7 centers in the United States. Subjects were free of clinically significant conditions as determined by history, physical examination, clinical laboratory test results and semen analysis. Results from this study, including the effect of dutasteride and finasteride on serum hormones and spermatogenesis, were published recently.¹⁴

Subjects who had any significant laboratory abnormalities, an American Urological Association Symptom Index for prostate symptoms score greater than 8, or history of vasectomy were excluded from the study. In addition, subjects were excluded from participation if they were using finasteride, dutasteride, saw palmetto, anabolic steroids, estrogen, corticosteroids, spironolactone, cimetidine, tamsulosin, terazosin or doxazosin. Male

pattern baldness was not an exclusion criterion. All subjects gave informed consent before study participation and the investigational review boards for human subjects approved this study at all sites.

Study Design

This was a randomized, double-blinded, double-dummy, placebo controlled, comparative, parallel group, multicenter study in healthy male subjects. Subjects who met inclusion criteria were randomized by a predetermined schedule with a block size of 3 to receive treatment for 52 weeks consisting of 0.5 mg dutasteride daily plus placebo finasteride daily, or 5.0 mg finasteride daily plus placebo dutasteride daily, or placebo dutasteride and placebo finasteride daily. Study drugs were over encapsulated so that placebo, dutasteride and finasteride appeared the same, and were administered orally once daily for 52 weeks. Treatment compliance was monitored by pill count at clinic visits. Mean compliance ($\pm$ SD) was 99.0% $\pm$ 10.4% for placebo, 99.5% $\pm$ 23.7% for finasteride and 98.9% $\pm$ 19.6% for dutasteride. After the completion of drug exposure, subjects were followed for an additional 26 weeks in a followup period.

Measurements

Bone mineral density was measured at screening, after 52 weeks of treatment and after 24 weeks of followup at the AP lumbar spine (L1–L4) and in the total hip by dual x-ray absorptiometry using Hologic densitometers (Hologic, Waltham, Massachusetts). The bone markers serum osteocalcin, serum bone alkaline phosphatase and urinary N-telopeptide (urine OsteomarkTM) were measured at baseline, at treatment weeks 8, 26 and 52, and at followup weeks 8, 12 and 24 at a single laboratory. Osteocalcin was measured by radioimmunoassay (Diagnostic Systems Laboratories, Inc., Webster, Texas), and the mid range intra-assay and inter-assay CVs were both 7.2%. Bone specific alkaline phosphatase was measured by immunoassay (Metra Biosystems, Mountain View, California), and the mid range intra-assay and interassay CVs were 1.4% and 4.8%, respectively. Urinary N-telopeptide was measured by immunoassay (Wampole Laboratories, Princeton, New Jersey) and corrected for serum creatinine, and the mid range intra-assay and inter-assay CVs were 4.5% and 8.9%, respectively. All hormone measurements were run on the same assay to decrease variability. PSA was measured in serum at baseline, treatment weeks 26 and 52, and followup week 24. Serum lipoproteins were measured on serum after an overnight fast at baseline, treatment weeks 24 and 52, and followup week 24. Samples were analyzed for serum total cholesterol and triglycerides, and HDL and LDL concentrations were calculated. For the assessment of sexual function during treatment we used the validated Brief Sexual Function Inventory.¹⁵ This 5-point Likert scale, 11-question inventory assesses 3 domains of male sexual function (sexual drive, erectile function and ejaculatory function), and also queries subjects about their perception of problems in each area (freedom from problems). It also includes a question regarding overall satisfaction with global sexual function. For purposes of analysis domain subscores are calculated and can be compared over time. Subjects completed this questionnaire at clinic visits at baseline, after 26 and 52 weeks of treatment, and 24 weeks into the followup period.

Statistical Analyses

Data were analyzed using ANOVA, SAS® version 8. Least squares means or geometric least square means and a pooled median baseline were used to determine differences among groups and compared with baseline. The analysis model consisted of treatment, baseline values and test center. Standard diagnostic tools were used to check assumptions of the models, with formal testing of the residual normality. For analysis of the sexual function data, mean scores and standard deviations were computed for ease of presentation, and an extended chi-square

model was used to determine significance among groups at a given point or compared with baseline. For all comparisons $p < 0.05$ was considered significant.

RESULTS

Subjects

A total of 99 subjects, mean age 34 ± 8 years old, were randomized at baseline to receive 0.5 mg dutasteride (33), 5 mg finasteride (34) or placebo (32). As published previously dutasteride and finasteride significantly suppressed serum DHT compared with placebo (dutasteride 94%, finasteride 73%, $p < 0.001$ for both compared with placebo), and transiently increased serum testosterone. However, there was no effect on circulating levels of serum estradiol, luteinizing hormone, follicle-stimulating hormone or sex hormone-binding globulin.¹⁴

BMD and Metabolism

All subjects had normal bone mineral density in gm/cm^2 at baseline in the lumbar spine (placebo 1.096 ± 0.14 , finasteride 1.088 ± 0.15 , dutasteride 1.064 ± 0.14) and in the total hip (placebo 1.064 ± 0.15 , finasteride 1.082 ± 0.13 , dutasteride 1.033 ± 0.12) with no significant baseline differences in BMD parameters among groups.

During treatment mean BMD of the lumbar spine and total hip did not change significantly when considered as a percent change from baseline (fig. 1). Two subjects at 1 site, 1 in the finasteride group and 1 in the dutasteride group, experienced a 20% decrease in bone mineral density between baseline and week 52 of treatment. However, BMD for both of these individuals was markedly increased at baseline, and in neither case did the treatment BMD decrease below the mean for the placebo group or fall outside of the normal range. Followup BMD in these individuals was normal and almost identical to the BMD obtained at the end of treatment. Serum osteocalcin, bone specific alkaline phosphatase (markers of bone formation) and urinary n-telopeptide (a marker of bone resorption) did not significantly change during therapy (table 1).

Lipids, PSA and Hemoglobin

Baseline cholesterol values did not differ significantly among the 3 treatment groups. In addition, there were no significant differences in total cholesterol, HDL cholesterol or LDL cholesterol at any time during treatment or recovery (fig. 2). Serum triglyceride concentrations were also normal at baseline and during treatment in all subjects. However, during recovery 1 subject in the placebo group had a serum triglyceride level of 2,700 but did not complain of any symptoms (eg abdominal pain from pancreatitis) during the visit.

Mean serum PSA decreased with treatment in the finasteride and dutasteride groups at 26 and 52 weeks of treatment ($p < 0.001$, fig. 3). Serum PSA returned to baseline during followup and there were no prostate specific adverse events during the study except 2 episodes of prostatitis on dutasteride which were not considered drug related.

Mean hemoglobin concentrations at baseline did not differ significantly among groups at baseline, during treatment or in recovery (table 2). No trends for an increase in hemoglobin were observed. In only 6 instances did hemoglobin increase above 16.5 gm/dl (hematocrit of approximately 50%) and none of these increases were sustained. Four subjects (1 in placebo, 1 in the finasteride group and 2 in the dutasteride group) had a decrease in hemoglobin below the lower limit of the normal range. However, in no subject did the hemoglobin concentration decrease below 12.8 gm/dl (hematocrit approximately 38%). Moreover, no change was noted in mean platelet counts or white blood cell count and no subject had clinically significant decreases in these cell counts during treatment (data not shown).

Sexual Function

In the finasteride group there were slight, statistically significant decreases in sex drive at week 26 of treatment and during followup, in erectile function after 26 and 52 weeks of treatment, and in freedom from problems with sexual activity at weeks 26 and 52 of treatment (table 3.) In the dutasteride group significant decreases in ejaculatory function and in freedom from problems with sexual activity were noted after 52 weeks of treatment. In contrast, there was no decrease in overall satisfaction with sexual activity during treatment with either medication.

DISCUSSION

This study shows that 1 year of marked suppression of serum DHT from the administration of the 5ARIs finasteride or dutasteride has no clinically significant effect on bone mineral density, markers of bone turnover or serum lipoproteins in normal young men. Since there were no changes in serum estradiol and only a transient increase in serum testosterone, these findings suggest that serum DHT may not be necessary for the maintenance of BMD and likely has no effect on lipoprotein homeostasis in eugonadal men.¹⁴ As a result long-term administration of these agents to men seems unlikely to increase the risk of osteoporosis or cardiovascular disease via alterations in serum lipoproteins.

Studies of drug effects on BMD are difficult due to the slow turnover of bone tissue. This was addressed in this study by using a 1-year duration of drug exposure to allow the detection of changes in BMD that would not be seen with a shorter treatment period. As a result, the lack of significant changes in BMD with treatment with 5ARIs is likely to be a true, although this study was not powered to find small changes in BMD. Similarly long-term administration of finasteride has not been associated with decreases in BMD.⁶ Moreover, the lack of significant changes in the serum and urine bone markers is consistent with a minimal effect on bone metabolism.

The administration of androgens to men with hypogonadism is known to affect serum cholesterol, leading to decreases in total, LDL and HDL cholesterol. Since DHT is a potent androgen, one might expect inhibition of DHT to increase serum HDL. However, finasteride administration has no significant effect on HDL.¹⁶ It was previously unknown whether the administration of a dual 5ARI such as dutasteride would also be lipid neutral since the predominant isozyme of 5 α -reductase in the liver (the site of most cholesterol metabolism) is type I, and type I isozyme is not inhibited by finasteride.³ In this current study we have shown that near complete inhibition of circulating DHT with a dual type 1 and type 2 5 α -reductase inhibitor has no significant effect on total or HDL cholesterol. Therefore, the effects of androgens on lipoprotein metabolism are likely to be largely mediated by testosterone or its active metabolite estradiol rather than by DHT.

As expected in the subjects on active treatment, significant decreases in serum PSA were noted during treatment in this study. These decreases were less than those observed previously in studies of 5ARIs in men with BPH.¹⁷ This difference is likely due to the younger age and lower baseline PSA values of the subjects enrolled in this study compared to men with BPH as well as the relatively high lower limit of quantitation of the assay used. The long-term impact of 5ARIs on the prostate is a subject of much discussion. In particular the Prostate Cancer Prevention Trial showed a 25% decrease in new cases of prostate cancer in older men treated with finasteride therapy.¹⁸ However, this decrease in prostate cancer incidence was partially offset by a slight increase in more aggressive tumors in the group receiving finasteride. Additional studies of 5ARIs for the prevention of prostate cancer, such as the REDUCE study (Reduction by Dutasteride of Prostate Cancer Events) using dutasteride, are under way to determine if chronic 5ARI inhibition might be useful for prostate cancer chemoprophylaxis. No significant effect on hematopoiesis was noted with treatment with either 5ARI. This finding

implies that testosterone or estradiol rather than DHT likely mediates the increase in hemoglobin associated with androgens.

Lastly, slight decreases in sexual function were noted during treatment and these changes were largely reversed during recovery. The clinical relevance of these small reductions in measurements of sexual function is unclear. It is notable that the overall satisfaction score did not change during treatment, implying that the slight changes in sex drive, erectile and ejaculatory function experienced by subjects did not adversely affect global sexual function or sexual satisfaction. In addition, the scores observed in this study on treatment were all within the published normal ranges for men who are free of complaints regarding their sexual function.¹⁵ The chronic use of finasteride in older men with BPH is known to be associated with sexual side effects. In a single large cohort of more than 14,000 patients impotence occurred in 2.1% and was the most commonly reported adverse reaction.⁷ Recently among 4,200 men treated with dutasteride it was demonstrated that sexual function side effects with dutasteride administration were much more common in individuals who also had concomitant testosterone (and/or estradiol) deficiency, demonstrating an interaction between testosterone deficiency and the decreased DHT concentration mediated by 5ARI inhibition.¹⁹ It seems likely that, in contrast with bone and lipoprotein metabolism, the maintenance of sexual function is a result of testosterone and DHT. Since many young men are taking 5ARIs for the prevention of male pattern baldness, more study of the impact of the chronic administration of these agents on sexual function is warranted.

CONCLUSIONS

We have demonstrated that chronic administration of a 5ARI, either dutasteride or finasteride, has no demonstrable effect on BMD, bone turnover or serum lipoproteins, and a small, reversible impact on serum PSA and sexual function. As a result chronic inhibition of 5 α -reductase is unlikely to affect the development of osteoporosis or the risk of cardiovascular disease via alterations in serum lipoproteins in men.

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Abbreviations and Acronyms

5ARI	5 α -reductase inhibitor
BMD	bone mineral density
BPH	benign prostatic hyperplasia
DHT	dihydrotestosterone
HDL	high density lipoprotein
LDL	

low density lipoprotein

PSA

prostate specific antigen

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Fig. 1. Mean percent change ($\pm$ SD) in bone mineral density of lumbar spine (A) and total hip (B) in healthy young men treated with 5 mg finasteride (*Fin*) daily, 0.5 mg dutasteride (*Dut*) daily or placebo (*Pla*) for 52 weeks.

Fig. 2. Mean ($\pm$ SD) serum total cholesterol (A), HDL cholesterol (B) and LDL cholesterol (C) in healthy young men treated with 5 mg finasteride daily, 0.5 mg dutasteride daily or placebo for 52 weeks. Broken lines represent upper (all) and lower (HDL only) limits of normal range.

Fig. 3.

Median serum PSA (25th to 75th percentiles) in healthy young men treated with 5 mg finasteride daily, 0.5 mg dutasteride daily or placebo for 52 weeks. Note that assay sensitivity of 0.5 ng/ml explains why 25th percentiles and medians are same for finasteride and dutasteride during treatment. Asterisk indicates $p < 0.001$ compared with placebo, ϕ indicates $p < 0.05$ compared with placebo.

Table 1

Markers of bone metabolism during treatment

	Treatment			Followup		
	Baseline	Wk 8	Wk 26	Wk 52	Wk 8	Wk 12
Mean $\pm$ SD ng/ml bone alkaline phosphatase:						
Placebo	14.1 $\pm$ 5.9	14.1 $\pm$ 6.9	12.8 $\pm$ 5.0	13.5 $\pm$ 5.9	13.8 $\pm$ 4.7	12.9 $\pm$ 5.0
Finasteride	16.9 $\pm$ 17.6	12.6 $\pm$ 3.4	12.5 $\pm$ 3.7	13.2 $\pm$ 2.9	12.3 $\pm$ 2.6	11.9 $\pm$ 2.9
Dutasteride	12.2 $\pm$ 4.1	12.9 $\pm$ 5.2	12.0 $\pm$ 3.3	12.2 $\pm$ 4.2	12.3 $\pm$ 3.9	12.0 $\pm$ 4.7
Mean $\pm$ SD ng/ml osteocalcin:						
Placebo	11.5 $\pm$ 5.0	10.9 $\pm$ 5.2	11.7 $\pm$ 4.0	10.9 $\pm$ 2.4	12.4 $\pm$ 6.0	12.8 $\pm$ 5.0
Finasteride	12.5 $\pm$ 3.5	11.8 $\pm$ 3.3	11.1 $\pm$ 3.6	10.9 $\pm$ 2.4	12.0 $\pm$ 3.5	12.1 $\pm$ 2.9
Dutasteride	11.6 $\pm$ 4.0	11.5 $\pm$ 4.1	11.4 $\pm$ 3.2	10.8 $\pm$ 3.1	12.8 $\pm$ 3.9	12.9 $\pm$ 4.0
Mean $\pm$ SD nMol/mmol creatinine urinary N-telopeptide:						
Placebo	45.2 $\pm$ 20.3	45.8 $\pm$ 25.7	46.1 $\pm$ 21.5	41.0 $\pm$ 14.8	42.7 $\pm$ 18.2	39.7 $\pm$ 20.7
Finasteride	50.5 $\pm$ 40.1	44.1 $\pm$ 19.3	38.6 $\pm$ 9.8	40.8 $\pm$ 28.9	36.2 $\pm$ 9.3	42.2 $\pm$ 18.0
Dutasteride	39.8 $\pm$ 16.6	40.3 $\pm$ 13.8	38.3 $\pm$ 11.2	37.0 $\pm$ 12.3	38.4 $\pm$ 14.9	35.4 $\pm$ 14.8
						31.3 $\pm$ 13.0

* Compared to placebo and dutasteride $p < 0.05$.

Table 2

Hemoglobin concentrations

	Mean $\pm$ SD		
	Placebo	Finasteride	Dutasteride
Baseline	15.0 $\pm$ 0.8	15.2 $\pm$ 1.0	15.1 $\pm$ 0.7
Treatment wk 26	14.9 $\pm$ 0.8	15.0 $\pm$ 0.8	15.1 $\pm$ 0.9
Treatment wk 52	15.0 $\pm$ 0.9	15.2 $\pm$ 0.8	15.2 $\pm$ 0.9
24 Wks after treatment	15.0 $\pm$ 0.8	15.3 $\pm$ 0.8	15.1 $\pm$ 0.7

Table 3
Sexual function during treatment

	Mean ± SD			
	Baseline	Treatment Wk 26	Treatment Wk 52	Wk 24 Followup
Sex drive (0–8): *				
Placebo	6.53 ± 0.74	6.61 ± 0.87	6.83 ± 0.75	6.78 ± 0.83
Finasteride	6.09 ± 0.82	5.48 ± 0.93 [†]	5.86 ± 0.86	5.74 ± 1.02 [‡]
Dutasteride	6.25 ± 0.74	6.18 ± 0.88	5.89 ± 0.89	6.48 ± 0.80
Erectile function (0–12): §				
Placebo	10.61 ± 0.65	10.70 ± 0.70	10.61 ± 0.68	10.78 ± 0.60
Finasteride	10.74 ± 0.69	10.09 ± 0.82 ^{//}	10.03 ± 0.82 ^{//}	10.20 ± 0.81
Dutasteride	10.82 ± 0.73	10.82 ± 0.74	10.28 ± 0.87	10.65 ± 0.67
Ejaculatory function (0–8): ¶				
Placebo	7.65 ± 0.44	7.61 ± 0.45	7.39 ± 0.51	7.48 ± 0.53
Finasteride	7.60 ± 0.40	7.17 ± 0.75	7.23 ± 0.58	7.26 ± 0.63
Dutasteride	7.56 ± 0.46	7.45 ± 0.59	6.96 ± 0.84 ^{//}	7.52 ± 0.55
Freedom from problems with sexual activity (0–12): **				
Placebo	11.52 ± 0.37	11.35 ± 0.45	11.26 ± 0.47	11.52 ± 0.37
Finasteride	11.09 ± 0.55	10.17 ± 1.00 [†]	10.09 ± 0.91 [†]	10.79 ± 0.75
Dutasteride	11.68 ± 0.31	11.14 ± 0.65	10.59 ± 0.59 ^{//}	11.22 ± 0.63
Overall satisfaction with sexual activity (0–4): ††				
Placebo	3.35 ± 0.57	3.26 ± 0.69	3.39 ± 0.58	3.39 ± 0.58
Finasteride	3.17 ± 0.78	3.17 ± 0.83	3.05 ± 0.90	3.05 ± 0.91
Dutasteride	2.86 ± 0.97	3.18 ± 0.67	2.96 ± 0.81	3.07 ± 0.96

Higher values connote higher degrees of satisfaction.

^{*} Sum of two 4-point Likert scale responses to questions regarding frequency and level of sexual drive.

[†] Compared with baseline and placebo $p < 0.05$.

[‡] Compared with placebo $p < 0.05$.

[§] Sum of three 4-point Likert scale responses to questions regarding frequency of erections, firmness of erections and ease of sexual activity with erections.

^{//} Compared with baseline $p < 0.05$.

[¶] Sum of two 4-point Likert scale responses to questions regarding ease of ejaculation and volume of ejaculate.

^{**} Sum of three 4-point Likert scale responses to questions regarding lack of problems associated with sex drive, erectile and ejaculatory function.

^{††} Single 4-point Likert scale response to question regarding overall level of satisfaction with sex life in the preceding 30 days.