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Exogenous Testosterone or Testosterone with Finasteride Increases Bone Mineral Density in Older Men with Low Serum Testosterone

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Older men, particularly those with low serum testosterone (T) levels, might benefit from T therapy to improve bone mineral density (BMD) and reduce fracture risk. Concerns exist, however, about the impact of T therapy on the prostate in older men. We hypothesized that the combination of T and finasteride (F), a 5α-reductase inhibitor, might increase BMD in older men without adverse effects on the prostate. Seventy men aged 65 yr or older, with a serum T less than 12.1 nmol/liter on two occasions, were randomly assigned to receive one of three regimens for 36 months: T enanthate, 200 mg im every 2 wk with placebo pills daily (T-only); T enanthate, 200 mg every 2 wk with 5 mg F daily (T+F); or placebo injections and pills (placebo). Low BMD was not an inclusion criterion. We obtained serial measurements of BMD of the lumbar spine and hip by dual x-ray absorptiometry. Prostate-specific antigen (PSA) and prostate size were measured at baseline and during treatment to assess the impact of therapy on the prostate. Fifty men completed the 36-month protocol. By an intent-to-treat analysis including all men for as long as they contributed data, T therapy for 36 months increased BMD in these men at the lumbar spine [10.2 ± 1.4% (mean percentage increase from baseline ± SEM; T-only) and 9.3 ± 1.4% (T+F) *vs.* 1.3 ± 1.4% for placebo ($P < 0.001$)] and in the hip [2.7 ± 0.7% (T-only) and 2.2 ± 0.7% (T+F) *vs.* −0.2 ± 0.7% for placebo, ($P \leq 0.02$)]. Significant increases in BMD were seen also in the intertrochanteric and trochanteric regions of the hip. After 6 months of therapy, urinary deoxypyridinoline (a bone-resorption marker) decreased significantly compared with baseline in both the T-only and T+F groups ($P < 0.001$) but was not significantly reduced compared with the placebo group. Over 36 months, PSA increased significantly from baseline in the T-only group ($P < 0.001$). Prostate volume increased in all groups during the 36-month treatment period, but this increase was significantly less in the T+F group compared with both the T-only and placebo groups ($P = 0.02$). These results demonstrate that T therapy in older men with low serum T increases vertebral and hip BMD over 36 months, both when administered alone and when combined with F. This finding suggests that dihydrotestosterone is not essential for the beneficial effects of T on BMD in men. In addition, the concomitant administration of F with T appears to attenuate the impact of T therapy on prostate size and PSA and might reduce the chance of benign prostatic hypertrophy or other prostate-related complications in older men on T therapy. These findings have important implications for the prevention and treatment of osteoporosis in older men with low T levels. (*J Clin Endocrinol Metab* 89: 503–510, 2004)

TWENTY PERCENT OF men over age 60 have serum testosterone (T) concentrations below the normal range for young men (1, 2). Because low T levels are associated with an increased risk of osteoporosis and fracture (3–7), T therapy in older men might increase bone mineral density (BMD) and reduce fracture risk. Studies in young, hypogonadal men have demonstrated that T therapy increases BMD (8–11), but few studies have investigated older patients, who are at greater risk of fracture. Two randomized clinical trials of transdermal T treatment in men over the age of 64 yr have been published (12, 13). In the first study, vertebral but not hip BMD increased, and only in those with low pretreatment T levels (12). In the second study, T prevented the loss of hip BMD observed in the placebo-treated men (13). Therefore, significant questions still exist about the ability of T therapy in older men to have significant impact on bone health.

The relative roles of T and its metabolite, dihydrotestosterone (DHT), in regulating BMD are not clear. Because DHT contributes to the development of benign prostatic hypertrophy (BPH) and possibly prostate cancer, increasing T levels without also increasing DHT might be preferable in older men, especially if DHT has little or no effect on BMD. Finasteride (F) inhibits DHT production by blocking the enzyme 5α-reductase, which converts T to DHT, and has been used safely to treat BPH in older men without compromising BMD (14–16).

We hypothesized that long-term im T therapy in older men who had serum T below the range of normal for young adult men would significantly increase BMD. Furthermore, we hypothesized that the addition of the 5α-reductase inhibitor F would have no impact on T-mediated increases in BMD but

Abbreviations: BMD, Bone mineral density; BPH, benign prostatic hypertrophy; CV, coefficient of variation; DHT, dihydrotestosterone; E2, estradiol; F, finasteride; po, *per os*; PSA, prostate-specific antigen; T, testosterone; TE, T enanthate.

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would minimize the potential for adverse effects on prostate health. Therefore, we conducted a randomized, double-blind, placebo-controlled trial of im T administration, with or without F, to test these hypotheses.

Subjects and Methods

Subjects

Men aged 65 yr and older were recruited using advertisements and direct mailings. The inclusion criterion was a nonfasting, morning serum total T level below 12.1 nmol/liter (350 ng/dl) for 2 d. Exclusion criteria included the following: severe illness; use of medications including anabolic steroids, antiandrogens, glucocorticoids, bisphosphonates, diuretics, calcitonin, seizure medications, or warfarin; Paget's disease; smoking or heavy alcohol use; sleep apnea; hematocrit greater than 48%; total cholesterol above 300 mg/dl; abnormal kidney, liver, thyroid, adrenal, or pituitary function; regular exercise more than three times a week; prostate issues [prostate cancer, a prostate nodule on exam, prostate-specific antigen (PSA) >4.0 ng/ml, or International Prostate Symptom Score >8]; urinary postvoid residual by ultrasound of more than 149 ml; or an abnormal transrectal ultrasound. Reduced BMD was not an inclusion criterion. The Institutional Review Board of Emory University, where all subject interactions occurred, approved the study, and subjects gave written informed consent before screening.

A total of 676 men were evaluated for eligibility. Of these, 283 men were potentially eligible and underwent T measurement. One hundred ten men met the T criterion and underwent further screening tests; 70 men were enrolled. Forty men who passed initial screening were not enrolled for the following reasons: abnormal PSA, prostate ultrasound, postvoid residual, or symptom score (11); pituitary, thyroid, or adrenal disease (5); medical illness (4); second T levels above 350 ng/dl (4); total cholesterol above 300 mg/dl (1); or being eligible but refusing enrollment (15).

Study design

Participants were randomized to one of three treatment groups: 1) T-only group, T enanthate (TE; Schein Pharmaceuticals, Florham Park, NJ) 200 mg im every 2 wk, plus placebo pill orally [*per os* (po)] daily; 2) T+F group, TE 200 mg im every 2 wk, plus F (Merck & Co., Rahway, NJ) 5 mg po daily; or 3) placebo group, sesame oil placebo 1 ml im every 2 wk, plus placebo pill po daily. The estimate of sample size for the trial was based on the percentage change in BMD from baseline to 6-month follow-up. Assuming a clinically important increase on average of 1% in the T+F group, no change on average in the placebo group, and an estimated SD in each group of 1%, a sample size of 17 men per group ensured approximately 80% statistical power to detect a treatment difference of 1% (significance level, 0.05; two-sided test) if the true difference between groups was a 1% BMD increase from baseline to 6-month follow-up. Allowing for a 30% dropout rate over 3 yr, 70 patients were randomized in the trial.

The order of treatment assignment was randomly computer-generated in permuted blocks of six. Participants were treated for 36 months. Only the research pharmacist and safety monitoring board knew of the randomization. A nurse administered the injections, and 98% occurred within 2 d of the scheduled time. There was 95% compliance with the daily F or placebo in the enrolled subjects based on monthly pill counts. The study design included the potential for dose reduction of T or placebo injection by decrements of 0.2 ml (40 mg of TE for subjects actually receiving T) for a hematocrit of more than 52% on safety monitoring performed at 2, 4, 8, 12, 18, 24, and 30 months. Calcium and vitamin D supplements were not provided, but patients were allowed to continue these medications if they were taking them already. Participants were queried at the beginning and end of the study in regard to the intake of these supplements, with no significant change in their use being noted. Specifically, two men in the placebo group, one man in the T-only group, and none in the T+F group were taking calcium supplements during the study. No subject was taking additional vitamin D.

For men who discontinued the study prematurely, telephone follow-up was conducted to ascertain clinical outcomes.

Measurements

At baseline and after 6, 12, 18, 24, and 36 months of treatment, BMD was measured at the lumbar spine (L1–L4; anteroposterior view only) and in the nondominant hip by dual x-ray absorptiometry using a Hologic QDR-2000 densitometer (Hologic, Waltham MA) that was standardized daily. The intraperson coefficient of variation (CV) was 1.0% for both the spine and the hip. T and Z scores were calculated using male databases; the manufacturer's database was used for the spine, and the National Health and Nutrition Examination Survey III was used for all of the hip measurements. One of the investigators (N.B.W.) who was blinded to treatment analyzed all of the BMD measurements and excluded from analysis vertebrae that showed localized degenerative change, compression fractures, or other confounding factors. One or two vertebrae were deleted from analysis if there was obvious degenerative change on the image and/or if it was 1 SD or more higher than the lowest vertebrae (six placebo subjects, five T-only subjects, and five T+F subjects). If three or more vertebrae showed evidence of degenerative change, the spine measurement was considered invalid and was not used (no placebo subjects, two T-only subjects, and one T+F subject).

Blood was drawn for hormone measurements in the morning at baseline and immediately before injections after 2, 4, 6, 8, 12, 18, 24, 30, and 36 months of treatment. Samples at baseline 6, 12, 18, 24, and 36 months were fasting samples, whereas the other samples were nonfasting. Blood was drawn for markers of bone metabolism after a 12-h fast at baseline and after 6 months of treatment. For a subset of men (n = 22), additional morning blood was drawn at the end of the first study year on d 3 or 4, 7, and 11 of the T-dosing period to obtain between-nadir samples. Serum samples for 25-hydroxyvitamin D and intact PTH were assayed immediately. All other samples were stored frozen at −70 C until the end of the study, when serum samples from each participant were assayed concurrently. A 2-h morning urine was collected for measurement of deoxypyridinoline at baseline and after 6 months of treatment. T, SHBG, and estradiol (E2) were measured using fluoroimmunoassays (Delfia, Wallac Oy, Turku, Finland). The intraassay and interassay CVs for midrange measurements were 4.5 and 9.5% for T, 4.0 and 11.1% for SHBG, and 3.6 and 6.0% for E2. The normal range is 12–33 nmol/liter for T and 60–220 pmol/liter for E2. DHT was measured by RIA (Endocrine Sciences, Calabasas Hills, CA); the midrange intraassay and interassay CVs were 6.6 and 14%, respectively. Non-SHBG-bound, bioavailable T was assayed using RIA after ammonium sulfate precipitation [Centre Hospitalier de l'Universite at Laval University (CHUL) Research Center, Sainte-Foy, Quebec, Canada]; the midrange intraassay and interassay CVs were 7.4 and 12%, respectively. Osteocalcin was measured by RIA (Diagnostic Systems Laboratories, Inc., Webster, TX); the midrange intraassay and interassay CVs were both 7.2%. Bone-specific alkaline phosphatase was measured by immunoassay (Metra Biosystems, Mountain View, CA); the midrange intraassay and interassay CVs were 1.4 and 4.8%, respectively. Urinary deoxypyridinoline was measured by chromatography after acid hydrolysis and was normalized to urinary creatinine; midrange intraassay and interassay CVs were 8 and 15%, respectively. Intact PTH was measured by a chemiluminescent assay (Diagnostic Products Corp., Los Angeles, CA); midrange intraassay and interassay CVs were 5.1 and 5.3%, respectively.

Participant monitoring

Participants were examined monthly. Measurements of hematocrit and transaminases occurred every 2 months for 1 yr, and every 6 months thereafter. Prostate volume was assessed by transrectal ultrasound (Bruel & Kjaer, Boras, Sweden) at baseline (model 3535) and at the end of treatment (model 1846 PM) using established techniques (17, 18). PSA levels were measured every 4 months during the first year and every 6 months thereafter; digital rectal examination was performed every 6 months.

Statistical analysis

The primary analyses of the data were performed according to patients' original treatment assignment (*i.e.* intention-to-treat analyses), and all men were included in the analyses for as long as they contributed data. Baseline characteristics between treatment groups were compared with the Kruskal-Wallis test. Repeated-measures analyses for each of the

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four BMD measurements were analyzed as percentage change from baseline with a means model with SAS Proc Mixed (version 8; SAS Institute, Inc., Cary, NC) providing separate estimates of the means by time on the study (6, 12, 18, 24, 30, and 36 months) and treatment groups. An unstructured variance-covariance form among the repeated measurements was assumed for each outcome, and estimates of the SE values of parameters were used to perform statistical tests and construct 95% confidence intervals. Student's *t* tests were used to compare the pairwise differences between the model-based treatment means (least-squares means) at each time point or treatment month. The model-based means are unbiased with unbalanced and missing data, as long as the missing data are noninformative (missing at random). A dropout process is assumed to be missing at random if, depending on the observed data, the dropout is independent of the unobserved measurements. Mean changes over time within a treatment group were tested for linear trend. Repeated-measures analyses were also performed for T, DHT, E2, and PSA after a log transformation, and for prostate volume, hematocrit, hemoglobin, and lipids. The Wilcoxon signed-rank test was used to compare change from baseline to 6 months within each treatment group for six markers of bone metabolism. Statistical tests were two-sided. A Bonferroni adjustment ($P < 0.0167$) was used for the three pairwise comparisons performed at each treatment month.

Results

Seventy men, with a mean age of 71 ± 4 yr (range, 65–83 yr), participated in the study. Twenty-four were randomized to T-only, 22 to T+F, and 24 to placebo. Fifty men completed the entire 36 months of the study. Of the 20 men who did not complete the study, six were in the placebo group, and seven each were in the T-only and T+F groups. Reasons for discontinuation included the following: personal reasons (10 men), intercurrent illness (7 men), or a new diagnosis of prostate cancer (3 men). At baseline, the three treatment groups did not differ significantly from each other in age, body mass index, hormone levels, BMD, prostate volume, or PSA (Table 1). Twenty-four of the 70 men (10 in the placebo group, 8 in the T-only, and 6 in the T+F group) had baseline serum E2 levels that were below the lower limit of normal. The baseline BMD for the hip and lumbar spine for the participants was similar to that for a standard male population of the same age (Z scores, Table 1). A total of seven men, two each in the placebo and T+F groups and three in the T-only group, had low baseline lumbar-spine BMD (T score more than 2.5 SD below peak bone mass for young men), whereas four men, two in the placebo group and one each in the T-only and T+F groups, had low baseline hip BMD. There were no significant differences in the baseline characteristics between the men who discontinued and those who completed the study. Reduction of T dosage was necessary in 14 men (seven in the T-only group and seven in the T+F group *vs.* none in the placebo group). After the decrease in T dosage, the final mean (±SD) dose of TE was 158 ± 36 mg for the T-only group and 164 ± 40 mg for the T+F group every 2 wk.

Mean nadir serum total T, bioavailable T, and E2 levels in the T-only and T+F groups significantly increased throughout the treatment period (Fig. 1, A–C), whereas these hormone levels did not change in the placebo group. Nadir serum total T and E2 levels tended to be higher in the T+F group compared with the T-only group, but this difference

TABLE 1. Baseline characteristics (mean ± SD) of 70 older men administered im T alone, T with F, or placebo for 36 months

Characteristic	Placebo (n = 24)	T-only group (n = 24)	T + F group (n = 22)	*P*
Age (yr)	71 ± 5	71 ± 4	71 ± 4	0.99
Body mass index (kg/m^2)	27.8 ± 3.6	28.7 ± 3.6	27.0 ± 2.7	0.24
Hormones				
Total testosterone (nmol/liter)	10.5 ± 1.7	9.9 ± 1.6	10.1 ± 2.1	0.36
Dihydrotestosterone (nmol/liter)	1.0 ± 0.5	0.8 ± 0.3	0.9 ± 0.2	0.48
Estradiol (pmol/liter)	83.3 ± 44.4	71.5 ± 33.7	84.0 ± 33.3	0.47
SHBG (nmol/liter)	44.0 ± 18.1	45.2 ± 16.6	48.2 ± 15.0	0.55
Bioavailable T (nmol/liter)	3.5 ± 1.3	3.3 ± 1.2	3.4 ± 1.2	0.62
BMD				
Lumbar spine				
Density (g/cm^2)	1.04 ± 0.15	1.06 ± 0.16	1.03 ± 0.19	0.81
T score[a]	−0.48 ± 1.47	−0.30 ± 1.56	−0.53 ± 1.66	
Z score[a]	0.44 ± 1.49	0.69 ± 1.62	0.51 ± 1.67	
Total hip				
Density (g/cm^2)	0.96 ± 0.13	0.96 ± 0.14	0.90 ± 0.23	0.67
T score	−0.87 ± 0.89	−0.84 ± 1.13	−1.02 ± 0.80	
Z score	0.30 ± 0.86	0.24 ± 1.21	0.12 ± 0.79	
Intertrochanter				
Density (g/cm^2)	1.11 ± 0.15	1.11 ± 0.17	1.11 ± 0.13	0.96
T score	−0.90 ± 0.88	−0.77 ± 1.17	−0.80 ± 0.96	
Z score	0.06 ± 1.10	0.29 ± 1.21	0.16 ± 0.82	
Trochanter				
Density (g/cm^2)	0.74 ± 0.11	0.75 ± 0.11	0.71 ± 0.10	0.29
T score	−0.92 ± 2.32	−0.39 ± 1.10	−0.73 ± 0.86	
Z score	0.27 ± 1.16	0.45 ± 1.17	0.13 ± 0.85	
Femoral neck				
Density (g/cm^2)	0.81 ± 0.12	0.78 ± 0.13	0.74 ± 0.09	0.19
T score	−1.56 ± 1.07	−1.77 ± 1.16	−2.03 ± 0.87	
Z score	0.42 ± 1.06	0.19 ± 1.17	0.03 ± 0.86	
Prostate parameters				
PSA (ng/dl)	1.4 ± 1.1	0.9 ± 0.8	1.0 ± 0.6	0.08
Prostate volume (cm^3)	32 ± 14	29 ± 11	33 ± 16	0.80

[a] T score compares the BMD to the mean for young normal males and Z score compares it with age-matched controls.

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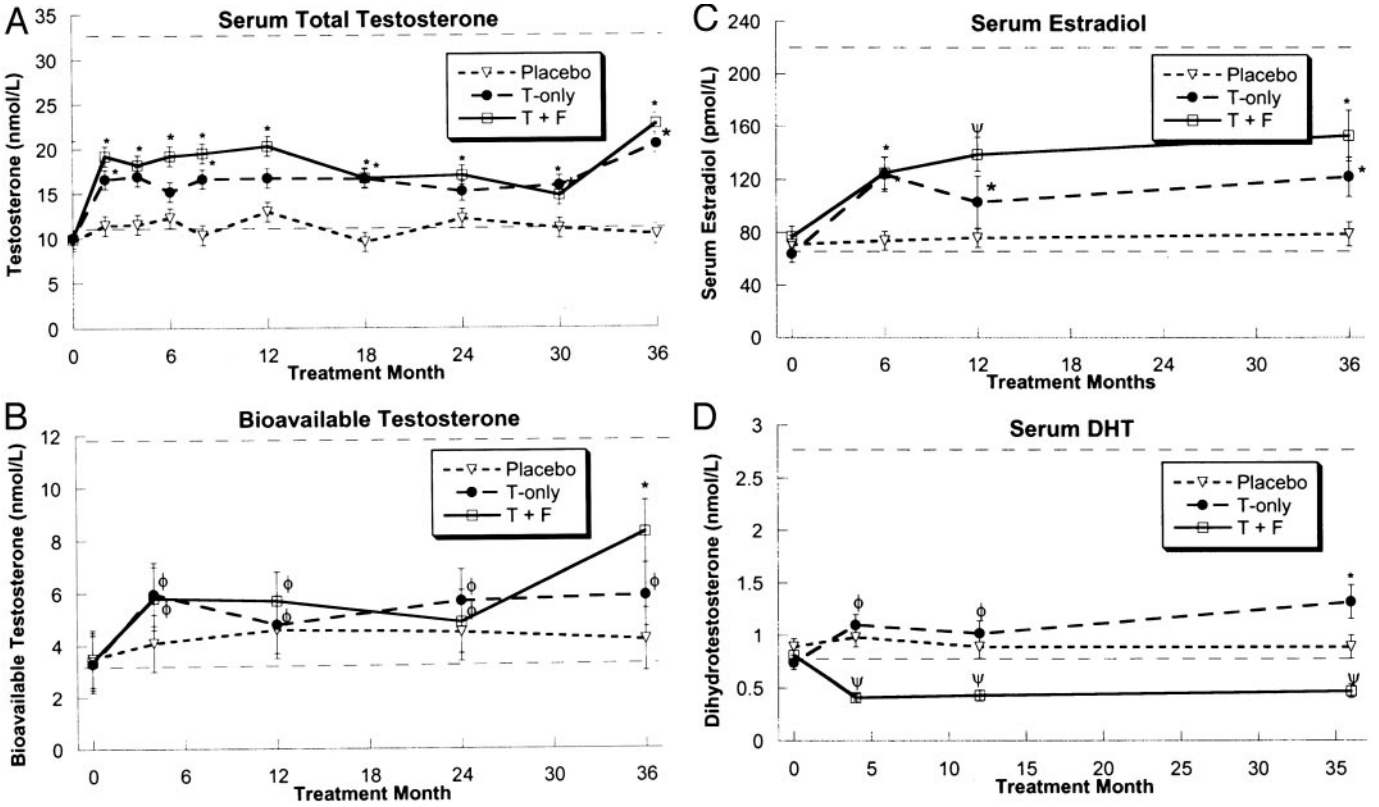

FIG. 1. Geometric mean (± SEM) nadir serum total T (A), bioavailable (non-SHBG-bound) T (B), E2 (C), and DHT (D) in older men with low T who were treated with either T (T-only), T and F (T+F), or placebo for 36 months. *Horizontal dotted lines* represent normal ranges. *, $P < 0.05$ compared with baseline and placebo; ψ, $P < 0.05$ compared with baseline, placebo, and T-only; ϕ, $P < 0.05$ compared with baseline.

did not reach statistical significance for any time point for total T and was only significant at month 12 for E2 ($P = 0.03$). For the subset of men from whom blood was sampled at multiple times throughout the 2-wk T-dosing period (six men in the placebo group, seven men in the T-only group, and nine men in the T+F group), peak serum total T levels were at or above the normal serum T range for the two T treatment groups, with a mean peak value for the T-only group being 35.9 ± 12.1 nmol/liter (mean ± SD) and that for the T+F group being 43.5 ± 7.6 nmol/liter. Average total T levels during the 2-wk dosing interval were 25.8 ± 6.0, 33.0 ± 6.4, and 11.8 ± 2.3 nmol/liter for the T-only, T+F, and placebo groups, respectively. In comparing these two T treatment groups, there was no difference in peak T levels ($P = 0.13$), but the average total T levels were somewhat higher in the T+F group ($P = 0.04$).

Mean nadir serum DHT levels did not change throughout the study in the placebo group, increased significantly in the T-only group, and decreased in the T+F group ($P < 0.001$ compared with baseline and placebo) by 6 months and remained suppressed throughout treatment (Fig. 1D). The maximum decline in serum DHT levels in the T+F group was 50% below baseline, which was reached at treatment month 4.

BMD and metabolism

BMD of the lumbar spine, total hip, and trochanteric and intertrochanteric regions increased in both the T-only and the T+F groups during the study period, whereas those in the placebo group did not change ($P < 0.001$; Table 2 and Fig. 2, A–D). The mean percentage increase from baseline in BMD of the lumbar spine was significant ($P < 0.001$) for the T-only and T+F groups, but the mean did not change for men in the placebo group ($P = 0.39$ for linear trend). There was no significant change over the 36 months in the BMD at the femoral neck in any of three treatment groups ($P = 0.16$). In the T groups, increases in lumbar BMD were positively correlated with magnitude of increase in both serum total T ($r = 0.44$; $P = 0.001$), bioavailable T ($r = 0.45$ and $P = 0.009$), and serum E2 ($r = 0.45$; $P = 0.0006$) but were not related to baseline BMD; to baseline levels of total T, bioavailable T, DHT, or E2; or to baseline levels of T or E2 after correction for baseline SHBG levels.

After 6 months of therapy, serum osteocalcin (a bone formation marker), intact PTH, and 25-hydroxyvitamin D did not change in any group (Table 3). In contrast, urinary deoxypyridinoline, a bone resorption marker, decreased significantly in both the T-only and T+F groups (both $P < 0.001$) but was unchanged in the placebo group ($P = 0.30$). Bone-specific alkaline phosphatase, a bone formation marker, decreased significantly in the T-only group ($P = 0.049$).

Prostate and hematological effects

Forty-nine of the 50 subjects who completed the 36-month study underwent end-of-treatment prostate ultrasound, and

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TABLE 2. Mean BMD (g/cm^2) and 95% confidence interval measured by dual-energy x-ray absorptiometry in older men administered in T alone, T with F (T+F), or placebo at the lumbar spine, total hip, femoral neck, and intertrochanteric and trochanteric regions[a]

	Baseline	6 months	12 months	18 months	24 months	36 months
Lumbar spine						
T only	1.06 (0.98–1.13)	1.09 (1.02–1.16)[b]	1.10 (1.03–1.17)[b]	1.13 (1.05–1.21)[b]	1.13 (1.05–1.20)[b]	1.16 (1.08–1.24)[b]
T+F	1.03 (0.96–1.10)	1.07 (0.99–1.14)[b]	1.08 (1.00–1.15)[b]	1.10 (1.02–1.17)[b]	1.10 (1.03–1.17)[b]	1.13 (1.05–1.20)[b]
Placebo	1.04 (0.97–1.11)	1.05 (0.97–1.12)	1.05 (0.98–1.13)	1.04 (0.97–1.12)	1.05 (0.97–1.12)	1.06 (0.98–1.14)
Total hip						
T only	0.96 (0.90–1.00)	0.97 (0.91–1.02)	0.96 (0.91–1.02)	0.97 (0.92–1.03)[b]	0.97 (0.92–1.03)[b]	0.98 (0.92–1.04)[b]
T+F	0.94 (0.89–1.00)	0.94 (0.88–0.99)	0.96 (0.90–1.01)	0.95 (0.89–1.01)	0.95 (0.90–1.01)	0.96 (0.90–1.02)[b]
Placebo	0.96 (0.90–1.01)	0.95 (0.90–1.01)	0.95 (0.90–1.00)	0.95 (0.90–1.00)	0.95 (0.91–1.01)	0.95 (0.90–1.01)
Intertrochanteric region						
T only	1.11 (1.05–1.17)	1.13 (1.06–1.19)	1.13 (1.06–1.19)	1.13 (1.07–1.20)[b]	1.13 (1.07–1.20)	1.15 (1.08–1.21)[b]
T+F	1.11 (1.04–1.17)	1.11 (1.04–1.18)	1.13 (1.06–1.19)	1.11 (1.05–1.18)	1.12 (1.06–1.19)	1.14 (1.07–1.21)[b]
Placebo	1.11 (1.04–1.17)	1.10 (1.04–1.17)	1.10 (1.04–1.16)	1.10 (1.03–1.16)	1.10 (1.04–1.16)	1.10 (1.04–1.17)
Trochanteric region						
T only	0.75 (0.70–0.79)	0.76 (0.71–0.80)[b]	0.76 (0.71–0.81)	0.77 (0.72–0.81)[b]	0.78 (0.73–0.82)[b]	0.78 (0.73–0.83)[b]
T+F	0.71 (0.66–0.76)	0.71 (0.67–0.76)	0.73 (0.68–0.78)[b]	0.73 (0.68–0.78)[b]	0.73 (0.68–0.78)[b]	0.75 (0.69–0.80)[b]
Placebo	0.74 (0.69–0.78)	0.74 (0.69–0.78)	0.74 (0.69–0.78)	0.74 (0.69–0.78)	0.73 (0.69–0.78)	0.74 (0.69–0.79)
Femoral neck						
T only	0.78 (0.73–0.82)	0.79 (0.74–0.83)	0.78 (0.74–0.83)	0.79 (0.74–0.84)[b]	0.79 (0.74–0.83)	0.79 (0.74–0.84)[b]
T+F	0.74 (0.69–0.79)	0.75 (0.70–0.79)	0.76 (0.71–0.80)	0.76 (0.71–0.81)	0.76 (0.71–0.81)	0.77 (0.72–0.82)[b]
Placebo	0.81 (0.76–0.85)	0.81 (0.76–0.85)	0.80 (0.76–0.85)	0.80 (0.76–0.85)	0.81 (0.76–0.85)	0.81 (0.76–0.86)

[a] Includes data from all measurements available at a given time point.
[b] $P < 0.01$ compared with baseline.

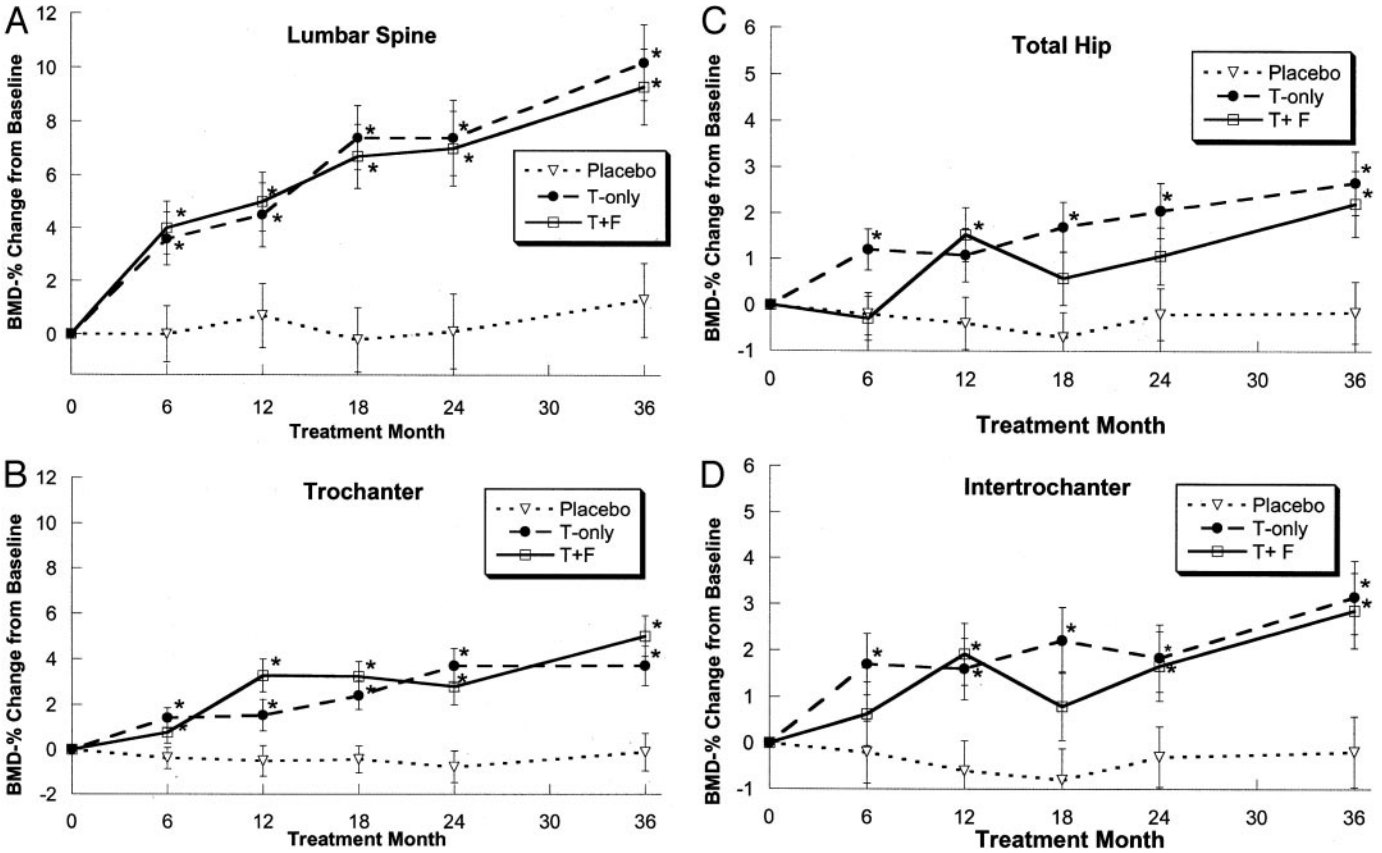

FIG. 2. Mean percentage increase (± SEM) in BMD of the lumbar spine (A), trochanteric (B), total hip (C), and intertrochanteric (D) regions in older men with low T who were treated with either T (T-only), T and F (T+F), or placebo for 36 months. *, $P < 0.05$ compared with baseline and placebo.

all subjects had an end-of-treatment PSA. There was a small but significant increase in serum PSA in the T-only group ($P < 0.001$ by month 36), but there was no change in PSA in either the placebo or T+F group at any time during the study (Table 4). Prostate volume increased significantly in all groups over the 3-yr study period. The increase in prostate volume in the T-only group was similar to the increase seen in the placebo treatment group ($P = 0.35$), whereas the in-

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TABLE 3. Markers of bone metabolism during treatment (median, 75th-25th percentiles) in older men administered im T alone, T with F, or placebo after 6 months of therapy

	Placebo		T only		T+F	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Osteocalcin (ng/ml)	2.06 (1.79)	1.79 (2.44)	2.35 (2.35)	2.40 (1.37)	2.38 (2.16)	2.02 (2.08)
BSAP (IU/liter)	14.3 (4.8)	14.3 (5.2)	14.6 (7.5)	12.0 (5.2)[a]	16.0 (5.6)	13.9 (4.7)
U-deoxypyridinoline (μmol/mol Cr)	5.8 (2.0)	6.1 (2.5)	6.2 (2.3)	5.0 (1.6)[b]	6.0 (2.0)	4.5 (1.6)[b]
PTH (pg/ml)	45 (28)	42 (15)	44 (28)	50 (40)	40 (19)	52 (27)
25 hydroxy-vitamin D (ng/ml)	34 (20)	44 (19)	35 (21)	39 (24)	41 (12)	48 (13)

BSAP, Bone-specific alkaline phosphatase; U, urinary; PTH, intact PTH; Cr, creatinine.
[a] $P < 0.05$ compared to baseline.
[b] $P < 0.001$ compared to baseline.

crease in prostate volume in the T+F group was significantly less than in the T-only group ($P = 0.02$).

One man in the placebo group, two in the T-only group, and no subjects in the T+F group had a diagnosis of prostate cancer, leading to discontinuation of study participation ($P = 0.46$). The two men with prostate cancer in the T-only group were diagnosed after 7 and 8 months of study participation. The indication for biopsy in one case was an abnormal digital rectal exam and in the other case was asthenia and fever. In both cases, one of six biopsy samples revealed Gleason grade 5 disease. For the man with the abnormal digital rectal exam, the positive biopsy occurred in the opposite lobe from the abnormal exam finding. The individual in the placebo group with prostate cancer was diagnosed after 24 months in the study; the indication for biopsy was an elevated PSA. Of the 17 remaining men who discontinued participation in the study, 15 were free of prostate cancer or other prostate diseases at the conclusion of the study. Two men were lost to follow-up.

Mean hematocrit and hemoglobin values increased significantly during treatment in the T-only and T+F groups ($P < 0.001$ compared with baseline and placebo) but were unchanged in the placebo group (Table 4). Increase in hematocrit was positively associated with elevations in T ($r = 0.41$; $P < 0.001$). In the T-only group, one man suffered a cerebral hemorrhage during treatment, and another man developed new symptoms of sleep apnea confirmed by a sleep study. There were no other serious adverse cardiovascular, cerebrovascular, or pulmonary events.

Discussion

This study demonstrates that im T therapy in older men with low serum total T levels increases BMD in the lumbar spine and hip over 3 yr. The increase in BMD would be expected to decrease fracture risk. The increases in BMD seen in this study are similar in magnitude both to those observed with T therapy in younger hypogonadal men (8–11) and to those seen with bisphosphonate therapy in men with osteoporosis (19, 20). The increases seen in BMD were not limited to the spine but also involved most areas of the hip that were measured. Previous studies of T therapy in older men have reported either smaller increases in lumbar spine BMD (12) or no increase in hip BMD with T therapy (12, 13). There could be a number of reasons why the findings of this study differ from the findings of these previous studies. For one, the men enrolled in this study all had baseline serum total T levels that were below the normal range for young men, which was not the case in one of the previous studies (12). In addition, the serum levels of total T and E2 achieved with im T injections in this study were two to three times higher than those achieved in studies using T patches in older men (12, 13). Such large increases over baseline T and E2 levels might account for much of the difference between the increases in BMD seen in these studies. Although the dose-response range for bone in regard to T (or E2) in older men has not been established yet, these data may suggest that a certain threshold of serum T (or E2) must be reached and/or a certain magnitude of change from baseline levels must be achieved before significant effects of the sex steroids on bone are achieved in older men. It also is important to note that, in contrast to previous studies in older men, subjects in our study were not administered supplemental calcium and vitamin D. This may have increased the magnitude of the differences between placebo and treatment groups we observed in our study; however, dramatic improvements in BMD were seen without calcium and vitamin D supplementation. Whether supplementation in combination with T would result in even greater increases in BMD should be the subject of future research.

Both the T-only and the T+F groups had similar increases in serum nadir total T and E2 levels and in BMD; however, there was a significant decrease in serum DHT in the T+F group. This suggests that conversion to DHT is not essential for the effect of T on BMD. Because F incompletely blocks the conversion of T to DHT (21) and men in our study achieved at best a 50% reduction in serum DHT levels, it is still possible that low levels of DHT are required for stimulating increases in BMD.

The beneficial effects of T therapy on BMD may be mediated by its conversion to E2. The increases in E2 serum levels from baseline with T therapy in this study were substantial. The impact of E2 on BMD in men has been demonstrated in a man with aromatase deficiency who had high serum T levels but low BMD. Treatment with E2 resulted in epiphyseal closure and increased BMD (22). Furthermore, a second man with an E2 receptor mutation was found to have unfused epiphyses and low BMD (23). Other work has suggested that bioavailable E2 may be the best predictor of BMD in older men (24, 25). Although it is likely that E2 plays a major role in maintenance of BMD in men, further studies using nonaromatizable androgens will be required before we will completely understand relative roles of T and E2 in bone formation in men.

The mechanism by which androgens and/or estrogens

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TABLE 4. Hematocrit, hemoglobin, prostate size, and PSA during treatment [means (95% confidence interval)]

	Placebo			T-only			T+F		
	Baseline	Month 18	Month 36	Baseline	Month 18	Month 36	Baseline	Month 18	Month 36
Hematology									
Hematocrit (%)	43.5 (42.3–44.8)	42.7 (41.7–44.5)	42.9 (41.5–44.4)	42.5 (41.2–43.8)	48.9 (47.4–50.4)[a]	48.6 (47.1–50.0)[a]	43.2 (41.8–44.5)	48.2 (46.3–49.7)[a]	47.4 (46.0–49.0)[a]
Hemoglobin (g/dl)	14.7 (14.3–15.2)	14.5 (14.2–15.2)	14.6 (14.1–15.1)	14.5 (14.1–14.9)	16.5 (16.1–17.0)[a]	16.6 (16.1–17.1)[a]	14.6 (14.2–15.1)	16.6 (16.1–17.0)[a]	16.2 (15.7–16.7)[a]
Prostate									
Prostate size (cc^3)	32 (26–38)	ND	42 (36–49)[a]	29 (23–34)	ND	43 (37–49)[a]	33 (27–38)	ND	38 (32–44)[a, b]
PSA (ng/ml)	1.4 (1.1–1.9)	1.5 (1.0–2.1)	1.7 (1.2–2.3)	1.0 (0.7–1.3)	1.4 (1.0–2.0)[a]	1.4 (1.0–2.0)[a]	1.0 (0.7–1.3)	0.8 (0.5–1.0)	1.1 (0.8–1.6)

ND, Not done. PSA is expressed as the geometric mean.
[a] $P < 0.01$ compared with baseline.
[b] $P = 0.02$ compared with placebo and T-only.

improve BMD is unclear, but androgen receptors have been identified in osteoblasts (26). In our study, most markers of bone formation were unchanged, but the most sensitive marker of bone resorption (27), urinary deoxypyridinoline, decreased significantly. This suggests that T therapy reduces bone resorption more than it increases bone formation. This finding is in agreement with a recently published study in younger men (28). This "antiresorptive" effect of T also might be mediated by E2 (29) and is a main mechanism by which E2 is thought to increase BMD in postmenopausal women (30).

Regarding the prostate, all groups showed increases in prostate volume that were greater than those observed previously in prospective studies of older men (31, 32). The change in ultrasound equipment between baseline and the end of the study may have contributed to the seemingly larger-than-expected magnitude of volume change between baseline and end-of-study. However, because this would have affected equally all treatment groups, the relative volume change differences seen between treatment groups should still be valid. Notably, the T+F group had significantly less increase in prostate volume than either the T-only or placebo groups. The attenuation of prostate volume enlargement seen in this study with the concomitant use of a 5α-reductase inhibitor, rather than a reduction in prostate volume that is usually reported with such therapy (32), is mirrored by the less-than-expected reduction in serum DHT levels in the T+F group and may have occurred because of the high serum T levels produced by the T-injection regimen used. Nonetheless, this attenuation of prostate growth by 5α-reductase inhibition might be important in preventing symptomatic BPH and possibly reducing the risk of prostate cancer in older men treated with long-term T therapy; however, our trial lacked sufficient numbers of subjects to detect any possible benefit of F on the risk of these outcomes. Notably, the recently published prostate cancer prevention trial showed a 25% reduction in new cases of prostate cancer in older men treated with F therapy (33). Clearly, larger studies of T therapy with 5α-reductase inhibitors in older men will be required before a small increased risk of prostatic complications can be excluded.

Subjects in our study did have a higher rate of erythrocytosis than seen in previous trials of T administration in older men using transcutaneous patches (10, 11). Thirty percent of subjects receiving 200 mg of TE every other week in our study developed a hematocrit greater than 52% and required a reduction in the T dose to an average of 158 mg. This finding is probably due to the high serum T levels, especially peak T levels, that were produced in this study and is consistent with rates of erythrocytosis seen in other studies in which older males have been treated with im T (34). Therefore, it is possible that a dose of 150 mg, rather than 200 mg, of TE every 2 wk might be a safer dosage in older men to prevent problematic erythrocytosis; however, there are not data to demonstrate that this dose will prevent bone loss. It is important to note that no ischemic strokes, heart attacks, or episodes of thromboembolism were observed in our study; however, this study lacked sufficient power to rule out a small increase in such events.

In summary, we conclude that T therapy in older men with

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low serum T levels markedly increases BMD in both the spine and the hip over 3 yr. The addition of F to T does not diminish increases in BMD but does decrease prostate growth and increases in PSA compared with treatment with either T alone or placebo. Given its beneficial effects on BMD, larger, long-term randomized studies of T therapy with and without inhibitors of 5α-reductase should be conducted to better define the risks and benefits of T therapy and its impact on the risk of osteoporotic fractures in older men.

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