Effect of Testosterone Treatment on Bone Mineral Density in Men Over 65 Years of Age*

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ABSTRACT

As men age, their serum testosterone concentrations decrease, as do their bone densities. Because bone density is also low in hypogonadal men, we hypothesized that increasing the serum testosterone concentrations of men over 65 yr to those found in young men would increase their bone densities.

We randomized 108 men over 65 yr of age to wear either a testosterone patch or a placebo patch double blindly for 36 months. We measured bone mineral density by dual energy x-ray absorptiometry before and during treatment. Ninety-six men completed the entire 36-month protocol.

The mean serum testosterone concentration in the men treated with testosterone increased from 367 ± 79 ng/dL (± SD; 12.7 ± 2.7 nmol/L) before treatment to 625 ± 249 ng/dL (21.7 ± 8.6 nmol/L; P < 0.001) at 6 months of treatment and remained at that level for the duration of the study. The mean bone mineral density of the lumbar spine increased (P < 0.001) in both the placebo-treated (2.5 ± 0.6%) and testosterone-treated (4.2 ± 0.8%) groups, but the mean changes did not differ between the groups. Linear regression analysis, however, demonstrated that the lower the pretreatment serum testosterone concentration, the greater the effect of testosterone treatment on lumbar spine bone density from 0–36 months (P = 0.02). This analysis showed a minimal effect (0.9 ± 1.0%) of testosterone treatment on bone mineral density for a pretreatment serum testosterone concentration of 400 ng/dL (13.9 nmol/L), but an increase of 5.9 ± 2.2% for a pretreatment testosterone concentration of 200 ng/dL (6.9 nmol/L).

Increasing the serum testosterone concentrations of normal men over 65 yr of age to the midnormal range for young men did not increase lumbar spine bone density overall, but did increase it in those men with low pretreatment serum testosterone concentrations. (J Clin Endocrinol Metab 84: 1966–1972, 1999)

AS MEN AGE, their serum testosterone concentrations decrease. Cross-sectional studies in men show a gradual decrease in serum testosterone during adulthood (1, 2), so the mean value at age 80 yr is approximately 75% of that at age 30 yr. One study that followed a cohort of men for 15 yr confirmed this fall (3). The serum concentration of sex hormone-binding globulin increases as men age (1), so that the fall in the free or bioavailable testosterone concentration with increasing age is even greater than that in total testosterone (1, 2, 4). The mean free testosterone concentration at age 80 yr is approximately 50% of that at age 20 yr (1, 2).

One possible consequence of this decrease in testosterone is a decrease in bone density. As men age, their bone density decreases (5, 6), as does that of men whose serum testosterone is low because of pituitary or testicular disease (7–9). When hypogonadal men are treated with testosterone, their bone densities increase (10).

We hypothesized that increasing the serum testosterone concentrations of elderly men to those levels found in young men would increase their bone densities. We tested this hypothesis by selecting healthy men over 65 yr of age, assigning them randomly to receive either testosterone or placebo, and measuring bone mineral density repeatedly during 3 yr of treatment.

Subjects and Methods

Subjects

We recruited healthy men over 65 yr of age by direct mailings to alumni of the University of Pennsylvania and Temple University and by newspaper and television announcements. We included men who had a serum testosterone concentration at least 1 sd below the mean for healthy young men (<475 ng/dL; 16.5 nmol/L) and a bone mineral density of the lumbar spine (L2-L4) below the mean for healthy young men (~1.26 g/cm²).

We excluded men who had a history of pituitary or testicular disease or were taking androgen preparations. We also excluded men who had diseases that affect bone, such as chronic renal disease or malabsorption, or were taking medications or drugs that affect bone, such as bisphosphonates, diphenylhydantoin, or more than three alcoholic drinks a day. Additionally, we excluded men who had a history of prostate cancer, a palpable prostate nodule, a serum prostate-specific antigen concentration above 4.0 ng/mL, a Boyarsky symptom score greater than 16 (11), a corrected urine flow rate less than 16 mL/min (12), or a postvoiding residual urine volume in the bladder by ultrasound greater than 100 mL.

Over 1000 men volunteered and were interviewed by telephone, and 598 were screened in person and by blood sampling. One hundred and eight men met the above criteria and enrolled. The committee on studies involving humans of the University of Pennsylvania approved the protocol, and each subject gave informed consent in writing.
Study design

Subjects were stratified by pretreatment serum testosterone [≥350 ng/dL (≥12.1 nmol/L) vs. 351–475 ng/dL (12.2–16.5 nmol/L)] and bone mineral density (<85% and 85–100% of the values for 20- to 40-year-old men). Within each stratum subjects were assigned randomly to receive either testosterone or placebo. The randomization code was known only to the data manager (J.H.J.), research pharmacist, and safety monitoring board until the last subject completed his participation.

Testosterone was administered by scrotal patch (Testoderm, provided by Alza Corp., Palo Alto, CA); placebo patches were identical in appearance to testosterone patches. Each subject was asked to wear a patch at all times except when bathing, change the patch once a day, and shave the scrotum twice a week. Each subject began by wearing a 60-cm² testosterone patch, which delivers approximately 6 mg testosterone/24 h, or a 60-cm² placebo patch. The data manager reviewed serum testosterone concentrations every 3 months and directed a decrease in patch size to 40 cm² if a man’s serum testosterone was above 1000 ng/dL (34.7 nmol/L) or a reeducation in patch technique if a man in the testosterone-treated group had a value less than 250 ng/dL above baseline. To maintain the blinding in both of the above manipulations, the testosterone-treated group had a value less than 250 ng/dL above baseline. To maintain the blinding in both of the above manipulations, the data manager directed that a man in the placebo-treated group be treated similarly.

We asked men who were consuming less than four dairy servings a day or equivalent before initiation of treatment to take one tablet a day of OsCal 500 D (500 mg elemental calcium with 125 U vitamin D; SmithKline Beecham, Philadelphia, PA), which we provided. On this basis, we provided OsCal to all but six men in the placebo group and all but four men in the testosterone group.

Assessment of bone mineral density

We measured bone mineral density in the lumbar spine (L2–L4) and three sites in the hip before treatment and after 6, 12, 24, and 36 months of treatment by dual energy x-ray absorptiometry using a Lunar Corp. (Madison, WI) DPX scanner with acquisition software versions 3.1–3.61. Coefficients of variation for this technique at our site were 0.9% for L2–L4, 1.2% for the femoral neck, 2.9% for Ward’s triangle, and 1.5% for the trochanter. Scanning a phantom every 2 weeks during the course of the study gave stable results. All scans from the same subject were analyzed by a single operator (P.H.) at a single sitting without knowledge of the subject’s treatment status. Lateral radiographs of the lumbar spine were taken before treatment and again after 36 months of treatment.

Assays related to testosterone and bone metabolism

Serum for testosterone, sex hormone-binding globulin, and bone-specific alkaline phosphatase determinations was drawn in the morning three times before beginning treatment and 3–5 h after patch application once at 3 and 6 months and then every 6 months during treatment. Urine was collected for 24 h once before treatment and after 6, 12, 24, and 36 months of treatment for creatinine and N-telopeptide determinations. All samples were frozen at −70 °C until the end of the study. Serum testosterone was measured by RIA, and sex hormone-binding globulin was measured by immunoradiometric assay using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX). The serum concentration of free testosterone was calculated from the total testosterone and sex hormone-binding globulin concentrations using a computer program provided by Dr. Stephen Plymate based on equations developed by Sodergard (13). Serum bone-specific alkaline phosphatase was measured by immunoradiometric assay using a kit (Tandem R Ostase) from Beckman Coulter, Inc. (Columbia, MD). Urinary N-telopeptide was measured by enzyme-linked immunosorbant assay using a kit (Osteomark) from Ostex International, Inc. (Seattle, WA). Intraassay coefficients of variation for all of the assays were less than 5%, and interassay coefficients of variation were less than 10%. For each assay, all samples from each subject were measured in the same assay run.

Assessment of potential deleterious effects of testosterone

We tested each man for the possible development of prostate diseases and erythrocytosis at 3 months, 6 months, and then every 6 months. We tested for sleep apnea at 6 and 12 months and then every 12 months. We tested for prostate cancer by manual examination and prostate-specific antigen. If a nodule was detected or if the prostate-specific antigen increased by 1.5 ng/mL in 2 yr (14) or by 2.0 ng/mL or more (trigger values) at any time, confirmed by repeat determination, the subject was referred for prostate biopsy. We tested for urinary obstruction by the Boyarsky symptom score (11), for urine flow rate (12) using a Uroflow 1000 urine flow meter (Medtronic-Dantec Corp., Allendale, NJ), and for residual urine in the bladder after voiding by a hand-held ultrasound instrument (BladderScan BVI 200, Diagnostik Ultrasound Corp., Redmond, WA). Erythrocytosis was determined by hematocrit and hemoglobin. Sleep apnea was assessed by a portable instrument, Edentrace 680 (EdenTec Corp, Eden Prairie, MN). For each study, a respiratory distress index was calculated by adding the number of apneic (>10 s of cessation of airflow) and hypopneic (cessation of airflow <10 s but accompanied by a fall of ≥4% in oxyhemoglobin saturation) episodes during that night’s sleep and dividing by the number of hours of sleep.

Statistical analyses

All analyses were performed using an intent to treat approach. For the 12 subjects who did not complete the protocol, the last observation was carried forward to all study endpoints. Within each group, the significance of the change over time was tested using the paired t test. Between groups, the principal test was the independent sample t test, comparing the mean change over time between the two treatment groups. We confirmed the results of this analysis using an analysis of covariance, comparing the final values adjusted for the pretreatment values. Because these two tests gave similar results, only the results of the comparisons of the differences are presented. For bone mineral density, we also performed repeated measures ANOVA, incorporating all of the bone mineral density data over time.

We then used linear regression to determine whether the effect of testosterone treatment, as measured by the difference between the treatment groups in mean changes in bone mineral density during the 36 months of treatment, depended on the pretreatment serum testosterone concentration in a linear fashion. The regression model (15) used pretreatment serum testosterone, treatment group, and their interaction as predictor variables and the change in bone mineral density as the outcome variable. Fisher’s exact test was used to compare the frequency of dichotomous events between groups. All analyses were performed using either SAS version 6.12 or STATA version 5 (STATA Corp., College Station, TX). All P values reported are two-sided; a significance level of less than 0.05 was considered statistically significant.

Results

Of the 108 men who enrolled in the study and were randomized to receive either testosterone or placebo, 96 completed the entire 3 yr of the protocol. Of the 12 who discontinued treatment, 1 (placebo group) was asked to because he was found to have a history of prostate cancer that he had concealed, 1 (testosterone group) developed prostate cancer, 2 died (both in the placebo group), and 8 (5 in the placebo group and 3 in the testosterone group) discontinued treatment for personal reasons.

Before treatment, the two treatment groups did not differ significantly from each other in age, height, weight, or serum testosterone, sex hormone-binding globulin, or calculated free testosterone concentrations (Table 1).

Serum testosterone

The mean serum testosterone concentration in the placebo-treated group did not change during the 36 months of the study (Fig. 1). The mean serum testosterone concentration in the testosterone-treated group increased from 367 ± 79 ng/dL (±sd; 12.7 ± 2.7 nmol/L) before treatment to 625 ± 249 ng/dL (21.7 ± 8.6 nmol/L; P < 0.001) by the sixth month
of treatment and remained relatively stable for the remainder of the study (Fig. 1).

The mean serum sex hormone-binding globulin concentration fell in both groups by 6 months and then remained stable for the remainder of the study. The fall in the testosterone-treated group was not significantly different from that in the placebo-treated group (Fig. 1).

The mean serum free testosterone concentration in the placebo-treated group did not change during the course of the study (Fig. 1). The mean serum free testosterone concentration in the testosterone-treated group increased from 5.0 ± 1.6 ng/dL (0.17 ± 0.06 nmol/L) before treatment to 9.5 ± 4.2 ng/dL (0.35 ± 0.15 nmol/L) by the sixth month of treatment and remained relatively stable for the remainder of the study (Fig. 1).

**Bone mineral density and markers of bone metabolism**

The bone mineral densities of the lumbar spine (L2–L4) were similar in the two treatment groups before treatment and increased significantly (*P* < 0.001) during 3 yr of treatment in each group (Table 2). The increase was 0.030 ± 0.050 g/cm² (2.5 ± 0.6%) in the placebo group and 0.048 ± 0.060 g/cm² (4.2 ± 0.8%) in the testosterone group (Fig. 2). The increase was not significantly different in the men treated with testosterone from that in the men treated with placebo. Adjusting for baseline bone mineral density or baseline serum testosterone did not affect the analysis of the bone mineral density results, nor did excluding those vertebrae with obvious sclerotic areas.

To evaluate further the effect of testosterone treatment on the bone mineral density of L2–L4, we used linear regression analysis, which demonstrated a significant (*P* = 0.02) negative interaction between the pretreatment serum testosterone concentration and the testosterone treatment effect on bone mineral density from 0–36 months. This relationship indicates that the lower the pretreatment serum testosterone concentration, the greater the increase in bone mineral density after 36 months in the testosterone-treated men above that in the placebo-treated men. Specifically, the analysis demonstrates that for a pretreatment serum testosterone concentration of 400 ng/dL (13.9 nmol/L), the increase is 0.9 ± 1.0% (SE) greater than that after placebo treatment, but if the pretreatment testosterone concentration is 300 ng/dL (10.4 nmol/L), the increase is 3.4 ± 1.2%, and if the pretreatment testosterone is 200 ng/dL (6.9 nmol/L), the increase is 5.9 ± 2.2% (Fig. 3). Repeating this analysis after excluding those vertebrae with obvious sclerotic changes gave similar results.

Linear regression analysis showed no significant relationship between the increment in serum testosterone concentration during treatment and the increment in bone mineral density of L2–L4 during treatment, nor did it show a relationship between the pretreatment bone mineral density of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
<th>Placebo</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td></td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td>73.0 ± 5.9</td>
<td>73.1 ± 5.8</td>
</tr>
<tr>
<td>HT (cm)</td>
<td></td>
<td>173.7 ± 6.5</td>
<td>174.5 ± 6.9</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td></td>
<td>81.1 ± 11.2</td>
<td>82.7 ± 9.5</td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td></td>
<td>369 ± 75</td>
<td>367 ± 79</td>
</tr>
<tr>
<td>Sex hormone-binding globulin (nmol/L)</td>
<td></td>
<td>71.1 ± 24.6</td>
<td>76.0 ± 23.6</td>
</tr>
<tr>
<td>Free testosterone (ng/dL)</td>
<td></td>
<td>5.1 ± 1.2</td>
<td>5.0 ± 1.6</td>
</tr>
</tbody>
</table>

Plus-minus values are pretreatment mean ± SD for all 108 subjects in the study. There were no significant differences between the two groups in any parameter. To convert values for testosterone and free testosterone to nanomoles per L, multiply by 0.03467.
There was no significant change in the bone mineral densities of the three sites in the hip in either group during the 36 months of treatment (Table 2), nor was there a change in bone-specific alkaline phosphatase or urinary N-telopeptides in either group during treatment (Table 2).

Lumbar spine radiographs showed a compression fracture of only one L2–L4 vertebra of one subject before treatment and of only the same vertebra in the same subject at 36 months. In the 96 men who completed the study, the radiographs showed osteophytes in L2–L4 vertebrae of 56 men (29 in the testosterone group and 27 in the placebo group) before treatment and in 57 men (29 in the testosterone group and 28 in the placebo group) at 36 months.

Potential adverse effects of testosterone treatment

Several parameters were monitored because they reflect potential adverse effects of testosterone. Twenty-seven subjects had 29 clinically significant prostate events during the 3 yr of the study (Table 3), 16 in the testosterone-treated group and 11 in the placebo-treated group (by 2-sided Fisher’s exact test, \( P = 0.337 \)). The most common event was an increase in prostate-specific antigen above the trigger values (see Subjects and Methods); in 16 men the increase did not persist when the test was repeated 1–2 months later, and in 4 it did. Prostate biopsy in those 4 detected prostate cancer in 1.

The mean serum prostate-specific antigen concentration did not change during the 36 months of treatment in the placebo-treated group (Fig. 4), but increased by a relatively small, but statistically significant (\( P < 0.001 \)), amount by 6 months of treatment in the testosterone-treated group and
remained relatively stable for the remainder of the study (Fig. 4). The urine flow rate, volume of urine in the bladder after voiding, and Boyarski symptom score were similar in the two groups before treatment and did not change significantly in either group during treatment (Table 4).

Hemoglobin and hematocrit did not change in the placebo-treated group during treatment, but both increased significantly \((P < 0.001)\) in the testosterone-treated group within 6 months and remained relatively stable for the remainder of the study (Fig. 5). Of the 12 men who were anemic (hemoglobin, <12.5 g/dL; hematocrit, <40%) before treatment, 4 of the 7 in the testosterone-treated group experienced increases to normal during treatment, but so did 2 of the 5 men who were initially anemic in the placebo-treated group. Three men treated with testosterone developed persistent erythrocytosis (hemoglobin, >17.5 g/dL; hematocrit, >52%) during treatment.

The respiratory distress index, a measure of apneic and hypopnic episodes during sleep, was similar in the 2 groups before treatment and did not change in either group during treatment (Table 4). Two men, 1 in each treatment group, experienced persistent increases in respiratory distress index from fewer than 5 apneic and hypopnic episodes/h to more than 15 episodes/h during the course of the study.

### Discussion

Treatment of men over 65 yr of age with testosterone increased their mean serum testosterone concentrations to within the midnormal range for young men. This increase in serum testosterone was not associated with an overall greater increase in bone mineral density of the lumbar spine in the testosterone-treated group than in the placebo-treated group. Secondary analysis, however, showed a significant testosterone treatment effect on bone density of the lumbar spine inversely related to the pretreatment serum testosterone concentration. This analysis showed a minimal effect (0.9%) of testosterone treatment over that of placebo for a pretreatment serum testosterone concentration of 400 ng/dL (13.9 nmol/L), but an increase of 3.4% for a pretreatment serum testosterone of 300 ng/dL (10.4 nmol/L) and an increase of 5.9% for a pretreatment serum testosterone of 200 ng/dL (10.9 nmol/L).

An increase in bone mineral density of the lumbar spine after testosterone treatment only in those men whose pre-treatment serum testosterone concentration was relatively low is consistent with other information concerning the effect of testosterone on bone. In a study of 12 men who were castrated in adulthood and did not receive testosterone replacement, the bone mineral density of the spine was lower the longer the time after castration (9), suggesting that a decrease in the serum testosterone concentration decreases bone density. In a study of 29 hypogonadal men treated with 100 mg testosterone enanthate once a week for 18 months, bone mineral density of the spine increased by 5% (10), suggesting that an increase in the serum testosterone concentration of hypogonadal men to normal restores bone density at least in part. To what degree the effect of testosterone on bone occurs directly and to what degree it is mediated via conversion to estradiol is unclear, but some direct effect seems possible, because human osteoblast-like cells in culture express androgen receptors (16), and mouse bone cells in culture proliferate in response to androgens that cannot be converted to estrogens (17).

The failure of bone mineral density at three sites in the hip to increase during testosterone treatment even in men with relatively low pretreatment serum testosterone concentrations could be at least partly related to the slower response of this bone to changes in gonadal steroids. In postmenopausal women, the bone mineral density of the hip does not increase as much in response to estrogen treatment as does that of the spine (18–20).

The failure to observe an effect of testosterone on markers

### TABLE 3. Prostate events during 3 yr of testosterone or placebo treatment

<table>
<thead>
<tr>
<th>Prostate event</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Testosterone</td>
</tr>
<tr>
<td>Prostatitis(^a)</td>
<td>1</td>
</tr>
<tr>
<td>PSA increase, transient(^b)</td>
<td>10</td>
</tr>
<tr>
<td>PSA increase, persistent(^c)</td>
<td>3</td>
</tr>
<tr>
<td>Prostate nodule(^d)</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>1</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>1</td>
</tr>
<tr>
<td>Increase in residual urine vol(^e)</td>
<td>1</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>0</td>
</tr>
<tr>
<td>Total prostate events</td>
<td>18</td>
</tr>
<tr>
<td>Subjects who had prostate events</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\) Symptomatic prostatitis.

\(^b\) Transient increase, An increase above the trigger value (see Materials and Methods) not corroborated 1–2 months later. Persistent increase, An increase that was corroborated.

\(^c\) A nodule detected by palpation during treatment when none was detected before.

\(^d\) Volume greater than 200 mL on two consecutive determinations 6 months apart.
of bone turnover could reflect the relatively mild overall degree of hypogonadism in these men. In a study of men who were frankly hypogonadal and previously untreated, testosterone treatment decreased urinary deoxypyridinoline and bone-specific alkaline phosphatase (10), and in a study of elderly men whose pretreatment serum testosterone concentrations were below 350 ng/dL, testosterone treatment decreased urinary hydroxyproline excretion (21).

The increase in bone mineral density of the spine in both treatment groups could have resulted at least in part from an increase in calcium and vitamin D intake in both groups. On the basis of a dietary history before treatment, we instructed all but 6 men in the placebo group and all but 4 in the testosterone group to take 1 pill daily containing 500 mg elemental calcium and 125 U vitamin D. In a recent study of 176 men over 65 yr of age who took 500 mg elemental calcium and 700 U vitamin D daily for 3 yr (22), the mean increase in spinal bone mineral density was slightly, but significantly, greater than that in a placebo group and was of a magnitude (2.1%) similar to that in the men who took calcium but not testosterone in the present study (2.5%).

We also measured several parameters that reflect conditions that testosterone might exacerbate. Testosterone treatment was associated with a small increase in the mean serum prostate-specific antigen concentration, but no increases in other parameters that reflect prostate disease. Testosterone treatment was also associated with small increases in mean hemoglobin and hematocrit values and the development of erythrocytosis in three men. Testosterone treatment was not associated with an increase in the respiratory distress index. Testosterone treatment, in short, was not associated with obvious deleterious effects. However, because this study was not designed to have sufficient statistical power to evaluate potential deleterious effects, we cannot draw definite conclusions about the risk of administering testosterone to men over 65 yr of age.

We conclude that increasing the serum testosterone concentration of men over 65 yr of age for 3 yr did not increase lumbar spine bone density overall, but did increase it in men with low pretreatment serum testosterone concentrations.

**Acknowledgments**

We thank the study subjects for their conscientiousness, Dr. Linda Atkinson of Alza Corp. for providing Testoderm, Dr. Kenneth Rockwell for distribution of the testosterone patches, Dr. Stephen R. Plymate for providing the computer program for calculating the free testosterone concentration, SmithKline Beecham for providing OsCal tablets, and Drs. Charles Abrams, Murray Dalinka, Nancy Ellis, J. A. Grisso, and Allan Pack for advice.
References


REQUEST FOR CASES FOR NIH STUDY

The hyperparathyroidism-jaw tumor syndrome and familial isolated primary hyperparathyroidism are rare entities. Sporadic and familial cases are sought with hyperparathyroidism and fibro-osseous jaw tumors (distinct from the brown tumors caused by hyperparathyroidism). In families (i.e. two or more affected), the disorder may cause parathyroid adenoma or parathyroid carcinoma in combination with fibro-osseous jaw tumors, polycystic kidneys, Wilms tumor, or nephroblastoma. We seek one or more cases from such families, including those with familial isolated primary hyperparathyroidism. Some cases may be evaluated or treated at the NIH Clinical Center. Contact Laura James RN, Ph.D. (301-435-8146), William Simonds, M.D., 301-496-9299, or Stephen Marx, M.D., 301-496-5051, Bldg. 10 Room 9C-101, Bethesda, MD 20892-1802.