

Testosterone Replacement Therapy for Treatment of Osteoporosis in Men

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Abstract

Osteoporosis and osteoporotic fractures are associated with significant morbidity and mortality in older men. Declining testosterone levels may occur with aging, and hypogonadism can develop secondary to different pathological disorders. Both testosterone and estrogen play an essential role in maintaining bone mineral density in men. Recent studies have added to the data showing that testosterone replacement therapy (TRT) can increase bone mineral density (BMD); however, long-term studies examining the effect on fracture risk are still lacking. Thus, current evidence does not support the use of TRT solely to treat osteoporosis in hypogonadal men at high risk for fracture. However, TRT may have a role in men at lower risk for fracture or as an adjunct to other pharmacological agents.

Keywords

Male hypogonadism, Testosterone replacement therapy, Bone mineral density, Osteoporosis

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Introduction

Osteoporosis is a significant health problem in older adults that causes substantial morbidity and disability, mainly due to osteoporosis-related fractures¹. Although rates of osteoporotic fractures are higher in women^{2,3}, up to 40% of overall osteoporotic fractures affect men⁴. In addition, mortality after fracture is higher in men compared to women⁴⁻⁶. Hypogonadism is an important cause of secondary osteoporosis in men, with some studies reporting that 16–30% of osteoporosis in men is related to hypogonadism⁷. Epidemiologic studies suggest that both testosterone and estradiol play a role in attainment and maintenance of bone density. Testosterone treatment can increase bone density, but data for fracture risk are still lacking. This review aims to examine the most recent evidence of the effect of testosterone replacement therapy on bone health in men.

The effect of sex steroids on peak bone mass attainment

Although the main effect of testosterone on bone maintenance is mediated through its conversion to estradiol⁷, it also affects bone metabolism via conversion to active dihydrotestosterone (DHT) by 5 α -reductase, which binds to androgen receptors in bone^{4,7,8}. Androgen receptors have been reported to be present on osteoblasts, osteoclasts, osteocytes, and pluripotent parenchymal bone marrow stromal cells⁷. Testosterone's role in the osteoblast is essential for promoting trabecular bone, but not cortical bone formation, which is an important determinant of bone strength and fracture risk⁷. Testosterone regulates the differentiation and proliferation of osteoblasts and chondrocytes through positively regulating the expression of insulin-like growth factor-1 (IGF-1) and IGF-binding protein (IGF-BP) and thus promotes bone formation during puberty⁸. Additionally, testosterone deficiency promotes the activation of nuclear factor kappa-B ligand (RANKL) from osteoblasts, which results in increased bone resorption and a decrease in bone mineral density (BMD)⁸. Although the role of testosterone on osteocytes is less clear⁷, the presence of androgen receptors in osteocytes suggests that testosterone plays a role in its differentiation and prevention of age-related trabecular bone loss⁷. In addition to its effect on BMD, testosterone is essential for maintaining muscle strength and physical performance in men, with testosterone deficiency leading to sarcopenia and risk of falls⁸.

Estrogen has effects on both bone formation and resorption as it inhibits sclerostin, decreases osteoblast and osteocyte apoptosis, suppresses RANK-L, and induces apoptosis in osteoclasts⁹. We know from case studies of males with aromatase mutations, who cannot convert testosterone to estradiol, bone growth plate closure does not occur until treatment with estrogen¹⁰. In males described with an estrogen alpha receptor mutation, BMD was strikingly low and not responsive to estrogen administration despite increases in serum estradiol¹¹.

Mechanistic studies have helped us understand the importance of estradiol in bone metabolism of adult men. Finkelstein and

colleagues administered goserelin acetate (a GnRH agonist) to healthy young men¹². They then added back testosterone in varying daily doses (0/1.25/2.5/5/10 gram of topical gel) to one group and testosterone in the same doses with the addition of an aromatase inhibitor to another group over 16 weeks. There was a third control group of untreated men, reflecting endogenous testosterone and estradiol (E2) production. In the group with add back testosterone, areal bone mineral density (aBMD) trended down in concordance with lower testosterone levels but did not significantly differ from controls. However, in the group with testosterone plus aromatase inhibition, aBMD declined 1–2% in all groups independent of testosterone level. Changes were more apparent by quantitative computed tomography (qCT) measurements where E2 deficiency reduced trabecular BMD independent of testosterone dose as well as cortical and trabecular volumetric BMD (vBMD) at the tibia and radius. Serum C-telopeptide (CTX) increased significantly when testosterone was <200 ng/dl or serum E2 was <10 pg/ml. These findings suggested that hypogonadism affects the skeleton mainly due to estrogen deficiency¹².

Epidemiologic studies have examined the correlations between testosterone and serum E2 levels and osteoporosis. Fink and colleagues demonstrated a higher prevalence of osteoporosis in older men with both total testosterone and estrogen deficiency¹³. Other studies have investigated the relationship between sex steroids and BMD in aging men¹⁴. Data from MrOS showed that both testosterone and estrogen in elderly men were predictors of BMD¹⁵. The Rancho Bernardo Study (RBS) showed that bioavailable testosterone and estrogen were associated with higher BMD in men, with the strongest association being with bioavailable estrogen levels¹⁶.

Few studies have examined the relationship between circulating sex steroids and osteoporotic fracture in aging men, with conflicting results¹⁴. The Tromsø study showed that sex steroids were not associated with fracture risk¹⁷, and in the Concord Health and Ageing in Men Project (CHAMP) study, testosterone and estradiol levels were not significantly associated with hip or non-vertebral or hip fracture incidence¹⁸. In contrast, low free testosterone levels were positive predictors of prevalent osteoporotic fracture in older men in the MrOS study¹⁵. Estradiol is clearly crucial in skeletal health formation and maintenance; however, more data is needed on the linkage to osteoporotic fractures. Cellular senescence and changes related to aging need to be taken into consideration as well, as they are inexorably linked with bone loss^{19,20}.

Testosterone hormone replacement in the treatment of osteoporosis

Since testosterone, whether by its direct effects or as a pro-hormone, plays a vital role in maintaining BMD in men, it is expected that testosterone replacement therapy (TRT) would have a beneficial effect in improving BMD in hypogonadal men⁸. Several interventional studies over the past 5 years have examined the role of testosterone replacement in older men.

In a sub-analysis of the EARTH study done in Japan, 74 years old men with a history of osteopenia and hypogonadism were divided into a TRT group (35 patients) and a control group (34 patients)²¹. Hypogonadism was diagnosed based on the Japanese biochemical criteria where TRT is indicated for levels of free testosterone < 8.5 pg/ml and is an option for treatment with free testosterone levels between 8.5–11.8 pg/ml²¹. The TRT group received testosterone enanthate 250 mg every four weeks for 12 months, whereas the control group received no treatment²¹. There was a significant increase in BMD by 12 months in the TRT treatment group as well as the control group to a smaller degree²¹. However, the study did not evaluate the rate of fractures nor the adverse effects associated with testosterone treatment.

The Bone Trial of the Testosterone Trials (T-Trials) assessed whether testosterone treatment in older men with low testosterone levels would improve the volumetric bone mineral density (vBMD) and estimated bone strength²². Men 65 years and older with clinical evidence of hypogonadism and average serum testosterone concentration < 275 ng/dl on two occasions were divided into an intervention group and a control group. Inclusion was not based on low bone density, and men with severe osteoporosis were excluded, as were those using any medications affecting bone (other than calcium and Vitamin D)²². The intervention group received testosterone treatment in the form of a topical gel, and the control group was treated with a placebo gel for 1 year²². In addition, all participants received calcium-vitamin D supplements (600 mg-400 units) twice daily²². There was a significant increase in the mean lumbar spine vBMD of 7.5% (95% CI, 4.8% to 10.3%) in the testosterone treatment group, compared with 0.8% (95% CI, -1.9% to 3.4%) in the placebo group (95% CI, 4.8% to 8.7%; $P < 0.001$)²². Baseline testosterone, estradiol, or vBMD did not significantly affect the magnitude of trabecular vBMD, but the magnitude of the percent increase in spine trabecular vBMD from baseline to month 12 was significantly associated with changes in total testosterone ($\beta = 0.01$, $\rho = 0.25$, $P = .01$) and estradiol ($\beta = 0.17$, $\rho = 0.37$, $P < .001$) in the testosterone-treated group²². They reported that an increase in testosterone level by 200 ng/dL was associated with a 6.1% increase in trabecular vBMD. A 15 pg/mL increase in estradiol was associated with a 6.3% increase²². There was an increase in the peripheral and whole-bone vBMD of the spine and trabecular, peripheral, and whole-bone vBMD of the hip in the group who received testosterone treatment and a significant increase in the estimated bone strength of peripheral and whole bone²². There was no difference in the rate of fractures between the two groups (6 fractures occurred in each group during the treatment year)²². Furthermore, there was no increased incidence of cardiovascular or prostate adverse events observed in the testosterone-treated group²².

More recently, the T4Bone study examined the effect of testosterone treatment in bone microstructure using high-resolution peripheral quantitative computed tomography (HR-pQCT) in 136 men 50–74 years of age with impaired glucose tolerance or newly diagnosed type 2 diabetes mellitus (T2DM) and a

morning testosterone level < 403 ng/dl²³. Again, this trial was not looking at men with low BMD. For two years, the intervention group received intramuscular testosterone undecanoate 1000 mg every three months (after a 6-week loading dose)²³. Compared to placebo, testosterone treatment significantly increased the tibial cortical vBMD ($P < 0.001$), radial cortical vBMD ($P = 0.005$), total vBMD at both tibia ($P < 0.001$) and radius ($P = 0.002$)²³. There was also a significant increase in both the cortical area (tibia $P < 0.001$, radius $P = 0.002$) and in cortical thickness (tibia $P < 0.001$ and radius $P = 0.006$)²³. However, the effect of testosterone treatment on trabecular bone was not consistent²³. Men with lower baseline serum testosterone or lower baseline serum estradiol were not more likely to have a larger treatment effect and gain more bone during treatment²³. Testosterone treatment was associated with a significant decrease in bone turnover markers CTX ($P < 0.001$) and procollagen type 1 N-terminal propeptide (P1NP) ($P < 0.001$) compared to placebo²³. In addition, testosterone treatment, compared with placebo over 2 years, increased BMD at the lumbar spine ($P < 0.001$), at the total hip ($P < 0.001$), and at the femoral neck ($P < 0.001$)²³. Although testosterone treatment was not associated with a greater incidence of serious adverse events, it was associated with a greater risk of experiencing a hematocrit $\geq 54\%$, which occurred in 20% (61/308) of men assigned to testosterone versus 1% (3/293) in men assigned to placebo treatment²³. The study did not assess the effect of testosterone treatment on fracture outcomes²³.

Although the EARTH study, the Bone Trial of the T-Trials, and the T4Bone trial all showed a significant increase in bone density in hypogonadal men treated with testosterone, there are some significant differences between these trials (Table 1). Modalities and endpoints were different, and these trials cannot be compared head-to-head. However, testosterone treatment resulted in a more considerable increase in trabecular bone (7% increase in spine trabecular vBMD in 1 year) in the Bone Trial of the T-Trials, a modest increase in aBMD in EARTH ($5.0 \pm 5.0\%$ BMD at the AP spine in 12 months), while in the T4Bone trial, a minor increase (3% increase in tibial cortical vBMD in 2 years) in the cortical bone was observed^{21–24}. There are clear differences in the baseline characteristics of the participants. The testosterone threshold for eligibility was 403 ng/dl (14 nmol/L) in the T4Bone trial, while participants in the Bone Trial of the T-Trials had lower baseline testosterone levels (238.8–229 ng/dl)/(8.0–8.3 nmol/L) and participant in the EARTH study had low free testosterone levels ($7.52 \pm 2.38/ 6.71 \pm 2.27$ pg/ml)^{21–24}. Subsequently, estradiol levels were different between groups as well, which led to varying effects on cortical and trabecular bone. Men in the Bone Trial of the T-Trials were older, with an average age of 72 years old, in contrast to men in the T4Bone trial, who were younger, with a mean age of 60 years, while the age for men in the EARTH study ranged between 66.1 ± 8.4 years in the treatment group and 69.5 ± 7.3 years in the placebo group^{21–24}. Additionally, the techniques used for assessing the BMD were different²⁴. Quantitative computed tomography (QCT) was used in the Bone Trial, high resolution peripheral quantitative computed tomography (HRpQCT) was

Table 1. Comparison between the EARTH study, the Bone Trail of the T-Trials and the T4Bone trial.

	The EARTH study (Treatment/Placebo)	Bone Trial of the T-Trials (Treatment/Placebo)	T4Bone trial (Treatment/Placebo)
Mean age in years	66.1 ± 8.4/ 69.5 ± 7.3	72.3/ 72.4	60.0/ 60.3
BMI	22.4 ± 2.6/ 22.1 ± 3.2	30.7/31.8	34.1/34.8
Baseline BMD	Osteopenia	Normal	Normal
Baseline testosterone level	7.52 ± 2.38/ 6.71 ± 2.27 pg/ml (free testosterone)	229.6/238.8 ng/dl (8.0/8.3 nmol/ L) (total testosterone)	403/414 ng/dl (14.0/14.4 nmol/L) (total testosterone)
Baseline estradiol level	Not measured	20.5/22.4 pg/ml	55 pg/ml (202 pmol/L) in both groups
Anatomic site of assessment	BMD at the AP lumbar spine (L2–L4)	Axial bones (spine and hip)	Appendicular bones (radius and distal tibia)
The magnitude of increase in the primary endpoint in the treatment group	5.0 ± 5.0 % increase in BMD at the AP lumbar spine in 12 months	7% increase in spinal trabecular vBMD in 1 year	3% increase in tibial cortical vBMD in 2 years
Type of bone where effects observed	AP lumbar spine	A larger increase in trabecular bone	A larger increase in cortical bone
Modality	DXA scan	QCT	HRpQCT

AP: anterior-posterior, BMI: body mass index, BMD: Bone mineral density, vBMD: volumetric bone mineral density, DXA: dual-energy X-ray absorptiometry, QCT: quantitative computed tomography, HRpQCT: high resolution-peripheral quantitative computed tomography

used in the T4Bone trial²⁴, while DXA scan was used in the EARTH study²¹.

Recent studies have also investigated how DHT and estradiol levels during testosterone therapy may correlate with bone density changes²⁵. A recent secondary analysis of data from the T-Trials assessed the association of changes in total testosterone, estradiol, and DHT levels over the 12 months of testosterone treatment with changes in vBMD of the trabecular bone of the lumbar spine²⁵. Testosterone, DHT, and estradiol hormones were ranked for their relative contribution to predicting this change²⁵. Among 394 men in the testosterone arm of the T-Trials, the average change in estradiol was the strongest predictor of change in vBMD of the trabecular bone of the lumbar spine. The most significant increase in vBMD of the trabecular bone of the lumbar spine was among participants, with more substantial increases in estradiol levels²⁵. Across the range of increases in estradiol levels, the change in vBMD was more remarkable in participants with a greater change in testosterone and DHT levels than with a low change in testosterone and DHT levels. The result supports the view that both androgens and estrogens play roles in regulating bone health in men²⁵.

Lastly, there have been recent efforts to assess changes in bone quality in men with hypogonadism. The trabecular bone score (TBS) is an indirect measure of spinal bone microarchitecture obtained from texture analysis of DXA scans of the lumbar spine²⁶. TBS can provide information on bone microarchitecture

and fracture risk independent of DXA. In the Bone trial of the T-Trials, 211 hypogonadal men divided into testosterone and placebo groups had subsequent TBS measurements that assessed changes in bone quality. The mean percent change in TBS from baseline after 12 months of treatment was not significantly different between the two groups 1.6 (95% confidence intervals (CI), 0.2, 3.9) in the testosterone group and 1.4 (95% CI, -0.2, 3.1) in the placebo group (p=0.70); however, there was a significant increase in vBMD at the lumbar spine and aBMD between the two groups. This data suggested that TBS cannot be used clinically to monitor the effectiveness of treatment with testosterone on bone microstructure²⁷.

Summary/Conclusion

Testosterone plays an integral role in maintaining BMD in men. Although studies showed that testosterone replacement therapy (TRT) improves BMD in men with and without hypogonadism, there is not enough evidence of its impact on fracture risk. Additionally, since TRT can be associated with the risk of cardiovascular events and prostate cancer growth in older people, we should proceed with caution when recommending testosterone for bone health and ensure men are truly hypogonadal before treating with testosterone. Thus, the Endocrine Society recommends using a pharmacological agent with proven benefits in fracture risk reduction for treating osteoporosis in men. TRT can be considered for hypogonadal men at lower risk for fracture or in those who have contraindications to the other anti-osteoporotic agents. Long-term studies evaluating the effect of TRT on fracture risks are needed.

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