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Effect of testosterone treatment on the trabecular bone score in older men with low serum testosterone

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Abstract

Purpose: In the Bone Trial of the Testosterone Trials, testosterone treatment increased trabecular volumetric bone mineral density (vBMD) and increased estimated bone strength as determined by finite element analysis. The Trabecular Bone score (TBS) is an indirect measure of vertebral bone microarchitecture. TBS predicts fracture independent of lumbar spine areal (a)BMD. The objective of this study was to examine the effect of testosterone treatment on TBS compared to its effects on vBMD and aBMD.

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Drafting manuscript: JAC.
Revising and approving final manuscript: JAC, SSE, PJS, KEE, AVS, TMK
SSE takes full responsibility for the integrity of the data analysis.

Methods: 211 men were enrolled in the Bone Trial of the Testosterone Trials. Of these, 197 men had 2 repeat TBS and vBMD measurements; 105 men were allocated to receive testosterone and 92 men to placebo for one year. TBS, aBMD and vBMD were assessed at baseline and month 12.

Results: There was no difference in the percent change in TBS by randomized group: 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. In contrast, vBMD increased by 6% (95% CI 4.5–7.5) in the testosterone group compared to 0.4% (95% CI −1.65–0.88) in the placebo groups.

Conclusions: TBS is not clinically useful in monitoring the one-year effect of testosterone treatment on bone structure in older hypogonadal men.

SUMMARY

The Trabecular Bone score (TBS) is an indirect measure of vertebral bone microarchitecture. Our objective was to examine the effect of testosterone treatment on TBS. 197 hypogonadal men were randomized to testosterone or placebo. After 12 months, there was no difference in the changes in TBS by randomized group.

Keywords

Trabecular Bone Score (TBS); Hypogonadal men; Testosterone treatment; Bone mineral density; Testosterone Trials

INTRODUCTION

Osteoporosis and bone fractures increase exponentially with increasing age in men, with sharp increases after age 50.[1] Although the hip fracture rate in men is only one-half that in women, men are more likely to die after a hip fracture than women.[2] The serum testosterone concentration also decreases with increasing age in men.[3,4] Several lines of evidence suggest that the fall in testosterone with age in men plays a role in the increase in osteoporosis and bone fractures as they age. Severe hypogonadism, due to either pituitary or testicular disease or to pharmacologic treatment for prostate cancer, causes a more pronounced decrease in bone mineral density (BMD), and bone strength. In men who are hypogonadal, replacement of testosterone in men increases BMD, trabecular connectivity and bone strength.[5–8]A few previous randomized placebo- controlled trials have evaluated the effect of testosterone on areal (a) BMD in older men; most, but not all, reported a modest effect of testosterone on spine aBMD, reflecting the greater proportion or trabecular bone in the spine [5–8]. However, these studies were limited by small sample sizes, pretreatment testosterone concentrations that were not unequivocally low, poor adherence and heterogeneity with respect to testosterone formulation, dose and duration of treatment.

We reported results of the Bone Trial of the Testosterone Trials in 211 older men with moderately low testosterone for no other reason than age.[9] Findings demonstrated that testosterone treatment for one year, compared to placebo, markedly increased trabecular volumetric (v) BMD (the primary outcome), as determined by quantitative computed tomography (QCT), especially in the spine but also in the hip, and increased estimated bone strength, as determined by finite element analysis (FEA). However, QCT scans

are costly, have high radiation doses and are unlikely to be easily incorporated into routine clinical practice. The trabecular bone score (TBS) is an indirect measure of spinal bone microarchitecture that can be obtained from texture analysis of routine dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine.[10] TBS has been shown to be associated with bone microarchitecture and fracture risk, providing information independent of traditional aBMD by DXA. Several meta-analyses have reported that TBS predicts osteoporotic fractures independent of aBMD, clinical risk factors and the fracture risk assessment tool (FRAX ®). [11–13] It has been suggested that using TBS in conjunction with FRAX ® and aBMD increases the accuracy of fracture prediction and will improve personalized clinical osteoporosis management.[12]

The goal of this study was to test the hypothesis that older hypogonadal men enrolled in the Bone Trial of the Testosterone Trials who were allocated to testosterone treatment would experience significantly greater increases in TBS at 12 months compared to men allocated to placebo. We further hypothesized that the magnitude of effect of testosterone treatment on TBS will be similar to that of volumetric BMD by QCT.

METHODS

Participants

To be included in the Testosterone Trials, men had to be at least 65 years old, have subjective and objective evidence of impaired sexual or physical function or reduced vitality, and have a serum testosterone concentration on 2 morning specimens that averaged less than 275 ng/dL (27). Potential participants were excluded if they were at increased risk of conditions that testosterone treatment might exacerbate. Potential participants for the Bone Trial were also excluded if they were taking a medication known to affect bone, except for calcium and vitamin D preparations; if they did not have at least 1 evaluable lumbar vertebra; or if they had a DXA T-score at any site of less than −3.0. All men eligible for the Physical Function, Vitality and/or Sexual Function trial were eligible for the Bone Trial. Of the 211 men enrolled in the Bone Trial, 105 in the Testosterone group and 92 in the Placebo group had two repeat TBS measurements.

Lumbar spine vBMD by QCT

Computed tomographic scans of the lumbar spine were performed at baseline and month 12. The QCT reading center trained the technicians at each of the 9 clinical sites to ensure a consistent imaging technique. The spine scan extended from mid-T12 to mid-L4; L1 and L2 measurements were used preferentially, but if not assessable, L3 was used; the values of 2 vertebrae were averaged. Each image included an external bone mineral phantom (Mindways Software) beneath the participant for calibration. A second phantom (Mindways) was scanned monthly to detect any field nonuniformity or scanner drift. The mean (range) coefficient of variation for all scanners was 0.23% (0.13%–0.29%). Image processing, vBMD measurements, and finite element strength analyses were performed at a central site (O.N. Diagnostics), blinded to treatment group, by analysis of the CT scans using VirtuOst software. O.N. Diagnostics also maintained quality control of the CT data

collection. For the vertebrae, trabecular vBMD was measured using an elliptical region of interest in the trabecular centrum.

Lumbar spine aBMD by DXA

DXA scans of the lumbar spine were obtained at the baseline and 12-month visits using Hologic densitometers. Quality control of DXA was centrally monitored by the University of California San Francisco (UCSF) Coordinating Center, DXA Quality Assurance (QA) Center. The DXA operators at each of the 9 sites were certified at the beginning of the trial. Scans were analyzed locally, using the same software version at baseline and follow-up, and sent to the coordinating center for incorporation into a central database. Scans were flagged if they had an artifact or positioning problem or if the local technician had questions. A total of 21% of spine scans and 26% of hip scans were flagged. We also reviewed a random sample of scans for quality. Longitudinal performance of densitometers was monitored with regular scanning of a spine phantom. Femoral neck T- scores were calculated using The National Health and Nutrition Examination Survey reference aBMD data for white females, age 20–29. For the lumbar spine T-score, Hologic's reference data base for 30 year old white females was used.

Trabecular bone score

Anonymized spine DXA files from the Testosterone Trial database were archived at UCSF, the DXA QA Center. TBS measurements were obtained from these images using TBS iNsight Software, version 2.3; (Med-Imaps, Pessac, France). The DXA QA Center performed all the TBS measurements and transferred the results to the Data Coordinating Center for statistical analyses.

We randomized the order of the scans for TBS analysis so that the operator did not know whether the scan was the initial or follow-up scan. The software uses the anteroposterior spine raw image(s) from the densitometer, including the aBMD region of interest and edge detection, so that the TBS calculation is performed over exactly the same region of interest as the aBMD measurement. TBS was calculated as the mean value of the individual measurements for L1 to L4. Vertebral levels were excluded if there were artifacts e.g., presence of metal or if the level was substantially discordant with other levels. A BMD was considered discordant if it differed by more than 1.0 T score between adjacent levels.

Statistical analyses

We used the same analytical approach that was used for the primary outcome. We compared the mean, median, and distribution of baseline and 12-month change in TBS by randomized group. Analyses followed the intention-to-treat principle; men allocated to testosterone were compared with men allocated to placebo, regardless of adherence or T level achieved. All participants who had baseline and month 12 lumbar spine TBS values were included in the analyses. The effect of testosterone compared with placebo on percent change in TBS, aBMD and vBMD was evaluated by multivariable linear regression, adjusted for balancing factorsused to allocate men to testosterone or placebo (study site, baseline testosterone concentration, age and use of phosphodiesterase inhibitors) as required for the analysis of

interventions allocated by minimization. We also examined the correlation between changes in TBS, LS aBMD and LS vBMD.

RESULTS

Baseline characteristics of men in the 2 treatment arms were similar, including age (72 years), BMI, total and free testosterone levels, lumbar spine aBMD, vBMD and TBS, Table 1. The average lumbar spine and femoral neck T scores indicated that the majority of men were not osteoporotic. Indeed, 30% of men had femoral neck T scores in the low bone mass range (−2.5 to ≤−1.0) and only 1 % were in the osteoporotic range (<−2.5) with no difference by randomized group. The mean percent change in TBS from baseline to month 12 was 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, Figure 1. The percent change in TBS over the 12 months was much smaller than that observed for LS vBMD and aBMD: vBMD, Testosterone, 6.0% (95% CI, 4.5, 7.5); placebo, 0.4% (95% CI, −1.65, 0.88) and aBMD (testosterone, 2.4% (95% CI, 1.8, 3.0) and placebo, 1.4% (95% CI, 0.7, 2.2). Additional adjustment for BMI had no effect on the results (data not shown).

In the pooled group of men, there was a modest correlation between baseline TBS and baseline vBMD (r=0.10) and a somewhat stronger correlation with aBMD (r= 0.32). There was a very low correlation between changes in TBS and changes in vBMD (r=0.03) and changes in aBMD (r= 0.07).

DISCUSSION

Testosterone treatment of older men with low testosterone did not increase TBS even though it significantly increased the lumbar spine vBMD by QCT and aBMD by DXA. Of note, the effect size for vBMD was substantial for vBMD compared to aBMD.

Previous smaller studies have evaluated the effect of various osteoporosis treatment regimens on the TBS. Treatments that increased aBMD also tended to increase TBS, but the magnitude of the increase in TBS was much smaller than that of aBMD. For example, Krieg et al evaluated the effect of non-estrogen anti-resorptive drugs primarily bisphosphonates. Anti-resorptive agents increased aBMD by 1.9%/year but increased TBS by only 0.2%/year [(14)]. In a subset of 54 women enrolled in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Trial, zoledronic acid compared to placebo increased aBMD of the lumbar spine at 36 months +9.6% (p<0.0001) but increased TBS by only 1.4% (p=0.03) [(15)].

Generally, anabolic agents tend to have a greater effect on TBS than anti-resorptive agents. Abaloparatide improved TBS after 24 weeks at the higher doses of 80μg and 40μg; an increase in TBS greater than the least significant change was achieved by 52% of patients treated with Abaloparatide 80ug versus 30% of those treated with teriparatide [(16)]. In a subset of women in the FREEDOM study, denosumab increased TBS but the magnitude of the increase, although statistically significant(P<0.014) was much lower than lumbar spine aBMD. [(17)]

Most studies of TBS were carried out in women. However, in one study, 36 hypogonadal men, mean age 50.6 years (spine T-score −0.9) were treated with 50 mg of testosterone gel daily for 2 years. The TBS increased 1.8%; 56% men experienced an increase in TBS and among these men, the mean increase was 6.4% [(18)].

The mean TBS values in the men enrolled into the Testosterone trial were lower (≈1.2–1.3) than observed in the Manitoba study of healthy men, ≈1.32, perhaps reflecting their older age (73 vs 64 yrs). [(19)] It may also reflect greater BMI because the correlation between TBS with aBMD and vBMD was much stronger in non-obese vs. obese individuals. [(20)]

We found much weaker correlations between TBS and vBMD and aBMD than previously reported. In MrOS, TBS was correlated with LS vBMD but the association was non-linear. [(20)] Higher correlations were observed among men with normal TBS (r=0.71) compared to those with degraded TBS (r=0.09). The correlation also differed by body mass index (BMI) with slightly higher correlations among the men with lower BMI, (17–24 kg/m^2), r=0.47 compared to higher BMI, (30–37 kg/m^2), r=0.38. The lower correlations observed in the Testosterone Trial may reflect the relatively high rate of obesity with an average BMI of 31.2 kg/m^2.

The strength of this trial includes the unequivocally low testosterone concentrations of the participants, double-blind design, increase in serum testosterone to mid-normal for young men, and excellent participant retention. An important limitation is the relatively small sample size, limiting our ability to detect small differences in TBS changes. In addition, treatment duration was only 12 months; it's possible that longer duration of treatment with testosterone would improve TBS. This version of the TBS software (pre version 4) seems to be affected by body size on Hologic scanners. Our randomized design makes this less of an issue. Nevertheless, we performed an analysis adjusting for BMI and the results were the same. In the entire Testosterone trial, there was no difference in weight change by randomized group.

We conclude that although testosterone treatment of older, hypogonadal men significantly increases vBMD and aBMD, it does not increase TBS. These results suggest that TBS would not be clinically useful in monitoring the effect of testosterone treatment on bone structure over the short term in hypogonadal men.

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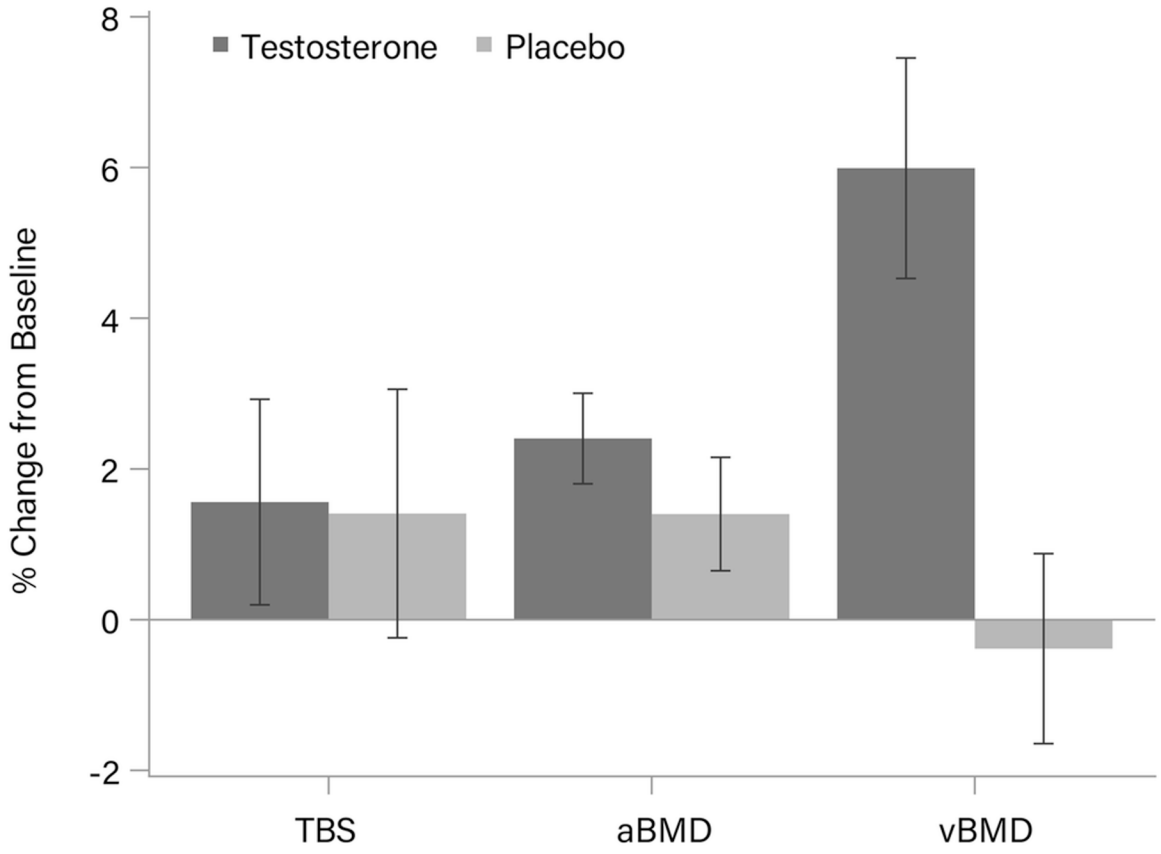

Figure 1:
Percent changes in Lumbar spine, TBS, aBMD and vBMD in men randomized to testosterone treatment for one year compared with placebo

Table 1.

Baseline Characteristics by Treatment Group: n(%) or Mean(SD)

Characteristics	Testosterone	Placebo
N	105 (100%)	92 (100%)
Age	72.4 ± 6.4	72.6 ± 5.6
Race		
Caucasian	90 (85.7%)	81 (88.0%)
African-American	5 (4.8%)	3 (3.3%)
Other	10 (9.5%)	8 (8.7%)
BMI (g/m^2)	30.8 ± 3.7	31.9 ± 3.2
Alcohol consumption (drinks/week)	2.5 ± 3.6	3.8 ± 5.1
Smoking history and current status		
History of Tobacco Smoking	67 (63.8%)	65 (70.7%)
Smoke cigarettes or cigars now	6 (5.7%)	6 (6.5%)
History of Diabetes	41 (39.0%)	36 (39.1%)
Total Testosterone (ng/dL)	229.9 ± 66.4	239.3 ± 64.7
Free Testosterone (pg/mL)	61.3 ± 20.3	64.8 ± 21.1
Estradiol (pg/mL)	20.6 ± 6.8	22.2 ± 6.0
TBS (unitless)	1.265 ± 0.141	1.241 ± 0.145
LS aBMD (g/cm^2)	1.176 ± 0.192	1.179 ± 0.193
LS T-Score	1.21±1.76	1.24±1.77
FN T-Score	−0.29±1.15	−0.33±1.20
QCT (g/cm^3)	102 ± 32	99 ± 27

LS, Lumbar spine; FN, femoral neck