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# Effect of Testosterone Replacement on Trabecular Architecture in Hypogonadal Men

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**ABSTRACT: We evaluated the effect of testosterone treatment on trabecular architecture by μMRI in 10 untreated severely hypogonadal men. After 2 years, μMRI parameters of trabecular connectivity improved significantly, suggesting the possibility that testosterone improves trabecular architecture.**

**Introduction:** Osteoporosis, characterized by low BMD and diminished bone quality, is a significant public health problem in men. Hypogonadal men have decreased BMD and deteriorated trabecular architecture compared with eugonadal men, and testosterone treatment improves their BMD. We tested the hypothesis that testosterone replacement in hypogonadal men would also improve their trabecular architecture.

**Materials and Methods:** We selected 10 untreated severely hypogonadal men and treated them with a testosterone gel for 24 months to maintain their serum testosterone concentrations within the normal range. Each subject was assessed before and after 6, 12, and 24 months of testosterone treatment by magnetic resonance microimaging (μMRI) of the distal tibia and by DXA of the spine and hip. The μMRI parameters reflect the integrity of the trabecular network and include the ratio of all surface voxels (representing plates) to curve voxels (representing rods) and the topological erosion index, a ratio of topological parameters expected to increase on trabecular deterioration to those expected to decrease. The higher the surface-to-curve ratio and the lower the topological erosion index, the more intact the trabecular network.

**Results:** Serum testosterone concentrations increased to midnormal after 3 months of treatment and remained normal thereafter. After 24 months of testosterone treatment, BMD of the spine increased 7.4% ($p < 0.001$), and of the total hip increased 3.8% ($p = 0.008$). Architectural parameters assessed by μMRI also changed: the surface-to-curve ratio increased 11% ($p = 0.004$) and the topological erosion index decreased 7.5% ($p = 0.004$).

**Conclusions:** These results suggest the possibility that testosterone replacement of hypogonadal men improves trabecular architecture.

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**Key words: testosterone, male hypogonadism, trabecular architecture, osteoporosis, magnetic resonance microimaging**

## INTRODUCTION

OSTEOPOROSIS IS A significant public health problem in men as well as in women. Vertebral fracture rates over age 50 are as high in men as in women,(1,2) and although hip fracture rates in men are only one-half that in women,(3,4) the mortality after hip fracture in men is double that in women.(5,6) Osteoporosis is characterized by bone loss and deterioration of the trabecular architecture. The normally interdigitating plates become fenestrated and eventually become rods, and the rods become disconnected, leading to decreased strength and increased tendency to fractures.(7–9)

Severe hypogonadism is a well-documented cause of osteoporosis in men, as in women. Men who are severely hypogonadal because of pituitary or testicular disease have lower BMD than eugonadal men,(10,11) and testosterone replacement of severely hypogonadal men increases their BMD.(10,12,13) We recently showed that men who are severely hypogonadal also have deteriorated trabecular architecture by magnetic resonance microimaging (μMRI). This noninvasive technique provides sufficiently high resolution to discern individual trabeculae and therefore can be considered to be a "virtual bone biopsy."(14) The purpose of this study was to determine if testosterone replacement of these severely hypogonadal men would reverse the deterioration of their trabecular architecture.

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Dr Gomberg serves as a consultant, received corporate appointments, and owns stock in MicroMRI Inc. Dr Wehrli owns stock in MicroMRI Inc. All other authors have no conflict of interest.

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## MATERIALS AND METHODS

The overall study design was to select 10 men who had severe and untreated hypogonadism caused by known disease, treat them with replacement doses of testosterone for 2 years, and assess their trabecular architecture during this time by μMRI. The Institutional Review Boards at the University of Pennsylvania and The Children's Hospital of Philadelphia approved this study. Each subject gave written informed consent before entry.

### *Subjects*

We recruited 10 untreated hypogonadal men from the Endocrinology Practice of the University of Pennsylvania. They had severely subnormal early morning serum testosterone concentrations on two occasions (mean, 88 ng/dl [3.1 nM]) as a consequence of documented pituitary or hypothalamic disease and had received no testosterone treatment for at least 4 years before enrollment. All 10 men had secondary hypogonadism: 8 pituitary adenomas, 1 pinealoma, and 1 Kallmann's syndrome. Hypogonadism developed in adulthood in nine; the 10th, a 46-year-old patient with Kallmann's, was treated with testosterone enanthate from 15 to 25 years of age before discontinuing it. The estimated duration of hypogonadism was 2–30 years (median, 5 years). Eight of the men had never been treated with testosterone; of the two who had been treated, one had not been treated for 4 years and the other for 20 years before entering the study. The median age at entry was 51 years (range, 31–78 years). Three men had previously been found to be hypothyroid and/or hypoadrenal and were stably replaced with thyroxine and/or hydrocortisone, which were continued during the study. One man was found to be hypothyroid and hypoadrenal shortly before entry into the study and was treated with replacement doses of thyroxine and hydrocortisone.

We also recruited 10 eugonadal men. They were required to have a serum testosterone concentration >300 ng/dl (10.4 nM) early in the morning on two occasions and a normal BMD of the spine for age (Z score +2 to –2). Each eugonadal man was matched exactly for race and within 10 years for age to a hypogonadal man. The median age at entry was 54 years (range, 28–74 years).

We excluded men in both groups whose dietary calcium intake was <750 mg/day, as determined by a food frequency questionnaire, who had any disease or took any medication that could affect bone, or who consumed more than two alcoholic beverages a day.

### *Treatment*

The testosterone preparation provided as treatment to the hypogonadal men was AndroGel, (Solvay Pharmaceuticals, Marietta, GA, USA), a hydroalcoholic gel containing 1% testosterone. The initial dose was 5 g of AndroGel (50 mg of testosterone), which the subjects self-administered once a day. The serum testosterone concentration was measured at 1, 3, 6, 12, 18, and 24 months. The dose of AndroGel was increased to as high as 10 g/day to maintain a serum testosterone concentration within the normal range (400–900 ng/dl) throughout the 24 months of the study. Because we required that each subject have a calcium intake >750 mg daily on entry, we did not prescribe calcium as part of the study.

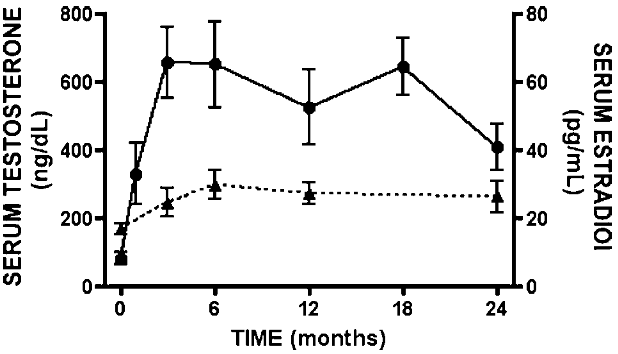

**FIG. 1.** Serum testosterone (●, solid line) and estradiol (▲, dashed line) concentrations when 10 hypogonadal men were treated with testosterone transdermally for 24 months. Values are means ± SE. To convert testosterone to nM, multiply by 0.0347. To convert estradiol to pM, multiply by 3.671.

Eugonadal men did not receive testosterone or other treatment but had a second determination of serum testosterone concentration at 24 months.

### *Efficacy parameters*

All men were assessed by DXA and μMRI at 0, 6, 12, and 24 months and were measured for body mass index (BMI) at the same times. Calcium intake was assessed by a food frequency questionnaire at 0, 12, and 24 months. The hypogonadal men were assessed for markers of bone metabolism at 0, 3, and 6 months.

### *BMD*

BMD of the anterior-posterior lumbar spine ($L_1$–$L_4$) and of the right hip was determined by DXA using Hologic densitometers (Hologic, Bedford, MA, USA): a QDR-4500A for the first year of the study and a Delphi A for the second. The Delphi A gave spine BMD values 1% lower, so those values were multiplied by 1.01. Scans from the same subject were evaluated using the "compare" feature of the DXA software (version 11.2:7). The CVs for long-term instrument stability, as assessed by daily measurements of a phantom, were <0.9%.

### *Markers of bone metabolism*

After an overnight fast, blood and a timed 2-h urine sample were collected. Serum and urine samples were frozen at –70°C. The markers and methods of assay were as follows: bone-specific alkaline phosphatase (BALP), immunoradiometric assay (Tandem-R Ostase, Beckman-Coulter, Fullerton, CA, USA); osteoprotegerin, enzyme-linked immunosorbent assay (American Laboratory Products, Windham, NH, USA); intact N-terminal propeptide of type I procollagen (PINP), radioimmunoassay (Orion Diagnostica UniQ, IDS, Fountain Hills, AZ, USA); cross-linked N-telopeptides of type I collagen (NTx), enzyme-linked immunosorbent assay (Osteomark; Ostex International, Se-

Table 1. BMD and Bone Architectural Parameters Before and After 24 Months of Testosterone Treatment of 10 Hypogonadal Men

| *Parameter* | *Time* | | *Change (0–24 months)* | *Percent change (0–24 months)* | *p** |
|---|---|---|---|---|---|
| | *0 months* | *24 months* | | | |
| BMD by DXA (g/cm$^2$) | | | | | |
| Spine BMD | 0.932 ± 0.200 | 1.000 ± 0.219 | 0.069 ± 0.053 | 7.4 ± 5.1 | <0.001 |
| Total hip BMD | 0.960 ± 0.166 | 0.994 ± 0.162 | 0.034 ± 0.029 | 3.8 ± 3.4 | 0.008 |
| Trochanter BMD | 0.713 ± 0.138 | 0.740 ± 0.136 | 0.027 ± 0.030 | 4.0 ± 4.7 | 0.04 |
| Intertrochanteric BMD | 1.157 ± 0.204 | 1.206 ± 0.205 | 0.049 ± 0.037 | 4.4 ± 3.7 | 0.004 |
| Femoral neck BMD | 0.812 ± 0.140 | 0.828 ± 0.145 | 0.016 ± 0.038 | 2.1 ± 5.1 | 0.3 |
| Architectural parameters by μMRI | | | | | |
| Bone volume fraction | 0.099 ± 0.013 | 0.103 ± 0.011 | 0.005 ± 0.004 | 5.0 ± 4.2 | <0.001 |
| Trabecular thickness (μ) | 118.8 ± 3.6 | 120.5 ± 3.8 | 1.7 ± 0.6 | 1.5 ± 0.5 | <0.001 |
| Surface-to-curve ratio | 6.3 ± 1.6 | 7.0 ± 1.5 | 0.6 ± 0.7 | 11.2 ± 11.5 | 0.004 |
| Topological erosion index | 1.32 ± 0.28 | 1.22 ± 0.25 | −0.11 ± 0.10 | −7.5 ± 6.7 | 0.004 |

Values are mean ± SD.

* *p* values were determined by multivariate analysis of variance, one-factor repeated measures design, using data from all four observation times: 0, 6, 12, and 24 months.

Table 2. BMD and Bone Architectural Parameters in 10 Eugonadal Men Followed for 24 Months

| *Parameter* | *Time* | | *Change (0–24 months)* | *Percent change (0–24 months)* | *p** |
|---|---|---|---|---|---|
| | *0 months* | *24 months* | | | |
| BMD by DXA (g/cm$^2$) | | | | | |
| Spine BMD | 1.125 ± 0.218 | 1.147 ± 0.245 | 0.022 ± 0.057 | 1.7 ± 4.5 | 0.3 |
| Total hip BMD | 1.047 ± 0.131 | 1.044 ± 0.123 | −0.003 ± 0.035 | −0.1 ± 3.2 | 0.7 |
| Architectural parameters by μMRI | | | | | |
| Bone volume fraction | 0.118 ± 0.007 | 0.118 ± 0.009 | −0.001 ± 0.003 | −0.5 ± 2.8 | 0.6 |
| Trabecular thickness (μ) | 123.1 ± 2.8 | 123.0 ± 2.5 | −0.1 ± 0.7 | −0.1 ± 0.6 | 0.8 |
| Surface-to-curve ratio | 11.0 ± 2.3 | 10.5 ± 2.1 | −0.5 ± 1.4 | −4.1 ± 12.3 | 0.5 |
| Topological erosion index | 0.89 ± 0.16 | 0.92 ± 0.14 | 0.03 ± 0.08 | 4.1 ± 9.1 | 0.5 |

Values are mean ± SD.

* *p* values were determined by multivariate analysis of variance, one factor repeated measures design, using data from all four observation times: 0, 6, 12, and 24 months.

attle, WA, USA). For each assay, all samples were measured in a single assay run. Intra-assay CVs for these assays were all <10%.

### *Testosterone and estradiol*

Serum testosterone was measured by a chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products, Los Angeles, CA, USA), and estradiol was measured by ultrasensitive immunoradiometric assay (DSL, Webster, TX, USA). Intra- and interassay CVs were <10%.

### *μMRI*

μMRI of the right distal tibia was performed using a 1.5-T whole body Signa MRI scanner (General Electric Medical Systems, Milwaukee, WI, USA) and a custom-designed, receive-only, phased-array, radiofrequency surface coil. The coil was placed on the anterior right tibia, with the lower edge 1 cm proximal to the midpoint of the medial malleolus, and the right foot was immobilized.(14) Twenty-eight contiguous images were obtained to map trabecular architecture using a pulse sequence previously described.(15) The acquisition voxel size was 137 × 137 × 410 $\mu m^3$. The data were processed using a custom-designed set of programs written in the programming languages C and IDL (Research Systems, Boulder, CO, USA).(16) The raw, k-space data were motion-corrected, filtered, and Fourier-transformed to obtain high-resolution images. To ensure that the same volume was analyzed at each time-point for each subject, the images corresponding to the 0-, 6-, 12-, and 24-month examinations of each subject were matched for architectural features by a program that performs in-plane rotations and 3-D translations iteratively, minimizing the differences between baseline and subsequent scans. After the volume of interest was selected manually on each of the matched slices by tracing a line ~1 mm from the endocortical boundary on the anterior one-half of the distal tibia, bone volume fraction maps were computed. Subvoxel processing yielded a voxel size of 69 × 69 × 103 $\mu m^3$.

Digital topological analysis of the trabecular network was performed on the entire volume of interest.(17) The topological class of each image voxel was determined, yielding the density of surface voxels, curve voxels, and voxels that are part of mutual junctions. The topological analysis began with binarization of the 3-D images, followed by skeletonization, which converted the platelike elements of the trabecular network to surfaces and the rodlike elements to

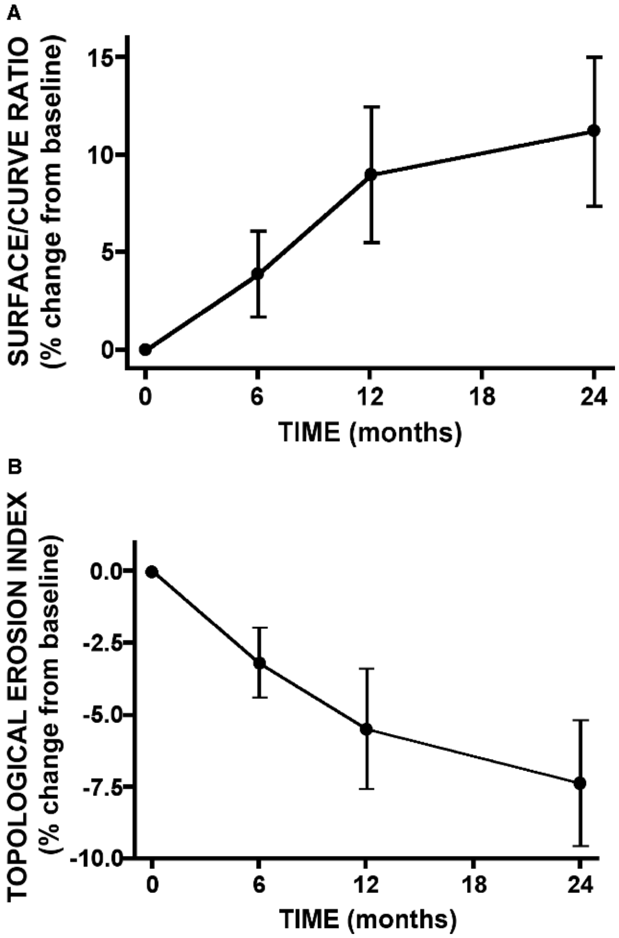

**FIG. 2.** Changes in the two principal composite μMRI parameters, surface-to-curve ratio and topological erosion index, when 10 hypogonadal men were treated with testosterone transdermally for 24 months. μMRI data were acquired from the distal tibia. Values shown are means ± SE. An increase in surface-to-curve ratio and a decrease in topological erosion index each suggest improvement in the trabecular connectivity. The change from 0 to 12 months was significant at $p = 0.02$ for both parameters and from 0 to 24 months at $p = 0.004$ for both parameters.

curves. Each voxel was classified as belonging to a surface, curve, or junction. In addition to the simple topological parameters, two composite parameters that have been found to be sensitive to bone loss were calculated. The first was the surface-to-curve ratio, the ratio of all surface voxels to all curve voxels. The higher the ratio, the more intact is the trabecular network, and vice versa. The second composite parameter was the topological erosion index, a ratio of parameters that are expected to increase on trabecular deterioration (curve edge and curve interior voxels, surface and profile edges, and curve–curve junction voxels) to those expected to decrease (surface interior voxels and surface–surface junctions). The lower the topological erosion index, the smaller the degree to which the trabecular network has deteriorated.(16) Trabecular thickness was determined by an independent program based on the concept of fuzzy distance transform.(18)

Reproducibility of the μMRI parameters was determined by calculating the CVs in eight eugonadal men evaluated at 0 and 6 months; the mean values were 2.3% for bone volume fraction (BVF), 0.4% for trabecular thickness, 6.7% for surface/curve ratio, and 4.3% for erosion index.

### *Statistical methods*

For all parameters, within-group comparisons from 0 to 24 months were tested by multivariate ANOVA appropriate for a one-factor repeated-measures design. If the differences among the four treatment times (0, 6, 12, and 24 months) were significant, pairwise comparisons of the pretreatment value with 6, 12, and 24 months were determined with Dunnett's test. Changes from 0 to 24 months between the hypogonadal and eugonadal groups were compared by the independent sample *t*-test and Wilcoxon's signed-rank test. Because the results were similar, only the *t*-test results are reported. The correlation between microarchitectural parameters and hormonal measurements was evaluated by the Spearman's $\rho$. Missing values were imputed by the method of last observation carried forward. A type I error rate of 0.05 was used for determining statistical significance. SAS statistical software, version 9.1 (SAS Institute, Cary, NC, USA), was used for all analyses.

## RESULTS

All 10 hypogonadal men completed the 24 months of study; 2 missed the 6-month visit. One eugonadal subject did not return for the 24-month visit.

### *Serum testosterone and estradiol concentrations, calcium intake, and BMI*

The serum testosterone concentration was markedly subnormal in hypogonadal men before treatment (88 ± 51 [SD] ng/dl [3.1 ± 1.8 nM]), rose strikingly to become midnormal by month 3 of testosterone treatment (656 ± 332 ng/dl [22.8 ± 11.5 nM]), and remained normal throughout the 24 months of treatment (Fig. 1). The serum estradiol concentration was 17 ± 5 pg/ml (62.4 ± 18.4 pM) at baseline, increased to 25 ± 13 pg/ml (91.8 ± 47.7 pM) by month 3 of testosterone treatment, and remained at that level (Fig. 1).

Calcium intake remained normal in hypogonadal subjects during the 24 months of testosterone treatment: 1175 ± 248 mg/day at 0 months and 1066 ± 375 mg/day at 24 months ($p = 0.7$). BMI also did not change: 30.3 ± 3.2 kg/m$^2$ at 0 months and 30.8 ± 2.1 kg/m$^2$ at 24 months ($p = 0.8$).

The serum testosterone concentration was normal in the eugonadal men at the beginning of the study (522 ± 126 ng/dl [18.1 ± 4.4 nM) and was still normal at the end (423 ± 101 ng/dl [14.7 ± 3.5 nM). Calcium intake remained normal in eugonadal subjects during the 24 months of the study: 989 ± 187 mg/day at 0 months and 1061 ± 279 mg/day at 24 months ($p = 0.7$). BMI also did not change: 29.0 ± 5.6 kg/m$^2$ at 0 months and 29.4 ± 6.4 kg/m$^2$ at 24 months ($p = 0.4$).

### *BMD*

In the 10 hypogonadal men, BMD increased significantly at the anterior-posterior spine (7.4%; $p < 0.001$), total hip,

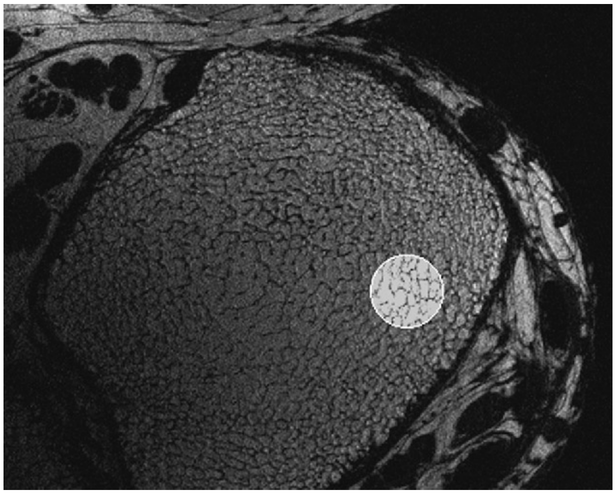

**FIG. 3.** A high-resolution cross-sectional slice through the tibia showing the trabecular architecture. The circle (6.85 mm diameter) shows the site from which the 3-D projection images shown in Fig. 4 were derived.

trochanter, and intertrochanteric region during 24 months of testosterone treatment (Table 1). In eugonadal men, BMD did not change significantly at any site during 24 months of observation (Table 2).

## *Markers of bone metabolism*

Serum PINP increased from baseline (41.4 ± 18.1 μg/liter) to 3 months (71.3 ± 32.1 μg/liter; $p = 0.02$) and decreased from 3 to 6 months (36.0 ± 21.1 μg/liter) of treatment ($p = 0.01$), but BALP did not change. Serum osteoprotegerin decreased slightly from baseline (4.72 ± 1.28 pM) to 6 months (4.29 ± 0.82 pM), with borderline significance ($p = 0.05$). Urine NTx did not change significantly from baseline to 6 months of treatment (45.8 ± 11.6 nmol/mmol creatinine at 0 months, 65.6 ± 43.5 nmol/mmol creatinine at 3 months, and 70.2 ± 46.7 nmol/mmol creatinine at 6 months; $p = 0.4$).

## *μMRI*

Both composite μMRI parameters of the integrity of the trabecular network improved significantly when the hypogonadal men were treated with testosterone for 24 months. The surface-to-curve ratio, a ratio of all surface voxels (representing plates) to all curve voxels (representing rods), increased by 9% ($p = 0.02$) after 12 months of testosterone treatment and by 11.2% ($p = 0.004$) after 24 months (Fig. 2; Table 1). The topological erosion index, a ratio of topological parameters expected to increase on trabecular deterioration to those expected to decrease, decreased by 5.6% ($p = 0.02$) after 12 months and by 7.5% ($p = 0.004$) after 24 months of testosterone treatment (Fig. 2; Table 1). The mean BVF, the fractional occupancy of voxels by bone, increased significantly (5%) from 0 to 24 months, and the trabecular thickness increased significantly (almost 2%), starting at 6 months of treatment, during treatment (Table 1). We did not find a significant correlation between the change in any of the μMRI parameters and the change in testosterone or estradiol.

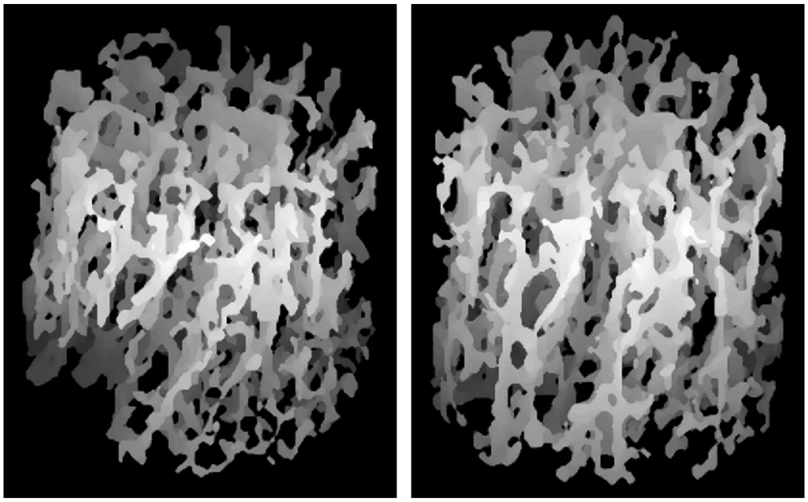

**FIG. 4.** High-resolution surface projection images of one hypogonadal subject (left) before and (right) after 24 months of testosterone treatment. Both images show a similar architectural configuration, showing that the μMRI technique is able to assess trabecular architecture of the same bone volume 24 months apart. These images also show more platelike architecture at 24 months of treatment than before treatment. This subject had the greatest improvement in architectural parameters of the 10 subjects: an increase of 33% in surface-to-curve ratio and a decrease of 22% in topological erosion index.

Figure 3 shows a cross-section of the distal tibia from which the magnetic resonance data were acquired. Figure 4 shows surface projection images from a single subject before testosterone treatment and after 24 months of treatment, showing similar architectural features in both, which shows that μMRI can be used to assess the same volume of trabecular bone longitudinally. Figure 4 also shows a more platelike architecture after 24 months of testosterone treatment than before treatment in this subject, who had the greatest quantitative improvement in topological parameters of the 10 subjects.

In the eugonadal men, none of the μMRI parameters changed significantly from 0 to 24 months (Table 2). The mean changes from 0 to 24 months in the hypogonadal men were significantly different from those in the eugonadal men for all of the μMRI parameters: BVF, $p = 0.005$; trabecular thickness, $p < 0.001$; surface-to-curve ratio, $p = 0.02$; topological erosion index, $p = 0.003$.

## DISCUSSION

Several studies have shown that testosterone has a beneficial effect on bone in men. Men who are severely hypogonadal have significantly lower BMD than eugonadal men,(10,11) and when eugonadal men are made hypogonadal medically(19–21) or surgically,(22) their BMD declines. Hypogonadal men also seem to have deterioration of their trabecular architecture, as we recently showed by μMRI,(14) similar to that of postmenopausal women.(16) Conversely, when hypogonadal men are treated with testosterone, BMD increases,(10,12,13) although the effect of this treatment on fracture incidence has not been studied. Until now, the possibility that testosterone replacement would restore trabecular connectivity in hypogonadal men had not been tested.

In this study, we selected men with severe and untreated hypogonadism, treated them with replacement doses of testosterone, and assessed their trabecular architecture by μMRI before and during treatment for 24 months. Because μMRI is noninvasive and has sufficient resolution to discern individual trabeculae, we were able to compare architectural parameters at the same anatomic site in the distal tibia at every time-point in each subject. We found that those μMRI parameters that reflect trabecular architecture, the surface-to-curve ratio and the topological erosion index, improved significantly.

The potential significance of these findings is that they suggest that testosterone replacement of hypogonadal men may not only retard bone resorption but may also reverse the deterioration of trabecular architecture caused by testosterone deficiency. The increase in the surface-to-curve ratio, which is the topologic representation of the ratio of trabecular plates to rods,(16) suggests that testosterone replacement partially restored trabecular connectivity. If testosterone had merely retarded bone resorption and allowed filling of bone resorption cavities, we would have expected an increase in μMRI parameters of trabecular thickness and bone volume fraction and in BMD but not in surface-to-curve ratio or topological erosion index. In fact, the surface-to-curve ratio and topological erosion index both improved to highly statistically significant degrees. The significance of an improvement in trabecular architecture would be that architecture contributes to bone's strength and resistance to fracture, independent of bone volume or density, as shown by several in vitro studies.(23–27)

One limitation of this study is that assessment of trabecular architecture by μMRI had to be performed at the distal tibia to achieve the resolution sufficient to discern individual trabeculae, even though this is not a common fracture site. The distal tibia, however, is rich in trabecular bone, like common sites of osteoporotic fractures, such as the spine and hip, and is also weight bearing. Another limitation is the lack of a placebo control group; however, we could not have allowed such severely hypogonadal men to go untreated for 24 months. The marked improvement in architectural parameters seen in the hypogonadal men, however, probably cannot be attributed to a change in the measurement technique, because the 10 matched eugonadal men followed simultaneously for 24 months showed no changes. The improvement in architectural parameters also cannot be attributed to changes in the subjects' calcium intake and BMI, which were quite similar at the beginning and end of the study. Finally, the improvement in architectural parameters cannot be attributed to changes in body composition, because, unlike DXA and CT, μMRI is not a transmission technique and is therefore not affected by changes in the composition of surrounding tissues.

We conclude that physiologic replacement of testosterone not only increases the amount of bone, but also improves parameters of trabecular architecture associated with bone strength.

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