

Original Article

Denosumab Densitometric Changes Assessed by Quantitative Computed Tomography at the Spine and Hip in Postmenopausal Women With Osteoporosis

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Abstract

FREEDOM was a phase 3 trial in 7808 women aged 60–90 yr with postmenopausal osteoporosis. Subjects received placebo or 60 mg denosumab subcutaneously every 6 mo for 3 yr in addition to daily calcium and vitamin D. Denosumab significantly decreased bone turnover; increased dual-energy X-ray absorptiometry (DXA) areal bone mineral density (aBMD); and significantly reduced new vertebral, nonvertebral, and hip fractures. In a subset of women (N = 209), lumbar spine, total hip, and femoral neck volumetric BMD (vBMD) were assessed by quantitative computed tomography at baseline and months 12, 24, and 36. Significant improvement from placebo and baseline was observed in aBMD and vBMD in the denosumab-treated subjects at all sites and time points measured. The vBMD difference from placebo reached 21.8%, 7.8%, and 5.9%, respectively, for the lumbar spine, total hip, and femoral neck at 36 mo (all $p \leq 0.0001$). Compared with placebo and baseline, significant increases were also observed in bone mineral content (BMC) at the total hip ($p < 0.0001$) largely related to significant BMC improvement in the cortical compartment ($p < 0.0001$). These results supplement the data from DXA on the positive effect of denosumab on BMD in both the cortical and trabecular compartments.

Key Words: Bone density; denosumab; osteoporosis; quantitative computed tomography.

Introduction

Osteoporosis is characterized by decreased bone strength, which results in an increased risk of fracture (1,2). Bone strength is determined by several factors, among which the density, microstructure, and geometry of both the cortical

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and trabecular bone compartments have predominant roles (3–6). As trabecular bone is lost in women after menopause, cortical bone becomes a proportionally greater contributor to bone strength (5,7,8).

Bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) is the most widely used technique to evaluate fracture risk, diagnose osteoporosis, and assess changes over time or in response to therapy. However, DXA only measures areal BMD (aBMD) 2-dimensionally (grams per square centimeter) and reflects the composite of both the cortical and trabecular components of the region measured. Quantitative computed tomography (QCT) can complement DXA by providing a 3-dimensional (grams per cubic centimeter) noninvasive measurement of volumetric BMD (vBMD) and can analyze both densitometric and geometric components of the integral regions and the cortical and trabecular bone compartments separately (9,10). QCT contributes relevant information for evaluating bone strength, and its utilization is therefore increasing in basic and clinical research in the assessment of bone geometry and BMD (11–13). However, similar to DXA, the interpretation of QCT data requires an understanding of the scope and limitations of the technique.

Denosumab (Prolia, Amgen Inc., Thousand Oaks, CA) is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand, a key modulator of osteoclast formation, function, and survival throughout the skeleton (14–17). Due to its systemic action and potency, denosumab exerts effects at both trabecular and predominantly cortical bone regions (18). Clinical trials, including the FREEDOM trial, have demonstrated that denosumab causes a rapid and significant decrease in bone turnover associated with significant progressive increases in DXA aBMD (19–25) and significant reductions in new vertebral, nonvertebral, and hip fracture risk in postmenopausal women with osteoporosis (22). A recent study using QCT reported that denosumab increased trabecular and cortical vBMD, bone mineral content (BMC), and strength of the radius in postmenopausal women with low aBMD (26).

Using QCT, we assessed the effect of denosumab on bone parameters at the lumbar spine and hip in a subset of postmenopausal women with osteoporosis who participated in the FREEDOM trial and compared changes observed with QCT to DXA measurements.

Materials and Methods

Subject Eligibility

Postmenopausal women aged 60–90 yr with a DXA BMD T-score less than –2.5 at the lumbar spine and/or total hip and –4.0 and greater at both sites were included in the study. Women were excluded if they had any severe or more than 2 moderate vertebral fractures, conditions that affected bone metabolism, or had taken oral bisphosphonates for more than 3 yr. Women were eligible if they had taken oral bisphosphonates for less than 3 yr but none in the 12 mo preceding the trial. The protocol

was approved by an independent ethics committee or institutional review board at each study site before the commencement of the study. Study centers in the FREEDOM trial with expertise and access to a qualified QCT scanner invited subjects to participate in this substudy of the lumbar spine and hip QCT measurements. Subjects with evaluable spine and hip scans at baseline and 1 or more postbaseline time points were included in the analysis.

Study Design

FREEDOM was an international, randomized, placebo-controlled trial in postmenopausal women with osteoporosis (22). Subjects received placebo or denosumab 60 mg subcutaneously every 6 mo for 36 mo, with daily supplements of calcium (≥ 1000 mg) and vitamin D (≥ 400 IU). Details of the study and the main results have been reported previously (22).

Assessments

Whole-body spiral computed tomography (CT) scanners manufactured by GE Healthcare (Waukesha, WI), Philips Healthcare (Suresnes, France), Siemens (AG, Erlangen, Germany), or Toshiba Medical Systems Corporation (Otawara-shi, Japan) were used. Scans were performed at 120 kV with a pitch of 1 using 100 mAs in the spine and 170 mAs in the hip and reconstructed using a field of view of 360 mm in the spine and 400 mm in the hip and a medium kernel. The reconstructed slice thickness was 1.25 mm or less. For the lumbar spine, L1 and L2 were scanned and for the proximal femur 1 cm above the hip to 2 cm below the lesser trochanter. The Mindways calibration phantom (Mindways Software Inc., Austin, TX) was used for calibration, and the Mindways QA phantom was used at each site to control longitudinal scanner stability. Study technicians were trained on these techniques and procedures, including subject positioning and phantom calibration.

Scans were analyzed in a blinded-to-treatment manner by a central laboratory (Synarc, Hamburg, Germany) using the QCTpro software (Mindways Software Inc.) by technologists trained and experienced in reviewing images obtained from subjects with osteoporosis. QCT scans were performed at baseline and months 12, 24, and 36. All visits of each patient were analyzed together by the same technologists to ensure the consistency of the analysis. In the spine, BMD of the central elliptical volume of interest was analyzed. In the hip, total, cortical and trabecular BMDs were determined.

To evaluate the consistency of the results obtained with QCT and DXA techniques, subjects with both evaluable QCT scans and DXA assessments (using Hologic, Inc. [Bedford, MA] or GE Healthcare [Waukesha, WI] Lunar densitometers) of the lumbar spine, total hip, and femoral neck regions at all time points (baseline and months 12, 24, and 36) were included in the analyses.

Study Endpoints

Endpoints for this QCT substudy were percent change from baseline vBMD in trabecular spine and overall (cortical and trabecular) vBMD, overall BMC, and overall volume

(cubic centimeter) at the total hip and femoral neck regions. Additionally, these variables were assessed in the cortical and trabecular compartments of the hip. BMC and volume were measured directly in the segmented CT images, and vBMD was derived as the ratio of BMC to volume.

Statistical Analysis

The percent change from baseline for vBMD, aBMD, 1 or more BMC and volume were determined. Data analyses assessed change over time relative to baseline for each treatment group and also compared denosumab with placebo at each time point measured. The estimates of percent changes from baseline in DXA and QCT parameters were calculated using an analysis of covariance model adjusting for treatment and baseline value.

Results are reported as least squares mean, associated 2-sided 95% confidence interval, and *p* value for the difference relative to baseline as well as the between-treatment difference at each time point.

Results

This substudy enrolled 209 (97 placebo and 112 denosumab) postmenopausal women, and 178 (85%; 86% placebo

and 85% denosumab) completed the evaluation at 3 yr. The main reasons for discontinuation were withdrawal of consent in 15 subjects (7%; 5% placebo and 9% denosumab) and adverse events in 8 subjects (4%; 4% placebo and 4% denosumab). Subject disposition and characteristics were balanced between treatment groups (Table 1) and similar to the overall FREEDOM trial (data previously reported) (22). The mean aBMD T-scores for the lumbar spine were -2.8 for placebo and -2.9 for denosumab; at the total hip region, the mean values were -2.0 and -1.9 for placebo and denosumab, respectively. Baseline mean vBMD measured at the trabecular spine was 65 mg/cm^3 for placebo and 67 mg/cm^3 for denosumab and 218 mg/cm^3 and 224 mg/cm^3 at the total hip region for the placebo and denosumab groups, respectively. Calibration issues and unavailability of analyzable scans at different time points limited the analyses to 86 subjects for the spine ($n = 41$ placebo; $n = 45$ denosumab) and 56 subjects for the hip ($n = 26$ placebo; $n = 32$ denosumab). Using all data from all subjects with QCT scans at any time point irrespective of the availability of the DXA scans did not alter the results presented or conclusions drawn from the study (data not shown).

Denosumab significantly increased vBMD and aBMD from baseline and compared with the placebo group at the spine, total hip, and femoral neck regions at months 12, 24, and 36 (Fig. 1). In the placebo group, trabecular spine vBMD declined from baseline, whereas lumbar spine aBMD largely remained stable. In the total hip and femoral neck regions, overall vBMD and aBMD declined in the placebo group. Denosumab was associated with continuous increases in QCT vBMD over time at the measured skeletal sites (Fig. 1). At month 36, denosumab increased the overall vBMD by 12.6% from baseline and 21.8% compared with placebo ($p < 0.0001$ for both) at the trabecular spine, 4.4% and 7.8% ($p < 0.0001$ for both) at the total hip region, and 2.9% and 5.9% ($p < 0.01$ for both) at the femoral neck, respectively. At the total hip and femoral neck, percent differences from placebo as measured by QCT and DXA were similar, whereas percent differences from placebo at the spine were larger for vBMD than aBMD. As expected, because the region of interest evaluated by QCT and DXA is similar for the hip but not the spine, the correlations of baseline BMD between techniques were higher for the hip ($r = 0.75$; $p < 0.0001$) than the spine ($r = 0.27$; $p = 0.0112$). At month 36, the percent changes from baseline in BMD assessed with DXA and QCT were similarly and moderately correlated for placebo subjects and for denosumab subjects at the hip ($r = 0.48$ and 0.41 , respectively, $p < 0.02$) and the spine ($r = 0.41$ and $r = 0.44$, respectively, $p < 0.01$).

The changes in overall vBMD, BMC, and volume were evaluated for the total hip region as well as separately in the trabecular and cortical compartments (Fig. 2). An increase from baseline in overall BMC at the total hip of 5.2% was observed in the denosumab group at month 36 (Fig. 2A). This increase was significant compared with both baseline and the placebo group, which experienced a decline over the 36-mo study. The overall bone volume at the total hip

Table 1
Subject Disposition and Baseline Characteristics

	Placebo	Denosumab 60 mg Q6M
Enrolled in QCT substudy, N	97	112
Completed QCT substudy, n (%)	83 (86)	95 (85)
Age (yr)	75 (6)	74 (5)
BMI (kg/m^2)	25 (4)	26 (4)
QCT: trabecular spine vBMD (mg/cm^3)	65 (20)	67 (21)
QCT: overall total hip vBMD (mg/cm^3)	218 (32)	224 (33)
QCT: overall femoral neck vBMD (mg/cm^3)	232 (33)	240 (37)
DXA: lumbar spine aBMD T-score	-2.8 (0.7)	-2.9 (0.7)
DXA: total hip aBMD T-score	-2.0 (0.7)	-1.9 (0.8)
DXA: femoral neck aBMD T-score	-2.4 (0.7)	-2.3 (0.6)
Prevalent vertebral fracture, n (%)	27 (28)	26 (23)

Note: Values are mean (standard deviation) unless indicated otherwise.

Abbr: aBMD, areal bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; Q6M, every 6 mo; QCT, quantitative computed tomography; vBMD, volumetric bone mineral density.

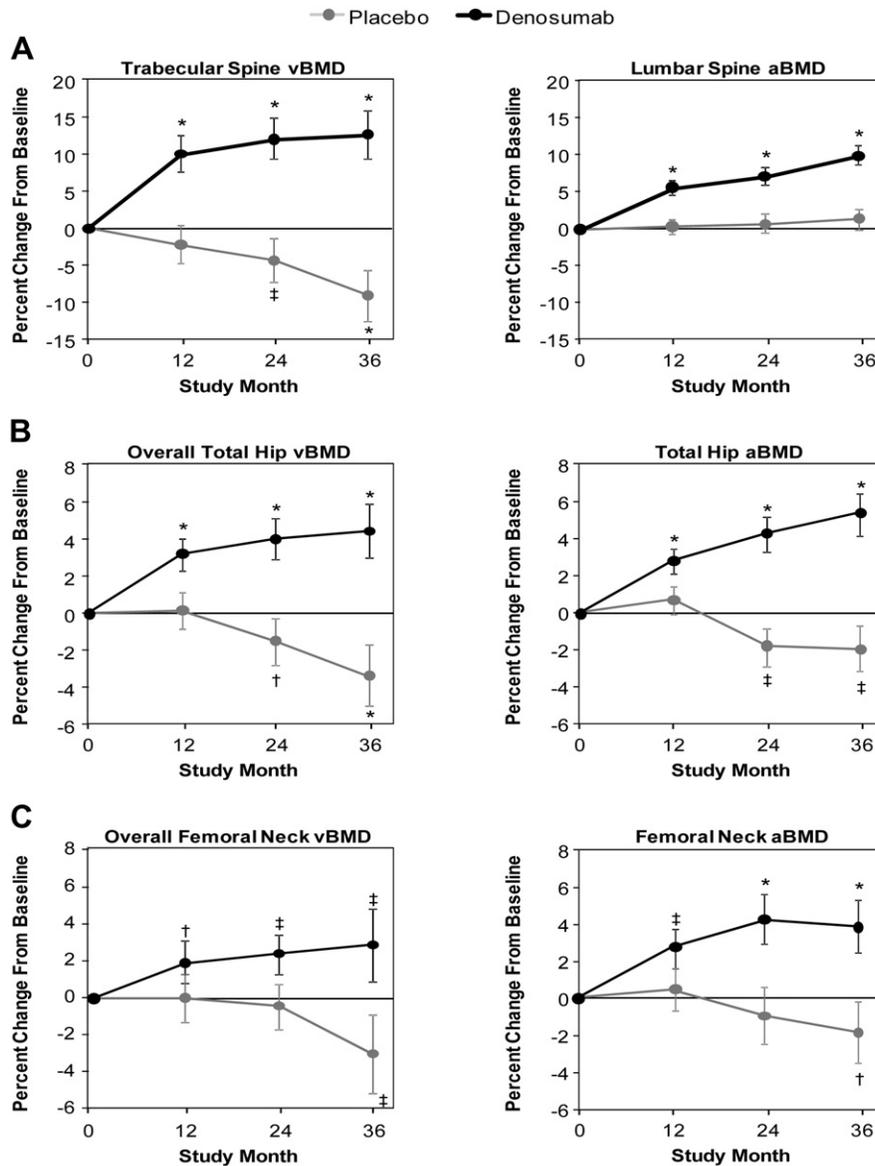


Fig. 1. Percent change from baseline through month 36 in the trabecular spine (A), total hip (B) and femoral neck (C) vBMD and aBMD as measured by QCT and DXA, respectively. The percent changes from baseline in QCT and DXA parameters were calculated using an analysis of covariance model adjusting for treatment and baseline value and are reported as least squares mean and associated 2-sided 95% confidence intervals for the treatment difference at each time point. The analysis included 41 placebo- and 45 denosumab-treated subjects at each time point for spine and 26 placebo- and 32 denosumab-treated subjects for overall total hip and femoral neck regions. †*p* < 0.05; ‡*p* < 0.01; **p* ≤ 0.0001 vs both baseline and placebo for denosumab; †*p* < 0.05; ‡*p* < 0.01; **p* ≤ 0.0001 vs baseline for placebo. aBMD, areal bone mineral density; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; vBMD, volumetric bone mineral density.

remained unchanged (−0.2%) in both treatment groups at month 36.

In the denosumab group, BMC in the cortical compartment of the total hip region increased from baseline by 8.7% at month 36 (Fig. 2B) and remained unchanged in the trabecular compartment (0.3%; Fig. 2C). Total hip BMC decreased in both cortical and trabecular compartments in the placebo

group (−2.8% and −3.0%, respectively). The increase in BMC in the denosumab group was significant in the cortical compartment of the total hip compared with both baseline and placebo (*p* < 0.0001 and *p* < 0.0001, respectively).

Although total hip volume did not change, apparent changes in cortical volume at the total hip were observed, with a 7.0% increase from baseline in the denosumab group and a reduction

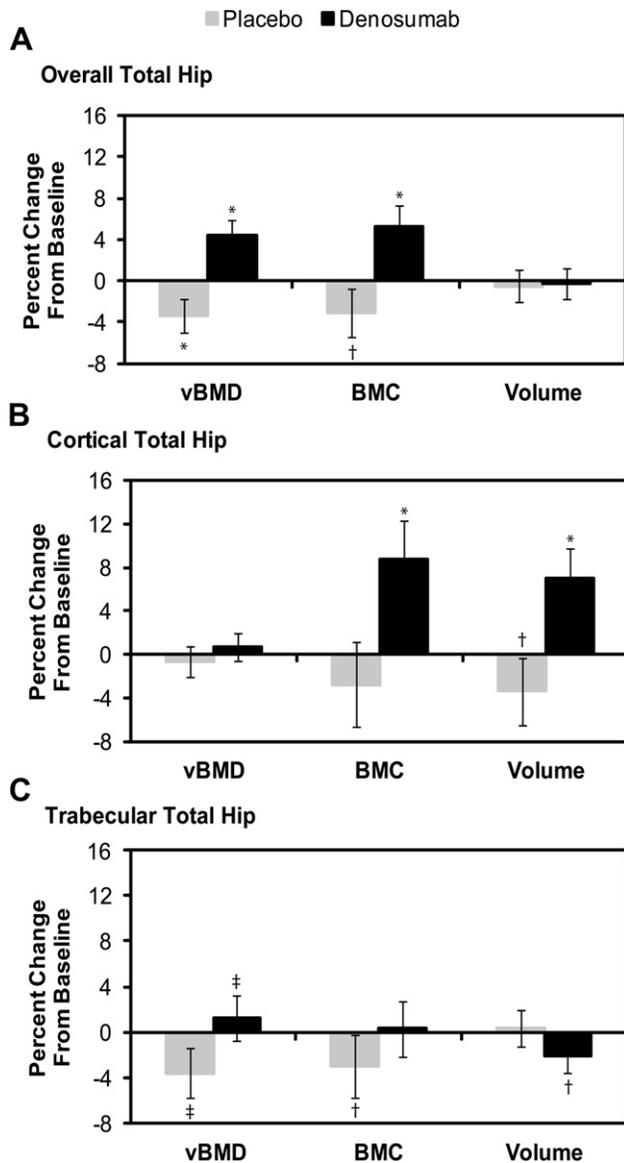


Fig. 2. Percent change from baseline at month 36 in vBMD, BMC and volume at the total hip including overall (A), cortical (B) and trabecular (C) compartments. The percent changes from baseline in quantitative computed tomography parameters were calculated using an analysis of covariance model adjusting for treatment and baseline value and are reported as least squares mean and associated 2-sided 95% confidence intervals for the treatment difference at month 36. The analysis included 26 placebo- and 32 denosumab-treated subjects. † $p < 0.05$; ‡ $p < 0.01$; * $p \leq 0.0001$ vs both baseline and placebo for denosumab; † $p < 0.05$; ‡ $p < 0.01$; * $p \leq 0.0001$ vs baseline for placebo. BMC, bone mineral content; vBMD, volumetric bone mineral density.

of 3.4% in the placebo group ($p < 0.0001$; Fig. 2B). In the trabecular compartment at the total hip, volume decreased in the denosumab group (-2.1% ; $p = 0.0053$) and remained unchanged in the placebo group (0.3% ; Fig. 2C).

Discussion

In this analysis of a subset of subjects from the FREEDOM trial who had evaluable spine and hip QCT and DXA assessments at all measured time points, treatment with denosumab significantly increased vBMD and aBMD in lumbar spine, total hip and femoral neck, as measured by QCT and DXA, respectively, at 12, 24, and 36 mo. The percent increases from placebo in bone density at the spine were larger when measured by QCT than DXA; this is mainly explained by the QCT methodology, which assesses changes at the spine in a predefined intravertebral region of interest containing only trabecular bone. At the total hip and femoral neck regions, both QCT and DXA demonstrated similar overall changes in denosumab subjects compared with placebo. At month 36, vBMD and BMC increased in the total hip region in the denosumab group, whereas volume remained unchanged, reflecting an increase in both bone density and mass over time with denosumab treatment. These changes were primarily due to a robust effect in the cortical compartment where significant positive changes in both BMC and volume were observed.

This study demonstrated that both QCT and DXA can be used to evaluate responses to denosumab therapy. The increase in aBMD after denosumab administration reported in this study is consistent with the results reported in the pivotal FREEDOM trial, which measured spine and hip aBMD (22). After 36 mo, denosumab was associated with a relative increase in aBMD of 6.0% at the total hip compared with placebo as reported in the FREEDOM trial and 7.8% and 7.3% measured with QCT and DXA, respectively, in this substudy. This study using QCT expands observations from other phase 2 and 3 denosumab clinical trials that have measured bone mass using DXA (20–23) by further evaluating changes in the cortical and trabecular compartments.

The change from baseline compared with placebo in aBMD at 36 mo reported in the FREEDOM trial at the lumbar spine was 9.2%, which also is consistent with the DXA measurement in this study (8.6%) (22). However, the change from baseline in trabecular spine vBMD relative to placebo was 21.8%. This apparent discrepancy underscores the difference between vBMD and aBMD and also shows the interpretational difficulties when using percent change. vBMD of the spine is measured entirely in the trabecular bone in a CT slice in the midportion of the vertebral body, whereas aBMD is an integral of an entire vertebral body as well as pedicles and vertebral arch, the 2 latter structures being predominantly cortical bone. Consequently, the vBMD in the trabecular spine is smaller than the aBMD of the entire vertebral body. Due to the large differences in the BMD denominator, the percent change becomes disproportionately larger in the QCT assessment of the spine. Importantly, a reduction was observed in the trabecular bone density in the placebo group with vBMD, whereas the aBMD increased slightly. This slight increase observed with DXA could have resulted from calcium and vitamin D supplementation or increased degenerative changes at the vertebral endplates, which are known to occur

over time and would not impact the assessment of vBMD with QCT. Indeed, the reduction in vBMD at the trabecular spine indicates that there is a real density loss in the placebo group, as observed in the hip parameters. The increased lumbar spine aBMD in the placebo group is, therefore, more likely to be due to age-dependent degenerative changes that are included in the aBMD but avoided by vBMD in the core of trabecular bone.

To interpret changes in vBMD in response to therapies, it is important to assess and report the corresponding BMC and volume changes (Fig. 2). In the overall total hip region, no change was observed in bone volume, but this integral measurement masked the extent of responses in the cortical and trabecular compartments of that region. An increase occurred in the cortical compartment, whereas apparent volume decreased in the trabecular compartment after denosumab therapy. The volume of the cortical and trabecular compartments of the total hip measured by current QCT methods is strongly influenced by the determination of the interface between the 2 compartments. This interface or transition zone is the endosteal cortical surface (endosteal envelope) where, in the presence of active bone resorption, increased cortical porosity results in “trabecularization” of cortical bone and a decrease in apparent cortical thickness and volume. The measured increases in cortical volume and BMC and the apparent loss of volume in the trabecular compartment with denosumab can be explained by a decrease in cortical porosity near the endosteal surface, converting “trabecularized” cortical bone into more dense cortical bone. In this manner, the trabecular-cortical interface shifts inward, resulting in an increase in measured cortical thickness and volume and the apparent decrease in trabecular volume (Fig. 3).

By halting and reversing cortical bone loss, denosumab increases cortical bone mass, which would be expected to

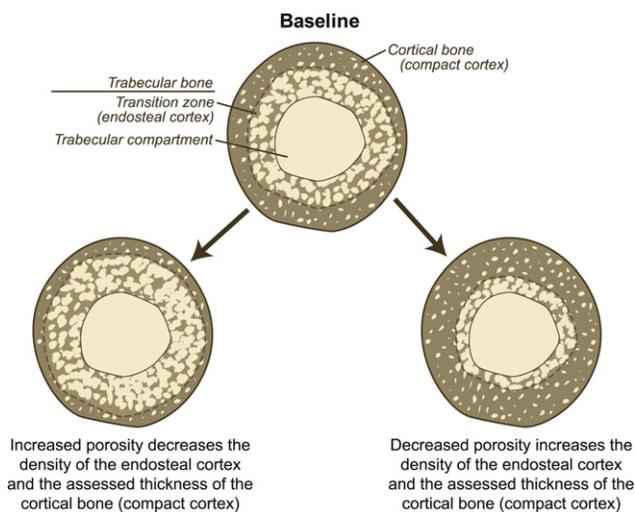


Fig. 3. Proposed schematic representation of quantitative computed tomography changes in bone compartments at baseline and after treatment with placebo or denosumab.

increase bone strength to a disproportionately greater extent than a simple increase in bone mass in the trabecular compartment. Indeed, it is well recognized that an increase in volume or thickness of the cortical bone would have a substantial positive effect on biomechanical parameters such as bending strength and buckling ratio (3). Overall, these QCT data demonstrated that denosumab was associated with improvements in both the trabecular and cortical compartments.

The study is limited by the somewhat small numbers of subjects, and it is not possible to relate individual bone changes to individual fracture events in the overall FREEDOM trial. However, using the same subset of images, we have previously reported that the changes in aBMD and vBMD at the spine and hip resulting from denosumab therapy were associated with large and significant improvement in estimated strength by finite element analysis (27). There are recognized technical limitations of the QCT technique, in particular, the partial volume effects resulting from limited spatial resolution of about 500 μm in plane and 1–1.25 mm slice thickness and beam hardening effects, which may affect measurement (26). To the extent possible, these limitations were mitigated by measures in place during the study to ensure scanner stability using appropriate phantoms.

In conclusion, the use of QCT enhances the evaluation of the skeletal response to denosumab therapy and is particularly useful in understanding the effects of denosumab on specific bone compartments by isolating and assessing cortical and trabecular bone separately. In particular, QCT adds to our understanding of bone strength and fracture risk reduction by allowing direct assessment of cortical and trabecular compartments, complementing DXA that measures a composite of the 2 compartments. Denosumab is associated with improvement in vBMD and BMC from baseline in the spine and hip. These improvements with denosumab therapy in the hip region are prominent in the cortical compartment, which may explain the increase in hip strength and nonvertebral fracture reduction observed in patients with osteoporosis treated with denosumab (28).

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