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Original Full Length Article

Comparison of proximal femur and vertebral body strength improvements in the FREEDOM trial using an alternative finite element methodology

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ABSTRACT

Denosumab reduced the incidence of new fractures in postmenopausal women with osteoporosis by 68% at the spine and 40% at the hip over 36 months compared with placebo in the FREEDOM study. This efficacy was supported by improvements from baseline in vertebral (18.2%) strength in axial compression and femoral (8.6%) strength in sideways fall configuration at 36 months, estimated in Newtons by an established voxel-based finite element (FE) methodology. Since FE analyses rely on the choice of meshes, material properties, and boundary conditions, the aim of this study was to independently confirm and compare the effects of denosumab on vertebral and femoral strength during the FREEDOM trial using an alternative smooth FE methodology. Unlike the previous FE study, effects on femoral strength in physiological stance configuration were also examined. QCT data for the proximal femur and two lumbar vertebrae were analyzed by smooth FE methodology at baseline, 12, 24, and 36 months for 51 treated (denosumab) and 47 control (placebo) subjects. QCT images were segmented and converted into smooth FE models to compute bone strength. L1 and L2 vertebral bodies were virtually loaded in axial compression and the proximal femora in both fall and stance configurations. Denosumab increased vertebral body strength by 10.8%, 14.0%, and 17.4% from baseline at 12, 24, and 36 months, respectively ($p < 0.0001$). Denosumab also increased femoral strength in the fall configuration by 4.3%, 5.1%, and 7.2% from baseline at 12, 24, and 36 months, respectively ($p < 0.0001$). Similar improvements were observed in the stance configuration with increases of 4.2%, 5.2%, and 5.2% from baseline ($p \leq 0.0007$). Differences between the increasing strengths with denosumab and the decreasing strengths with placebo were significant starting at 12 months (vertebral and femoral fall) or 24 months (femoral stance). Using an alternative smooth FE methodology, we confirmed the significant improvements in vertebral body and proximal femur strength previously observed with denosumab. Estimated increases in strength with denosumab and decreases with placebo were highly consistent between both FE techniques.

1. Introduction

More than 20 years after the first reports of patient-specific computational procedures to determine the strength of the human proximal femur [1] or vertebral body [2], computed tomography (CT)-based finite element analysis (FEA) has become a recognized tool to quantify skeletal fragility in individual patients and explore the effect of drugs for the treatment of osteoporosis. The complete CT-based FEA methodology from image acquisition through model generation to the final computing of strength has been validated extensively using *in vitro* biomechanical tests by numerous investigators [3,4]. Some, but not all studies demonstrated the superior value of FEA over DXA-based areal bone mineral density (aBMD) or quantitative computed tomography (QCT)-based volumetric bone mineral density (vBMD) in predicting *in vitro* proximal femur and vertebral body strength [5–7].

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More importantly, several recent publications confirmed that bone strength assessed by CT-based FEA is better or at least comparable to densitometric measures such as aBMD and vBMD for estimation of fracture risk [8–14]. Moreover, FEA may not only estimate the risk of fracture but may also reveal the location and mechanism of fracture for a given load case [15–19]. Finally, FEA may be used to understand specific clinical conditions such as the presence of an implant [20,21], metastatic defects [22–24], cement augmentation [25,26], or remodeling over a certain loading regime [27]. In support of its steadily growing recognition, FEA was included in several evaluations of osteoporosis treatments [28–35] and of the deleterious effect of spaceflight on bone strength [36].

CT-based FEA is a complex engineering methodology that involves image acquisition and processing steps, the definition of geometrical models, material properties of bone tissue, and loading conditions. A few authors have reviewed the challenges of its patient-specific application [37–40]. A key parameter limiting accurate calculation of bone strength from CT images remains the accurate assessment of local BMD [41]. Numerous studies were conducted to explore the influence of element size [42], mesh type [43], load configuration and application [44–47], failure criteria [48], material anisotropy [49–55], material mapping [56–58], and non-linear material behavior [59–62]. For proximal femur strength, the short term *in vivo* precision error including repositioning of the subjects reported as coefficient of variation of a given FEA procedure was estimated at 1.85% and the detectable limit at 5.85% [63].

Following the early work of Keyak and others [64,65], most researchers involved in clinical studies use coarse but efficient voxel-based FE meshes that do not distinguish between the trabecular and cortical compartments [28,30,66]. Sometimes one or several layers of outer voxel elements with specific homogeneous material properties (*e.g.* those of PMMA) are used to estimate the respective contribution of the trabecular and cortical compartments in femoral mechanics, but this approach is coarse and not rigorous as it does not take the actual coupling of the two compartments into account. An alternative and perhaps more accurate approach consists of using smooth tetrahedral meshes of the trabecular compartment that is covered with a layer of cortical elements [12,67].

Since morphology and the biomechanical role of the cortex depend on gender and evolve with aging and disease, it is legitimate to question the above voxel meshes used for evaluation of patient data in clinical studies. Interestingly, no comparison of FEA methodologies has been reported using the same set of CT images from the same patient cohort. In particular, it is unknown if an alternative FEA methodology validated with another set of *in vitro* experiments would predict the same effect on bone strength in a given clinical study.

Using voxel-based FE meshes, Keaveny et al. recently reported strength improvements of the vertebral body in axial compression and proximal femur in fall configuration in postmenopausal women with osteoporosis treated with denosumab during the first 3 years of the FREEDOM trial [68]. The effects of treatment on proximal femur strength in the physiological stance configuration were not examined.

The aim of the present study was to assess the effect of denosumab on vertebral body strength in axial compression and proximal femur strength in both fall and stance configurations in the same cohort using an alternative FE methodology using smooth meshes and to compare the results with those of the previous voxel-based FE approach.

2. Materials and methods

2.1. Study

The *F*racture *RE*duction *E*valuation of *D*enosumab in *O*steoporosis every 6 *M*onths (FREEDOM) study was an international, randomized, placebo-controlled trial. Postmenopausal women with osteoporosis were randomly assigned to receive subcutaneous injections of either denosumab 60 mg or placebo every 6 months for 36 months. The study protocol was approved by an independent ethics committee or review board at each study site. Randomization was stratified by 5-year age groups. The primary details and results of the study have been previously published [69]. Briefly, administration of denosumab reduced the incidence of new fractures in postmenopausal women with osteoporosis by 68% at the spine and 40% at the hip over 36 months compared with placebo. Additionally, this efficacy was supported by differential improvements from baseline in proximal femur and vertebral body (L1 & L2) strength at 36 months (18.2% and 8.6%, respectively) estimated in the same patient subset by an established voxel-based FE methodology [68]. In the present work, the efficacy of denosumab is explored with an alternative smooth FE approach, which is described below.

2.2. QCT methodology including segmentation

QCT data for the proximal femur and two lumbar vertebrae (L1 and L2) were obtained in qualified centers at baseline, 12, 24, and 36 months from a subset of the cohort consisting of 51 treated (denosumab) and 47 control (placebo) subjects. Details of the QCT imaging method have been published previously [68,70,71]. In short, CT scans were obtained using 13 whole body CT scanners from 4 different CT manufacturers at 120 kV with a pitch of 1 or close to 1 using 170 mAs in the hip and 100 mAs in the spine. For reconstruction, a medium kernel and a field of view of 200 mm, corresponding to an in plane pixel size of 390 μm centering on the left hip and of 360 mm, corresponding to an in plane pixel size of 703 μm in the spine were used. The reconstructed slice thickness was ≤1.25 mm. Hip scans covered 1 cm above the femoral head to 2 cm below the lesser trochanter, and spine scans covered the L1 and L2 vertebrae. In order to improve segmentation accuracy and to better exploit the intrinsic spatial resolution of the CT scanner, for the purpose of the analysis presented here, the reconstructed spine scans were resampled by a factor of two isotropically using windowed sync interpolation with Lanczos window of width 3 resulting in a voxel size of 352 × 352 × 500 μm (assuming a slice thickness of 1 mm) [72].

QCT scans of the spine and hip were analyzed in a blinded-to-treatment manner using the Medical Image Analysis Framework (MIAF; University of Erlangen, Germany) software [73,74]. Based on the 3D segmentation of the periosteal and endosteal bone surfaces, the integral volumes of interest (VOI) of the total hip and of the L1 and L2 vertebral bodies were partitioned into trabecular and cortical bone compartments. Details of the segmentation process for the hip [73] and the spine [74] have been described previously. Periosteal (outer, cortical mask) and endosteal surfaces (inner, trabecular mask), along with CT value measured in Hounsfield units (HU) to BMD calibration, were provided as input for the FE analysis. The constants of the linear calibration equation were derived from the analysis of the Mindways calibration phantom scanned simultaneously with each patient. Calibration differences between CT scanners were assessed and documented by Synarc by circulating a European Spine Phantom (ESP). The ESP analysis results were directly integrated into the MIAF analysis.

2.3. FE methodology

The FE methodology was blinded to treatment using medtool (Dr. Pahr Ingenieurs e.U.) [75]. In a preliminary step, the images of the L1 and L2 vertebral bodies were cropped to remove the posterior elements and in particular the endplates in order to obtain vertebral sections with parallel faces. This aims at simplifying the meshing procedure and minimizing the influence of osteophytes. As shown in a recent study, this procedure delivers strength and damage distribution results that are highly consistent with those obtained when the intact vertebral endplates were embedded in PMMA [76]. The distal portion of the proximal femur images was cropped approximately 2 cm below the