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Analysis of microstructural and mechanical alterations of trabecular bone in a simulated three-dimensional remodeling process

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ABSTRACT

Bone remodeling is a complex dynamic process, which modulates both bone mass and bone microstructure. In addition to bone mass, bone microstructure is an important contributor to bone quality in osteoporosis and fragility fractures. However, the quantitative knowledge of evolution of three-dimensional (3D) trabecular microstructure in adaptation to the external forces is currently limited. In this study, a new 3D simulation method of remodeling of human trabecular bone was developed to quantitatively study the dynamic evolution of bone mass and trabecular microstructure in response to different external loading conditions. The morphological features of trabecular plate and rod, such as thickness and number density in different orientations were monitored during the remodeling process using a novel imaging analysis technique, namely Individual Trabecula Segmentation (ITS). We showed that the volume fraction and microstructures of trabecular bone including, trabecular type and orientation, were determined by the applied mechanical load. Particularly, the morphological parameters of trabecular plates were more sensitive to the applied load, indicating that they played the major role in the mechanical properties of the trabecular bone. Reducing the applied load caused severe microstructural deteriorations of trabecular bone, such as trabecular plate perforation, rod breakage, and a conversion from plates to rods.

1. Introduction

The human skeleton is continuously renewed via bone remodeling through one's entire life. Compared to bone modeling that helps bone to attain its mature morphology during the growth, bone remodeling is predominant in adults (Frost, 1990). However, abnormal remodeling would cause serious skeletal pathologies. For example, increased activities of basic multicellular units (BMU) for women during menopause result in post-menopausal osteoporosis, featuring rapid and excessive bone loss and a deteriorated trabecular architecture that is more rod-like, thinner, and prone to fracture (Fang et al., 2010; Liu et al., 2008a; Seeman et al., 2004). Osteoporotic fracture caused by abnormal bone remodeling are one of the most common musculoskeletal impairments for the elderly, associated with substantial socio-economic consequences, which are expected to worsen as the size of the elderly population increases (Melton, 2003). Osteoporosis can also be caused by reduced mechanical loading in disuse, such as in prolonged bed rest or microgravity. Disuse osteoporosis in microgravity presents a significant hindrance for long-term space flights (Bikle et al., 1997; Carmeliet et al., 2001). The underlying mechanisms responsible for bone loss under the mechanical unloading conditions are still poorly understood.

Several computational models were developed to explain the mechanisms behind the effects of the local mechanical stimuli or estrogen depletion during menopause on bone remodeling. Jang and Kim (2008) simulated bone adaptation to external loads and achieved optimal architecture aligning along the loading directions using topology optimization method. However, the topology optimization method cannot consider the dynamic coupling between osteoclastic bone resorption and subsequent osteoblastic bone apposition. Fratzl and coworkers (Weinkamer et al., 2004) proposed a stochastic lattice model to predict bone development as well as architectural deterioration in aging. However, their simulation was implemented in a 2-dimensional model and based on an arbitrary bone microstructure. Huiskes and his group (Huiskes et al., 2000; Mullender and Huiskes, 1995) proposed a model to simulate bone adaptation and renewal in modeling and

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remodeling. The equilibrium bone mass and structure are considered as a balance between osteoclastic resorption and osteoblastic apposition which was modulated by osteocyte mechanosensing and signaling. In their model, bone apposition and resorption were simulated as changing the bone density of elements and thereby their stiffness. However, changing density and stiffness of bone tissue to implicitly simulate bone resorption and apposition was not physiological in terms of temporal and spatial relationship between osteoclastic and osteoblastic activities. Liu et al. (2008a) simulated three dimensional (3D) microstructural alterations of human trabecular bone during menopause with a stochastic remodeling model. Resorption cavities and subsequent refilling were implemented by directly removing (adding) surface voxels from (to) trabecular bone. However, this model could only predict bone mass and structure evolution during menopause, and it did not consider the mechanical effect on bone remodeling.

The present work aims to quantitatively evaluate the trabecular bone microstructural change in the remodeling process under different mechanical loadings using several cutting-edge modeling techniques. The voxel-based μ-FEM (micro Finite Element Method), where each voxel was converted to an 8-node brick element, was used for computation of stress and strain and other mechanical variables based on the element-by-element (EBE) methods (van Rietbergen et al., 1996). A novel morphological analysis technique (so called ITS) (Liu et al., 2008b, 2006) was adopted for analyzing the microstructural features of trabecular bone, such as plate and rod volume fraction, thickness, number density and orientation. Using these methods and techniques, we can simulate both bone mass change and microstructural evolution under various loading conditions. Thus, the microstructural parameters and the mechanical properties of trabecular bone in the remodeling process could be analyzed. Furthermore, the simulated results of different loading conditions were compared with the previous experimental data to validate the feasibility of this simulation approach.

2. Materials and methods

2.1. The μFEM model

The FEM model is produced from the μCT images of trabecular bone samples. The details of preparation of bone samples can be found in the Supporting Information. The bone tissue is assumed to be homogenous and isotropic with Young's modulus $E=15$ GPa and Poisson's ratio $v=0.3$ (Guo and Goldstein, 1997; Tanck et al., 2006). The EBE technique is applied to calculate strain energy density for each voxel of samples. The EBE method does not need assembling the system matrix and hence has modest memory requirements (Carey and Jiang, 1986). Additionally, the numbering of nodes and elements can be arbitrary, and computations can be done in parallel. Therefore we can add and delete elements of the model easily for simulating bone apposition and resorption, which can be very difficult for conventional FEM.

To apply external loading on the bone sample, one plate with the voxel-size thickness was added to each of the six surfaces of cubic domain (Ruimerman et al., 2001) (see Fig. 1). The loading mode was compressive in vertical direction while tensile in the horizontal direction (see Fig. 1). In the simulations, the sample was firstly loaded with a uniform stress of 4 MPa (Brown and DiGioia, 1984) to gain a homeostatic state from their initial morphologies (we denoted the stress of 4 MPa as the homeostatic loading condition and the equilibrium state at this loading as homeostatic state). Secondly, the samples were re-loaded with different magnitudes of stress from the homeostatic state to study the adaptation of the microstructure of trabecular bone to changed loading conditions. We designed four different loading conditions for the second part: (1) increasing the load to 6 MPa; (2) reducing the load to 2 MPa; (3) reducing the load to 1 MPa; (4) reducing the horizontal load to 1 MPa, while keeping the vertical load at 4 MPa.

To evaluate the microstructural and mechanical alterations of trabecular bone in different loading conditions, the following analyses were performed. First, ITS-based morphological analysis was performed to separately evaluate volume, number, thickness, and orientation of trabecular plates and rods (detailed method in Supporting Information S3). Then, apparent Young's moduli in three different directions (E_x, E_y and E_z) were evaluated by FEM (detailed method in Supporting Information S4).

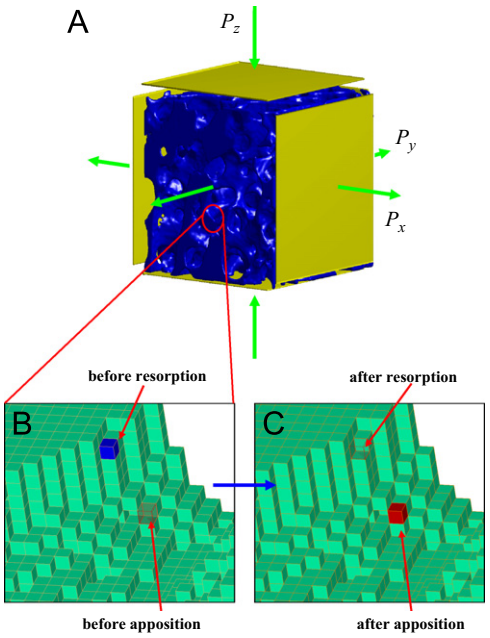

Fig. 1. Schematic illustration of bone resorption and apposition under the applied load. (A) Illustration of applying mechanical loading on the bone sample. The load was compressive in the vertical direction and tensile in the horizontal direction. Six plates with one voxel thickness (yellow) were added to the six corresponding surfaces of bone cubic domain (blue) in order to avoid stress shielding (Note that the frontal layer is not shown for the visibility of the microstructure of bone sample). Uniformly distributed stresses were imposed on the six planes of the cubic model. (B) The trabecular bond surface before bone apposition and resorption; (C) the trabecular bond surface after bone apposition and resorption: the dark blue voxel was removed from the trabecular surface simulating bone resorption, while the red voxel was added simulating bone apposition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Remodeling model

Here we adopted the remodeling model proposed by Huiskes and coworkers (Huiskes et al., 2000; Ruimerman et al., 2005) and extended it to our 3D simulation methods, while we explicitly allowed bone apposition or resorption on trabecular bone surface only. The rate of bone mass change at a particular trabecular surface location x at time t is determined by

$$\frac{dm_{tot}(x,t)}{dt}=\frac{dm_{bl}(x,t)}{dt}-\frac{dm_{cl}(x,t)}{dt} \tag{1}$$

where $dm_{bl}(x,t)/dt$ is osteoblastic bone apposition rate while $dm_{cl}(x,t)/dt$ is osteoclastic bone resorption rate.

Osteoblastic apposition is activated by the integrated osteocyte stimuli in the region adjacent to the remodeling surface point x, and this apposition rate can be expressed by

$$\frac{dm_{bl}(x,t)}{dt}=\tau(P(x,t)-k_{tr}),\quad \text{for } P(x,t)>k_{tr} \tag{2}$$

where τ is the proportional parameter. $P(x,t)$ is the total stimulus for bone apposition when it exceeds a certain threshold value k_{tr} and can be written as

$$P(x,t)=\sum_{i=1}^{N} f(x,x_i)\mu_i R(x_i,t),\quad \text{with } f(x,x_i)=e^{-d(x,x_i)/D} \tag{3}$$

Osteocytes within the influence region contribute to bone apposition stimulus P on trabecular surface point x. μ_i is the mechanosensitivity factor and $R(x_i,t)$ is the strain energy density sensed by osteocyte at location x_i. $f(x,x_i)$ is the damping function describing the decrease in signal intensity with respect to distance d and characteristic decay parameter D.

However, when $P(x,t)<k_{tr}$, osteoclastic resorption will happen which can be described as

$$\frac{dm_{cl}(x,t)}{dt}=-r_{cl} \tag{4}$$