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Full Length Article

Assessment of the effect of reduced compositional heterogeneity on fracture resistance of human cortical bone using finite element modeling

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ABSTRACT

The recent reports of atypical femoral fracture (AFF) and its possible association with prolonged bisphosphonate (BP) use highlighted the importance of a thorough understanding of mechanical modifications in bone due to bisphosphonate treatment. The reduced compositional heterogeneity is one of the modifications in bone due to extensive suppression of bone turnover. Although experimental evaluations suggested that compositional changes lead to a reduction in the heterogeneity of elastic properties, there is limited information on the extent of influence of reduced heterogeneity on fracture resistance of cortical bone. As a result, the goal of the current study is to evaluate the influence of varying the number of unique elastic and fracture properties for osteons, interstitial bone, and cement lines on fracture resistance across seven different human cortical bone specimens using finite element modeling. Fracture resistance of seven human cortical bone samples under homogeneous and three different heterogeneous material levels was evaluated using a compact tension test setup. The simulation results predicted that the crack volume was the highest for the models with homogeneous material properties. Increasing heterogeneity resulted in a lower amount of crack volume indicating an increase in fracture resistance of cortical bone. This reduction was observed up to a certain level of heterogeneity after which further beneficial effects of heterogeneity diminished suggesting a possible optimum level of heterogeneity for the bone tissue. The homogeneous models demonstrated limited areas of damage with extensive crack formation. On the other hand, the heterogeneity in the material properties led to increased damage volume and a more variable distribution of damage compared to the homogeneous models. This resulted in uncracked regions which tended to have less damage accumulation preventing extensive crack propagation. The results also showed that the percent osteonal area was inversely correlated with crack volume and more evenly distributed osteons led to a lower amount of crack growth for all levels of material heterogeneity. In summary, this study developed a new computational modeling approach that directly evaluated the influence of heterogeneity in elastic and fracture material properties on fracture resistance of cortical bone. The results established new information that showed the adverse effects of reduced heterogeneity on fracture resistance in cortical bone and demonstrated the nonlinear relationship between heterogeneity and fracture resistance. This new computational modeling approach provides a tool that can be used to improve the understanding of the effects of material level changes due to prolonged BP use on the overall bone fracture behavior. It may also bring additional insight into the causes of unusual fractures, such as AFF and their possible association with long term BP use.

1. Introduction

Bisphosphonates (BP) are the most commonly used osteoporosis treatment that has been effective in preventing osteoporotic fractures by suppressing bone turnover. The reduction in bone turnover preserves the microarchitecture of the bone and maintains or increases areal bone mineral density (BMD). Despite the beneficial effects of BPs, there is accumulating evidence of a potential complication in the form of atypical femoral fracture (AFF) [1,2]. AFF is a catastrophic failure of the femur occurring in the subtrochanteric region and diaphysis of the femur. Although the occurrence rate of AFF in the general population is quite low, it leads to high rate of morbidity and mortality [2]. These fractures have different characteristics than ordinary osteoporotic femoral fractures. Additionally, areal BMD is not a good predictor of AFF risk [3]. Although a causal relationship between AFF and BP has not yet been shown, several studies demonstrated a duration-dependent association between AFF and BP use [1,4–7].

The recent reports of AFF in patients who have undergone long-term BP treatment brought into attention the possibility of adverse mechanical modifications in bone due to extensive suppression of bone

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turnover [2,8]. One of these modifications has been suggested as reduced compositional heterogeneity of the bone [9,10]. Studies performed on bone biopsies from individuals under BP treatment have shown increased mineralization and collagen maturity as well as reduced mineral and matrix heterogeneity [9–14]. Similar results were obtained on biopsies from individuals with fracture history in small populations [15,16]. On the other hand, no association between fracture status and heterogeneity in mineralization and collagen maturity was found in a larger age-matched cohort [17]. In addition, several studies reported increasing trends in mineralization heterogeneity in fracture groups in pediatric patients [18] as well as in adults compared to nonfracture controls [19,20]. These results indicate that there have not been consistent findings on the relationship between tissue heterogeneity and fracture status.

The effects of compositional changes on mechanical properties have been explored in several studies. In one of these studies, elastic modulus determined from nanoindentation measurements on biopsies from patients who have received long-term BP treatment demonstrated a reduction in the heterogeneity of cortical bone elastic modulus compared to individuals with normal bone [21]. At larger length scales, reference point indentation (RPI) measurements demonstrated a deterioration in micro-indentation properties in AFF patients [3]. Furthermore, mechanical testing on alendronate-treated canine cortical bone showed a decreasing trend in energy to fracture [22] and reduced toughness [23]. In addition, a reduction in fatigue life using a metabolic acidosis sheep model of osteoporosis and high dose alendronate-treated canine cortical bone was observed compared to non-treated bone [24,25].

In addition to experimental studies, computational modeling was also utilized to evaluate the influence of compositional heterogeneity on mechanical properties. Several studies compared the amount of energy dissipation in models that incorporate homogeneous and heterogeneous material properties and concluded that the energy dissipation was higher in models with heterogeneous material properties [26]. Tissue heterogeneity was found to play a more significant role in inelastic properties than in elastic properties [27]. In addition, fracture mechanics-based simulations demonstrated that the variation in material properties between different compartments of cortical bone microstructure led to enhanced crack deflection improving fracture toughness [28]. These findings indicate that a more uniform bone composition both at submicro- and microscale may reduce the effectiveness of the fracture resistance of bone and may result in the progression of benign microcracks causing full fracture [8,29].

In summary, the existing literature demonstrates the statistical correlation between compositional changes and mechanical properties, but it does not directly identify the mechanistic link between the material level changes and fracture behavior of bone. Particularly, the direct effect of compositional changes on crack formation and propagation has not been explicitly evaluated experimentally or computationally. In order to address this question, the goal of the current study is to quantify the contribution of compositional heterogeneity on crack growth in cortical bone using finite element modeling. The computational evaluation approach developed here makes it possible to eliminate the confounding factors that exist in experimental evaluations and to identify the direct influence of heterogeneity on crack growth behavior in cortical bone. It presents direct evidence on how heterogeneity influences the fracture resistance of cortical bone and may provide additional insight into how the prolonged BP use impacts the mechanical properties of cortical bone. This may help improve the understanding of the possible association of BPs with AFF.

2. Materials and methods

The influence of compositional heterogeneity on crack growth behavior in cortical bone was assessed by simulating compact tension (CT) specimen fracture toughness tests on human cortical bone with different material heterogeneity levels. The details of the modeling approach are described in the subsequent sections.

2.1. Finite element model description

This study utilized transverse microscopy images of cortical bone from the mid-diaphysis of tibiae of seven male donors with an age range of 39–85 years (average = 64.57 ± 16.76 years) (Fig. 1a, c) denoted as M1 to M7 representing different microstructural distributions. The microscopy images were obtained using a camera attached to a microscope under bright light at 10× magnification and represent an area of $1.17 \times 0.89\ mm^2$.

The microscopy images were converted to two-dimensional sketches by identifying the microstructural features and approximating osteons and Haversian canals by ellipses (Fig. 2a, b) following the procedure developed in [28]. This approximation was introduced to eliminate the roughness of the osteon boundaries that can create numerical artefacts in the finite element simulations. Following the generation of 2D sketches, 3D models were obtained by extruding the models in the third dimension by an amount of 1 mm resulting in microstructural sections with an approximate volume of $1\ mm^3$ (Fig. 2c). The extrusion step relies on the assumption that the entire bone volume has identical microstructure. Although this is generally not the case, due to the small volume considered in the models, this assumption represents a valid approximation. The detailed microstructural sections explicitly represent the interstitial bone, osteons, Haversian canals, and cement lines (Fig. 1b, d). All models were generated using the finite element software, ABAQUS (version 6.13, Simulia, Providence, RI). The detailed microstructural sections were then inserted into a compact tension (CT) test specimen with a $1\ mm^3$ cutout section such that osteons were oriented perpendicular to the crack growth direction (Fig. 2d). The dimensions of the CT specimen were based on previous experimental studies [30]. An initial crack was introduced into the model in the mid-plane of the microstructural section with a depth of 0.1 mm. An incremental displacement boundary condition was applied on both top and bottom loading pin holes of the CT specimen to generate opening mode (Mode I) loading conditions. This loading provides a stress state that leads to an incremental crack growth and prevents the propagation of the crack through the entire volume of the specimen at once. The incremental displacement was applied until the crack reached the homogeneous CT specimen section. Since all models were evaluated at the same load level, the crack did not reach the end of the microstructural section for all models. CT specimen was fixed in all directions at the mid-plane at the far end from the loading point. All compartments of the finite element models were meshed with tetrahedral elements with the exception of cement lines which were represented with zero thickness triangular interface elements. The total number of elements in the models ranged between 1.5 and 1.7 million. The size of the elements was 20 μm in the microstructural section.

The CT specimen and each compartment in the detailed microstructural section were assigned isotropic elastic properties (Table 1). Crack formation and propagation in the osteons, interstitial bone and CT specimen were modeled by cohesive extended finite element method (XFEM) and in cement lines by cohesive interface elements as outlined in more detail in Section 2.2. In this modeling technique, ultimate strength and critical energy release rate need to be specified in addition to the elastic properties of the bone. CT specimen section does not include any microstructural detail, therefore, was assigned equivalent homogenized material properties that were held constant for all simulations based on experimental data reported in the literature [31–33] (Table 1). On the other hand, the material properties of the microstructural sections were varied between simulations to represent the influence of material heterogeneity. A total of four different cases was investigated for each model, including one simulation with homogeneous material properties (HM) and three simulations with heterogeneous material properties (HT). In the homogeneous models, each