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EVALUATING FLUORIDE TREATED BONE USING MICRO CT AND COMPUTATIONAL MODELING

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SUMMARY

In this study we evaluate the influence of low-dose fluoride treatment on 23 biopsies from patients treated with fluoride or a placebo. Computational finite element (FE) models of each biopsy were subjected to a range of non-destructive loads including compression, shear and torsion. The primary outcomes from this study were that mechanical strength was not significantly correlated to low-dose (less than 10 mg/day) of fluoride levels (one-way ANOVA, P-values of 0.78, 0.69 and 0.62 for compression, shear and torsion, respectively). However, when bulk bone material properties were derived from DXA bone mineral density (BMD) from each patient's proximal femur, a non-significant linear decline in mechanical strength with increase in fluoride was predicted. When the same material property was used for all bones (to evaluate bone architecture influence) then mechanical strength showed a characteristic concave upwards trend, consistent with the variation of micro CT derived percentage bone volume (BV/TV). The secondary outcomes from this study were that in compression, BV/TV was observed to be a strong surrogate measure for mechanical strength (R^2=0.83), while surface density (R^2=0.6), trabecular thickness (R^2=0.5) and intersection surface (R^2=0.5) also explained the variation of mechanical strength well. However, trabecular separation and trabecular number were mildly correlated with mechanical strength (R^2 of 0.31 and 0.35, respectively). Compression was the loading mode most strongly correlated to micro CT indices.

INTRODUCTION

Osteoporosis is a worldwide problem which affects around 1/5 men and 1/3 post-menopausal women. This disease is characterized by low bone mass, deterioration of bone micro-architecture, enhanced bone fragility and an increased fracture risk [1]. Postmenopausal osteoporosis, in particular, is caused by a decline in estrogen due to the onset of menopause and primarily affects the trabecular bone thus predisposing the individual to bone fractures [2]. At present, treatment for osteoporosis is dominated by medications that reduce bone resorption. Thus there is much interest in developing therapies that primarily stimulate the formation of bone. Elemental fluoride has been shown to stimulate the growth of osteoblasts [3], increase bone formation and increase the mineral density of trabecular bone [4]. Studies using high doses of fluoride have reported no improvement in bone density and also an increase in the bone fracture rate [4]. This is likely to be due to impairment in the mineralization of the bone. Data from studies that have used lower doses of fluoride have shown mixed results with some suggesting that there was a decline in vertebral fracture risk [5,6] while others have reported no effect. Accordingly, we conducted a year long clinical trial to assess the effects of low dose fluoride on bone mineral density and turnover rate in post-menopausal women. At the conclusion of the study, a subset of participants in the trial underwent a transiliac bone biopsy. This study looked at the effects of fluoride on the trabecular bone. Microstructure based computational models have shown to facilitate the study of the complex structure of trabecular bone as it is able to provide insight into trabecular failure. One advantage of computational modeling is that it is able to predict fracture loads by non-invasive means and it has been shown to achieve precision which is comparable to densitometry data and is able to predict fracture loads in the femur with up to 60% accuracy [7]. Computational evaluation of the microarchitecture of human biopsies may provide a virtual assessment of the influence of fluoride on mechanical resistance. As a secondary outcome of this study, we aim to assess how well standard micro CT measures correlate with mechanical strength. The aim of this study is to integrate microarchitectural data derived from CT with computational modeling to i) study the influence of fluoride on human biopsy strength; and ii) evaluate the correlation between microarchitectural indices and mechanical strength.

METHODS

Twenty three participants (out of 180) volunteered to provide a biopsy sample from their iliac crest as part of a 12 month long placebo controlled randomized trial of the effects of low-dose fluoride therapy in postmenopausal women with osteopenia. The women were randomized into four groups: placebo, 2.5, 5 or 10 mg/day of fluoride for twelve months. Bone mineral density was measured at the lumbar spine, proximal femur and the forearm using dual-energy x-ray absorptiometry. This therapy did not significantly affect bone density at any skeletal site but increased osteoid volume which is indicative of impaired mineralization. Figure 1 outlines the modeling framework developed for this study. First, biopsies were scanned using a micro-CT and standardized reconstructions were carried out. Secondly the data was digitally cleaned and a hexahedral voxel mesh was created for each sample. A validation study of the mesh resolution and boundary conditions was also conducted using a 3D printed version destructed using an Instron test. Thirdly, a computational finite element analysis was carried out on all 23 samples where each model was loaded to failure under modes of compression, torsion and shear according to the average Von Mises damage criteria which was determined from the validation test. Fourthly we assessed the computationally predicted failure loads (measure of bone strength) across the fluoride dosage levels and completed the analysis by looking for correlation with the 3D micro CT measures.

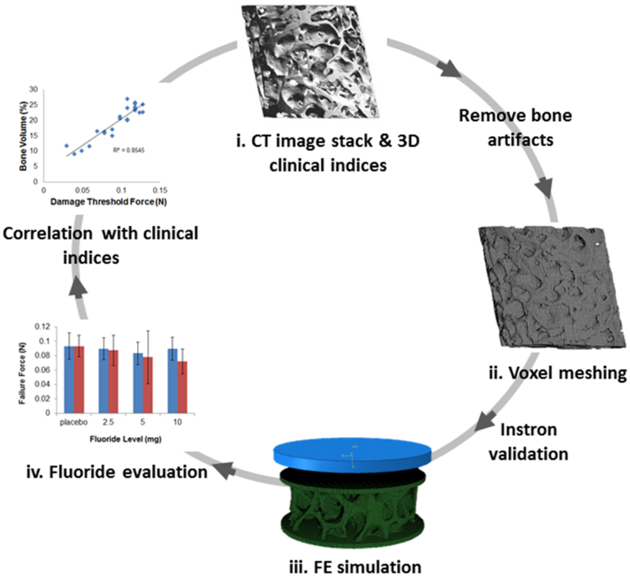

Figure 1: Modelling framework for this study including (i) CT scanning and measurement of indices; (ii) geometric mesh creation; (iii) computational finite element mechanics simulation; (iv) evaluation of effects of fluoride; and (v) correlation of damage loads with CT clinical indices.

RESULTS AND DISCUSSION

The primary analysis of this study was the influence of fluoride on mechanical strength (Figure 2). Treatment with low-dose fluoride did not significantly influence the mechanical failure force (using a one-way ANOVA with P-values of 0.78, 0.69 and 0.62 for compression, shear and torsion, respectively). This result was consistent with the BMD results by DXA from all 180 participants. There were consistent small, but non-significant reductions in mean failure force with the fluoride groups. The mean mechanical strength for compression, shear and torsion consistently decreased with increase in fluoride level from 0 mg (placebo) to 10 mg. This was characterized by a linearly decreasing strength when material properties were derived from patient specific DXA bone mineral density measures (BMD) measures (red). When a constant material property (Young's modulus of 1 GPa) was used for all biopsies then strength showed a concave upwards trend (blue). The concave upwards trend was consistent with percentage bone volume (BV/TV) and intersection surface (surface of bone intersecting with the region of interest), versus fluoride level (mg per day) as measured during the initial clinical trial independently from the computational measures.

The secondary outcomes from this study showed that in compression the micro CT derived percentage bone volume (BV/TV) is a strong surrogate measure for mechanical strength (R^2=0.83). This shows that 83% of the variation in mechanical strength can be explained by percentage bone volume (a purely structural parameter). One of the contributors to BV/TV, trabecular thickness (also from micro CT) could also explain ~50% of the variation in bone strength (R^2=0.5), while surface density (micro CT) may explain ~60% of the variation (R^2=0.6). Intersection surface, a parameter resulting from the bone surface intersecting with the selected region of interest also exhibited good correlation (even though not typically used except in bone remodeling studies) and accounted for 50% of the variation in strength (R^2=0.5). Trabecular separation and number were only mildly correlated with mechanical strength (R^2 of 0.31 and 0.35, respectively). Compression was the strongest correlated loading mode for most micro CT indices with shear and torsion slightly less.

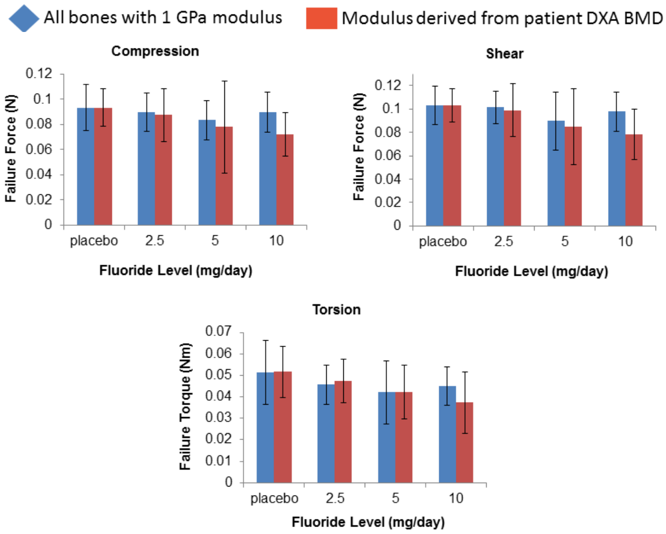

Figure 2: Failure force versus fluoride levels for compression, shear and torsion modes plotted for material properties (blue) and bulk material properties derived from patient BMD data (red).

CONCLUSIONS

Computational evaluation has confirmed that mechanical strength decreases with increase in fluoride consistent with clinical CT findings. Secondly, percentage bone volume, bone surface density, trabecular thickness and intersection surface are good surrogate measures for bone strength. Finally, compression tests had the strongest correlations followed by shear and then torsion with clinical CT indices.

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