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Age-Related Mineralization Heterogeneity in Human Femoral Cortical Bone

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Introduction: Mineralization heterogeneity may have a role in defining the relationship between microdamage and overall mineralization. Clearly, there are significantly more cracks in interstitial regions of bone [1,2] that may be a result of increased mineralization in those regions [3]. However, even though microdamage significantly increases with age [1,2], several studies indicate that average (or bulk) mineralization in bone decreases [4-6]with age. The objective of this research was to determine the relationship between area of hypermineralized bone and average (bulk) mineralization with age. It was hypothesized that although bone may contain hyper-mineralized regions, that average or bulk mineralization can decrease with age consistent with experimental data, when undermineralized regions also exist.

Methods: A semi-empirical micromechanical mineralization model was developed using MATLAB (Natick, MA). The model assumes bone consists of two constituents: osteonal and interstitial bone. The interstitial bone contains regions that are hyper-mineralized and under-mineralized. A relationship for the average mineral percentage ($\%Min_{avg}$) was developed to account for mineral percentages in secondary femoral osteonal area (SecOstArea, or OST) and interstitial area (1-OST):

$$\%Min_{avg} = OST * (\%Min_{OST}) + (1 - OST) * \%Min_{int} \quad (1)$$

Using the stiffness-mineral relationship of osteonal and interstitial bone [7,8], we arrive at the mineral percentages for the osteonal and interstitial constituents

$$\%Min_{OST} = \left[\left(\%Min_{avg} / (1 - OST\%)\right) - 2.836\right] / \left[(OST\% / (1 - OST\%)) + 1\right] \quad (2)$$

$$\%Min_{int} = \%Min_{OST} + 2.836 \quad (3)$$

The mineral in interstitial bone ($\%Min_{int}$) is written to account for the under-mineralized *($\%Min_{under}$)* and hyper-mineralized *($\%Min_{hyperr}$)* regions

$$\%Min_{int} = (1 - OST - hyperarea) * \%Min_{under} + (hyperarea) * \%Min_{hyper} \quad (4)$$

The hyper-mineralized regions near cracks are assumed to be 1.5 times the fully mineralized bone away from cracks [3]. The above relations are used to solve for the mineral percentage of under-mineralized and hyper-mineralized regions as a function of hypermineralized area fraction. The average (bulk) mineral content ($\%Min_{avg}$) (Figure 1) and secondary osteonal area corrected for pore size of human cortical bone (OST) were experimentally measured and used in the empirical relations developed here [4,9]. Linear regression analysis was used to determine relationships between mineral percentage and OST and age. JMP™ (SAS Institute, Cary, NC) was used for all analyses. Significance was set at $p<0.05$. Mineral percentage did change with age (Figure 1) however, OST did not change significantly with age (OST% = 63.4% ± 9.95%).

Results: A graphical representation of the model results shows the relationship between age, hypermineralized area fraction and average mineral percentage in hyper-mineralized (Fig. 2) and undermineralized (Fig. 3) interstitial bone regions. In the model, the weighted mineral percentages of the hyper- and under- mineralized interstitial bone and of the secondary osteonal bone equal the experimentally measured bulk mineral percentage (Figure 1). Results show that the interstitial mineral percentages decrease with age for constant for increasing hypermineralized area fraction (Figures 2 and 3) consistent with bulk mineral decreases with age (Figure 1). However, interstitial mineral percentages can also increase with age depending upon the relationship of the hyper-mineralization area fraction with age. Decreasing area fraction with age can result in increasing mineral percentage.

Discussion: Previous work has showed that microcracks initiate within more mineralized regions of bone and that mean mineralization of the damaged loci is significantly greater than the overall mineralization for each donor [3]. Given the reported age related increase in microdamage density [1,2], we might expect a corresponding increase in bone mineralization as previously proposed [10]. However, cortical bone specimens taken from the proximal femur become less mineralized in vivo with age [4-6,10]. Results of this model demonstrate that it is possible that bone that has more highly mineralized regions and also has under-mineralized regions can result in a lower average mineralization**.** Accordingly, even though microdamage has been found to be positively related to high**ly** mineralized regions, it may appear that it is negatively related to average mineralization. Relations between damage and hypermineralization and hyperminerlized area fraction likely vary with bone type, location and age.

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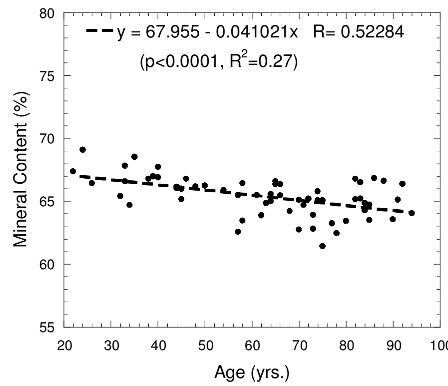

Figure 1. Bulk mineral percentage for human femur.

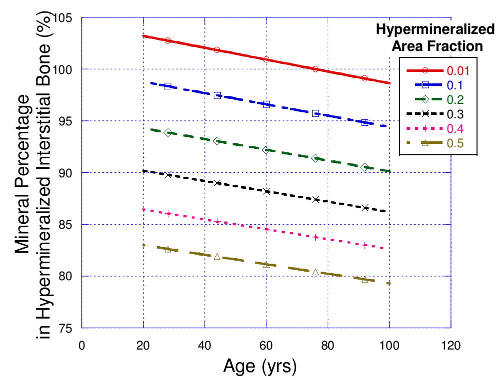

Figure 2. Mineral in hyper-mineralized bone.

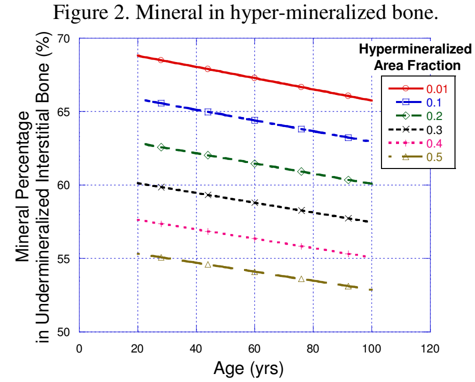

Figure 3. Mineral percentage in under-mineralized bone.