EFFECTS OF NON-ENZYMATIC GLYCATION ON THE BIOMECHANICAL BEHAVIOR OF BONE

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ABSTRACT

The incidence rate of fractures increases with age, and poses a major public health problem for the elderly population. While bone mass has been commonly used as an indicator for fracture risk, overlaps in bone mass between normal and high-risk fracture incidence groups suggests that other properties of bone, collectively known as bone quality, may help to explain the increased fracture risk in the elderly.

Some aspects of bone quality involve changes in the organic matrix, and these changes contribute to the deterioration of mechanical properties in aging bone. Collagen, the primary structural protein in the organic matrix of bone, can undergo a post-translational modification known as non-enzymatic glycation (NEG) that increases the degree of collagen crosslinking. NEG occurs through the presence of extracellular sugars causing the formation of intra- and inter- fibrillar collagen crosslinks known as advanced glycation end-products (AGEs). AGEs have been shown to accumulate with age and negatively impact biochemical and mechanical properties of the basement membrane, tendon, skin, articular cartilage, cardiovascular connective tissue, and cortical bone. The alterations of the organic network in bone caused by NEG may be relevant to increased bone fragility with aging and disease. The accumulation of AGEs may also adversely affect energy dissipation mechanisms in bone such as microdamage formation and crack growth toughening, and ultimately causing an increased propensity of bone to fracture.

Thus the goal of this doctoral research project is to investigate the role of NEG in age-related increase in bone fragility. Chemical, mechanical, and computational tools are used to mechanistically identify how collagen modifications affect the fracture resistance of cortical and cancellous bone at multiple levels. Several experimental models are presented here including an in vitro ribosylation model; an animal-drug model; and new microCT-based techniques for quantification of microdamage. A new constitutive relationship relating the biochemistry of the organic matrix with energy release rate is also proposed here and used in a numerical plasticity cohesive model for crack growth.

The furthered understanding of these mechanisms relating to fracture will aid in improving existing clinical diagnosis of bone fragility as well as provide new insights to the development of treatments and drug therapies.