THE BIOMOLECULAR BASIS OF BONE FRACTURE

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ABSTRACT

Osteoporosis is a significant health problem typically characterized by brittle bones and increased fracture risk. Although osteoporosis is traditionally associated with the loss of bone, overlaps in bone mass between fracture and non-fracture patients suggest that there are factors other than bone quantity, such as bone quality, that may influence fracture risk.

Bone quality encompasses features of bone's extracellular matrix composition and microarchitecture, which interact under applied loading to form microdamage. The formation of microdamage ultimately influences bone's fracture susceptibility. Bone's organic matrix is composed primarily of type I collagen and is altered by a host of post-translational modifications including non-enzymatic glycation. This spontaneous biochemical reaction occurring between extracellular sugars and amino acid residues results in the formation of crosslinks (advanced glycation end products) that form within and across collagen fibers. Although the effects of advanced glycation end products on the mechanical integrity of bone have been previously investigated, the mechanism through which non-enzymatic glycation modifies bone is unclear. In addition to the modifications of collagen, it has been recently shown that non-collageneous proteins also play an important part as determinants of bone quality. Of these proteins, osteocalcin and osteopontin are closely associated with each other, collagen, and bone mineral. However, very little is known about the role of these proteins in determining fracture risk.

The goal of this study is to explore a new path in osteoporosis research by analyzing the role of proteins and protein modifications in bone fracture. This project incorporates mechanical, biochemical, and imaging techniques to identify the key biomolecular determinants of bone quality and to investigate their effects on each other and on bone fragility. Results from this work indicated that changes in bone quality via alterations in the collagen and non-collagenous protein constituents contribute to the formation of microdamage that regulates bone toughness and influences fracture risk. This project provides an enhanced understanding of the

mechanism of bone fracture that will ultimately lead to improvements in the clinical diagnosis of bone fragility, and may aid in the identification of new drug targets to repair and regenerate bone.