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Aging and fragility of bone

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Bone structure is hierarchical with length scales ranging from nanometers to centimeters. Changes on any of these length scales can affect the integrity of the structure. Bone strength can be affected by alterations in nanostructure, e.g., non-enzymatic cross-linking of bone collagen, changes in microstructure, e.g., disruption of the trabecular network, or changes in macrostructure, e.g., periosteal bone apposition. As bone ages, its structure is affected at every length scale thus diminishing its functional capacity.

The main manifestation of aging is the diminution of toughening mechanisms within bone¹⁻³. As a result, cracks propagate easier through old bone tissue and bone absorbs less energy before it fractures, in other words, bone becomes more brittle as it ages⁴. This is a result in part of the embrittlement of bone collagen due to advanced glycation end products (AGEs)⁵. These non-enzymatic cross-links increase with age in collagen, making it more brittle⁶. The increase in AGEs is accelerated in diabetics. As a result, bone toughness is diminished by as much as 40% in some diabetic rat strains⁷.

The process of bone remodeling is a remarkable mechanism that replaces old bone and constantly renews the tissue. However, bone remodeling is also responsible for the stochastic removal of trabeculae⁸⁻¹⁰. In particular, rapid bone loss associated with high bone turnover can cause trabecular perforation and removal whereas slower bone loss may result only in thinning of trabeculae. The former is far more detrimental to bone strength. Bone loss that results in trabecular perforation reduces bone strength by 2- to 5-fold more than loss caused by trabecular thinning¹¹. Interesting, normal adaptive and reparative processes may contribute to

trabecular perforation. Typically, perforations occur when osteoclasts target the narrowest region of a trabecula. This region is also under the most stress and may accumulate microdamage more rapidly, which in turn attracts osteoclasts¹².

With aging, the outside dimensions of bones increase due to periosteal apposition¹³. This is accompanied with loss of bone on the inner surfaces. Bone loss is not uniform throughout the skeleton but may be much worse in specific regions. This regional bone loss appears to contribute to femoral neck fragility. The superior region of the neck loses bone at a much higher rate than the inferior region¹⁴, probably because of the stress distribution imposed on bone tissue due to daily activities¹⁵. Unfortunately, loss of bone in the superior region makes the hip much more susceptible to failure during a fall¹⁶.

Bone marrow stem cells lose their ability to differentiate into bone cells with age^{17,18}. Similarly, stem cells within the periosteum lose the ability to differentiate into chondrocytes¹⁹, which may explain why fracture healing becomes less efficient with age²⁰. The ability of mechanical loads to generate new bone formation declines with age and this might be due to a loss in the functional capacity of the osteocyte network²¹. It is well known that the number of osteocytes within bone tissue decreases with age, but we do not yet know the functional significance of this decline²². Nevertheless, anabolic therapy with parathyroid hormone remains effective despite the functional decline in bone cells caused by aging^{23,24}.

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