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Perspective Article

Bone material properties and mineral matrix contributions to fracture risk or age in women and men

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Abstract

The strength of bone is related to its mass and geometry, but also to the physical properties of the tissue itself. Bone tissue is composed primarily of collagen and mineral, each of which changes with age, and each of which can be affected by pharmaceutical treatments designed to prevent or reverse the loss of bone. With age, there is a decrease in collagen content, which is associated with an increased mean tissue mineralization, but there is no difference in cross-link levels compared to younger adult bone. In osteoporosis, however, there is a decrease in the reducible collagen cross-links without an alteration in collagen concentration; this would tend to increase bone fragility. In older people, the mean tissue age (MTA) increases, causing the tissue to become more highly mineralized. The increased bone turnover following menopause may reduce global MTA, and would reduce overall tissue mineralization. Bone strength and toughness are positively correlated to bone mineral content, but when bone tissue becomes too highly mineralized, it tends to become brittle. This reduces its toughness, and makes it more prone to fracture from repeated loads and accumulated microcracking. Most approved pharmaceutical treatments for osteoporosis suppress bone turnover, increasing MTA and mineralization of the tissue. This might have either or both of two effects. It could increase bone volume from refilling of the remodeling space, reducing the risk for fracture. Alternatively, the increased MTA could increase the propensity to develop microcracks, and reduce the toughness of bone, making it more likely to fracture. There may also be changes in the morphology of the mineral crystals that could affect the homogeneity of the tissue and impact mechanical properties. These changes might have large positive or negative effects on fracture incidence, and could contribute to the paradox that both large and small increases in density have about the same effect on fracture risk. Bone mineral density measured by DXA does not discriminate between density differences caused by volume changes, and those caused by changes in mineralization. As such, it does not entirely reflect material property changes in aging or osteoporotic bone that contribute to bone's risk for fracture.

Keywords: Collagen, Osteoporosis, Biomechanics, Mineral, Microdamage, Aging

The strength of bone, and its ability to resist fracture, is dependent on its mass and geometry, but also on intrinsic properties of the bone tissue itself. It is generally recognized, based on clinical observation, that pathologies that affect the material properties of the tissue, such as osteomalacia or osteopetrosis, increase the risk of fracture. However, the role that the material properties play to increase fracture risk varies depending on compensatory mass and geometric changes.

Bone from older individuals demonstrates decreased tensile plastic deformation (ie less energy in the post-yield region before fracture)[1,2]. This can perhaps be attributed to the slower bone turnover and increased mean tissue age of older bone[3], or to molecular changes in either the organic[4-7] or the inorganic[8-11] bone matrix[12]. The age-related reduction in the ability of bone to absorb energy prior to failure is clinically important in making osteoporotic bone more prone to failure from any impact load, such as one resulting from a fall. The loss of energy absorption capability, therefore, may be a primary factor increasing the risk of fracture in older women with low bone mass.

Bone tissue is composed primarily of collagen and mineral, each of which changes with age to alter the material properties of bone tissue. Although less well understood, microdamage tends to accumulate with age[13-17], and this too may have an effect on bone's tissue properties and ultimate fracture risk. The effects on bone material properties of each of these three matrix components will be discussed separately.

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Changes in collagen with age

The fatigue strength[18] and toughness[1,19] of bone decrease with age. Collagen may be the primary toughening mechanism in bone, having greater effects on bone toughness[20], than on strength or stiffness[17]. It has been shown in a mouse model of osteogenesis imperfecta that collagen defects can reduce the post-yield deformation of bone by 60%[21]. In studies using a baboon model, the percentage of denatured collagen compared to the total collagen content was significantly related to failure energy and to the fracture toughness of the tissue[20]. This means that collagen in bone is a primary arrestor of cracks, inhibiting their growth to critical dimension. This may be one explanation for the observation that aging has a more profound effect on the plastic deformation of bone than it has on elastic deformation[22]. It has been proposed that the intramolecular cross-links are important to enhance bone toughness, whereas the intermolecular bonds may be less important to toughness[21].

Studies on rat femora suggest that the decline in bone's mechanical properties with age may be dependent on the stability of the collagen[23,24]. With age, there is a decrease in collagen content[25], which is associated with an increased mean tissue mineralization, but there is no difference in cross-link levels compared to younger adult bone[4,21]. However, the stability of the cross-links may change with age[23,24], and this can have an effect on the fragility of the bone tissue. In humans, the declines tend to be more marked and more uniform in men than in women[5].

In osteoporosis, there is a decrease in the reducible collagen cross-links without an alteration in collagen concentration[6]; this would tend to increase bone fragility[4].

Changes in mineral with age

Older bone is more highly mineralized than younger bone, accounting for the tendency of bone from older individuals with higher material density to be weaker than that with lower material density, independent of porosity or volume[26-29]. Reports using infrared spectrometry[10,11] suggest that larger crystals are present in the bone of older, osteoporotic women and that this increased crystallinity itself could impair the mechanical properties of the tissue. More highly mineralized and more highly crystalline bone may permit earlier crack initiation by decreasing the amount of plastic deformation that can occur before ultimate failure. In older bone, increased porosity contributes to the effects of hypermineralization in that there is a smaller proportion of new, less mineralized but more ductile bone. This increases the contribution of the older hypermineralized tissue to bone's mechanical properties and reduces significantly the amount of energy the bone can absorb on impact. The effects of mineralization and porosity explain the observation that older bone has more damage than younger bone[13,15,16,30], and that older bone is more susceptible to damage at any given load. These relationships explain the increased fragility of older bone because bone can sustain very little post-yield strain before fracture, ie it becomes more brittle.

Changes in the morphology of the mineral crystal with age may contribute to increasing brittleness. Although the size of the apatite crystal itself may change very little[8], the normally elongated crystals may become more spherical in older, osteoporotic women and men[31]. It has been hypothesized that this can change the local stress distribution in the tissue and alter its load-bearing mechanical properties[31]. The precise effect of such changes in the mineral crystal on the mechanical properties of bone, however, is not known.

Bone strength and toughness are positively correlated to bone mineral content, but when bone tissue becomes too highly mineralized, it tends to become brittle[1]. This reduces its toughness, and makes it more prone to fracture from repeated loads and accumulated microcracking. Most approved pharmaceutical treatments for osteoporosis suppress bone turnover, increasing the mean tissue age and mineralization of the tissue. This might have either or both of two effects. It could increase bone volume from refilling of the remodeling space, reducing the risk for fracture. Alternatively, the increased mean tissue age could increase the propensity to develop microcracks, and reduce the toughness of bone, making it more likely to fracture. There may also be changes in the morphology of the mineral crystals that could affect the homogeneity of the tissue and impact mechanical properties[31]. These changes might have large positive or negative effects on fracture incidence, and could contribute to the paradox that both large and small increases in density have about the same effect on fracture risk.

Two recent reports, one in baboons[32] and one in post-menopausal women[33] show that treatment with alendronate will increase the tissue mineralization above that found in osteopenic subjects, but does not restore it to pre-ovariectomy or pre-menopausal levels. This suggests that alendronate will not increase tissue mineralization to levels that are detrimental, but will enhance the material properties of bone tissue through modest increases in mineral content, contributing to its efficacy in fracture reduction. Pharmaceutical treatments that alter collagen or mineral chemistry, independently from changes in content, could help to explain how the reduction in fracture risk stemming from several drug treatments is largely independent of the magnitude of bone mass increase.

Bone mineral density measured by DXA does not discriminate between density differences as a function of increased volume, or as a function of increased mineralization. As such, it does not entirely reflect material property changes in aging or osteoporotic bone that contribute to bone's risk for fracture.

Changes in microdamage with age

Microcracks accumulate approximately exponentially with age in cortical bone of the femoral diaphysis[13,30] and in cancellous bone from the femoral head[15] and neck[14,16]. Age accounts for 70-80% of the variation in microcrack density in

these regions. Cracks accumulate more quickly in women than in men after the age of 40 in the appendicular skeleton[13,34] but not in the axial skeleton[35].

Bone from elderly donors accumulates microcracks at a far greater rate than bone from younger donors[30]. In *ex vivo* mechanical tests, cracks were initiated in specimens from older women (mean age 72 ± 6 y) but not bone from younger women (mean age 26 ± 5 y), even with the same decline in elastic modulus in both groups[30], perhaps because it is easier to initiate new microdamage in older bone[1]. Cracks initiated in bone from older women grow at a greater rate than those in bone from younger donors[30]. This suggests that microdamage accumulation in bone from elderly women results from some inherent fragility in the tissue, rather than from a failure to detect and repair damage. This fragility may be one reason for the decreased fracture toughness[19,36] and smaller post-yield plastic deformation[1,2,26] that bone tissue can tolerate before complete fracture in older men and women.

Damage accumulation has greater effects on bone's resistance to fracture (ie toughness) than on its strength[1]. The numerical density of microcracks produced *in vivo* shows high correlations with three measures of toughness: the critical stress intensity factor, K_c, which is a measure of crack initiation (r^2 = range: 49-55%); a measure of damage accumulation preceding a macrocrack, the J-integral, (r^2 = range: 67-83%); and a measure of energy required for crack propagation (r^2 = 35-38%). Microdamage accumulation has an effect on bone toughness that can be demonstrated both from *ex vivo* mechanical loading studies, and from *in vivo* studies using pharmaceutical agents to suppress damage repair. Following suppression of remodeling, a 2-7 fold increase in microdamage accumulation is associated with a 20% reduction of tissue toughness in the rib[37] and lumbar vertebra[38]. *Ex vivo* studies show that microdamage accumulation reduces fracture toughness in tension significantly and may decrease fracture resistance[39,40]. This could be another explanation for the decreased toughness of bone that occurs with age[17,41]. Between 35 and 90 years of age, the energy required to initiate a crack in bone falls by 22%, and the energy required to propagate a crack through bone is reduced by nearly 50%[17]. During the same period, the number of microcracks increases nearly 10-fold, whereas the average crack length doubles[17,42]. This suggests that, under normal circumstances of aging, cracks are kept below a critical size for fracture.

Conclusion

In combination, these data seem to indicate that changes in collagen structure and mean tissue age (mineralization) underlie an age-associated reduction in bone toughness. The increased damage that occurs with age may be a consequence rather than a cause of the reduced toughness[17], although increased levels of microdamage, in combination with reduced repair and increased mean tissue age, can decrease toughness further.

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