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COMMENTARY

The relative influence of damage versus density on trabecular bone mechanical behavior

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It is well established that antiremodeling agents increase bone mineral density, improve whole bone strength and reduce fracture risk. Yet, reports of atypical femoral fractures in bisphosphonate users have raised concerns regarding the optimal use of these drugs.[1] Although atypical femoral fractures can occur in patients who have not been exposed to bisphosphonates,[2] several reports indicate that these fractures occur more often in those treated with bisphosphonates.[3] A causal association between bisphosphonate use and atypical fractures has not been established, and it may be that pre-existing abnormalities of the bone matrix contribute to these fractures. Alternatively, data indicating that bisphosphonate treatment is associated with altered mineralization, collagen crosslinking and microdamage[1] have led to speculation that deleterious effects of increased microdamage accumulation following severe and/or prolonged suppression of bone remodeling may contribute to the etiology of these fractures.[1] There are still many unanswered questions regarding how microdamage influences bone mechanical properties and to what extent microdamage accumulates with the use of antiremodeling agents in patients (as opposed to animal models) to influence fracture risk.[4] Some of these questions were addressed in a recent study by Garrison *et al.*[5] in which the relative effects of bone quantity, microarchitecture and microdamage on the failure properties of bovine trabecular bone were assessed. The authors determined that in trabecular bone, microstructure has a more significant impact than microdamage on bone fragility. Hence, the administration of antiresorptive treatments has a net beneficial effect on the mechanical properties of trabecular bone despite possible accumulation of microdamage.

Microdamage forms regularly in bone as a result of repetitive loading from daily activities, as well as during overloading situations such as traumatic injury. Understanding the contribution of microdamage to skeletal fragility is complicated by several observations: (1) microdamage occurs at several hierarchical length scales, including at the mineralized collagen fibrils, lamellar and osteonal levels;[6] (2) microdamage is not a single entity, but occurs in the form of either linear microcracks or diffuse damage;[7] (3) the type of damage formed depends on the imposed loading mode (e.g., tensile, compressive, torsional, mixed loading) and is influenced by the underlying bone microarchitecture;[8,9] and (4) microdamage formation is not necessarily bad for bone, as it is a major toughening mechanism and can dissipate energy, thereby inhibiting the formation of large-scale catastrophic cracks.[10,11]

The mechanisms by which antiremodeling agents are believed to reduce fracture risk include preservation of trabecular and cortical bone microarchitecture, reducing the number of 'stress risers' that weaken bone locally, and increasing bone tissue mineral density. These positive effects are balanced against the possible negative effects associated with reducing bone turnover, including accumulation of harmful microdamage and collagen crosslinks. Identifying the relative benefits versus possible harm to bone biomechanical properties is key to understanding how these drugs should be used to reduce fracture risk.

In the previously mentioned study by Garrison *et al.*,[5] damage was first induced in bovine trabecular bone specimens by either low or high amounts of compressive overloading (2.5 or 4.5% strain, respectively). Specimens were then tested to failure by shear loading to simulate the unusual loading pattern that may occur in a fall. The authors found that bone specimens in the high-damage group had worse resistance to shear loading compared with bone specimens in the low-damage group, and that shear strength in the low-damage group did not differ from undamaged control specimens. Toughness, or the ability to absorb energy before failure, of the trabecular bone specimens was negatively associated with microdamage but positively associated with bone quantity, as measured by bone volume fraction (BV/TV). Importantly, multiple regression analyses indicated that bone toughness was more sensitive to BV/TV than to damage quantity. Thus, Garrison *et al.*[5] conclude that although microdamage accumulation can be detrimental to trabecular bone strength, treatments that offer improvement in BV/TV at the expense of minimal microdamage accumulation may have a

net beneficial effect on bone. The results concur with their prior work showing that bone density and microarchitecture have a greater influence than microdamage on the toughness of bovine trabecular bone specimens tested in compression.[12]

Several factors should be considered when interpreting these findings. First, the experiments were conducted using bovine bone. A key advantage of using bovine trabecular bone samples is that the orientation of specimens relative to the trabecular alignment can be strictly controlled. Second, there is very little *in vivo* microdamage in bovine bone, so it can safely be assumed that the experimentally induced microdamage will be the influencing factor of the subsequent mechanical behavior. However, the volume fraction of bovine trabecular bone is three to four-fold higher than that of human osteoporotic trabecular bone, and it is unclear whether the observations made in the stronger, plate-like bovine bone would translate to the weaker, rod-like architecture of human trabecular bone, especially in osteoporotic patients whose structure consists predominantly of thin, poorly connected trabecular rods. Use of human cadaveric bone would offer a more appropriate model, and the possibility of variable amounts of pre-existing microdamage would not pose a major issue as three-dimensional imaging methods can be used to measure pre-existing microdamage.[9,13]

In Garrison *et al.*'s experiment, microdamage was quantified via modulus reduction, as was done in several other studies.[14–16] However, this method does not allow for the identification of microdamage morphology (linear microcracks or diffuse damage), which is important because each type of microdamage has different effects on bone's mechanical integrity.[7] Linear microcracks are composed of smaller cracks that can coalesce and propagate to produce a harmful fracture. On the other hand, the submicroscopic cracks that comprise diffuse damage are held together by matrix elements that allow for the release of energy under applied loads, and therefore provide bone with a toughening mechanism. The formation of specific microdamage morphologies is affected by the underlying bone microarchitecture, where rod-like trabeculae accumulate more linear microcracks than diffuse damage.[8,9,17,18] A helpful addition to this study would be to measure the specific microdamage morphologies formed during the overloading. This information would aid with interpretation of the results because linear microcracks and diffuse damage will contribute differently to toughness.

Finally, these experiments were conducted on excised trabecular bone specimens only. Hence, the results may not apply to cortical bone, which has a very different microarchitecture than cancellous bone, and thus the relative contribution of microstructure versus microdamage to bone mechanical properties may be different in cortical bone than in trabecular bone. In addition, these findings in trabecular bone cannot be reliably extrapolated to whole bone biomechanics.

However, despite these limitations, the study by Garrison *et al.* provides novel insights regarding the use of osteoporosis therapies.[5] As mentioned earlier, clinicians are increasingly concerned that microdamage accumulation may outweigh the beneficial effects of antiresorptive treatments on bone mineral density and microarchitecture. Garrison *et al.* show that bone quantity influences trabecular bone toughness to a greater extent than microdamage. Previous work in dogs with normal levels of bone turnover show that reduction of bone turnover by bisphosphonate treatment was associated with increased bone quantity and improved bone stiffness and failure load, but also increased microdamage accumulation and, in some though not all studies, reduced toughness.[19–22] Longer treatment duration (3 years versus 1 year) did not lead to greater microdamage accumulation,[23] and there was no association between the amount of microdamage and bone toughness.[24] These observations have led the authors of these studies to conclude that 'it is not clear that microdamage accumulation in bone under normal physiologic circumstances is even a relevant biomechanical concern for living bone'.[24]

It is expected that microdamage will accumulate following antiresorptive treatments in humans because bone remodeling would be reduced. However, it is not clear whether targeted remodeling associated with microdamage repair is specifically inhibited. In addition, the few conflicting studies on microdamage and antiresorptive therapies in humans to date have relied on measurements from iliac crest biopsies, a site that may not be optimal for detection of microdamage accumulation. Thus, based on the work by Garrison *et al.*, even if treatments for osteoporosis lead to microdamage accumulation, it is likely that they still offer a net positive influence on bone quantity and microarchitecture that ultimately reduces fracture risk in treated versus untreated patients. However, this idea needs to be clarified through further work on osteoporotic human bone because the impact of microdamage in bone with such fragile microarchitecture may have a different impact on its mechanical properties than that observed in this study.

In conclusion, bone quantity, microarchitecture, and properties of the bone matrix all contribute to skeletal fragility, but further work is still needed to determine their relative contributions to whole bone biomechanical properties and fracture risk. The work by Garrison *et al.*, albeit in bovine bone, shows that the relative contribution of bone quantity and microarchitecture to trabecular bone biomechanical properties outweighs that of bone microdamage. Clinically, predictions of fracture risk may benefit from assessment of bone microarchitecture and bone matrix mechanical properties. Although bone microarchitecture can be assessed at peripheral skeletal sites, additional work is needed to develop clinically feasible methods to assess microarchitecture at the axial skeleton and to measure mechanical characteristics of the bone matrix. Ultimately, improved understanding of the relative importance of the various determinants of bone biomechanical properties will help clinical decision-making regarding the initiation, monitoring, or interruption of osteoporosis treatments.

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