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Perspective Article

Hylonome

Transmenopausal and age-related changes in bone remodeling

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Our clinical experience with bisphosphonates, the so-called "anti-resorptive agents", has forced us to think differently about what causes bones to fracture inappropriately and why fractures can be prevented in the presence of small increases in bone mass[1]. The idea emerging is that while the amount of bone present in the skeleton is a strong determinant of fracture, the rate of bone remodeling appears to be a strong determinant of fracture as well. This realization has led to potential answers to phenomena previously difficult to explain, for example, the very strong age-dependent increase in the risk of fracture that is independent of bone mass as measured by DXA (or other) technology[2]. We now know that this is accompanied by a marked increase in activation frequency as measured in tetracycline-labeled transilial bone biopsies[3].

Thus, the idea that remodeling rates affect the incidence and prevalence of fracture independent of bone mass is an inescapable conclusion that has led to a change in the paradigm of fracture and osteoporosis.

How does an increase in remodeling rates cause an increase in fracture risk, and, conversely, reduction in remodeling rates cause a marked reduction in fracture risk, both largely independent of the amount of bone present.

Remodeling, particularly with long-term gradual removal of bone tissue, has features that suggest some answers. Remodeling in the aged skeleton is distributed largely in the cortex and on cortico-endosteal surfaces in a manner that causes the cortex to be thinned while trabeculation moves from the inner cortex outward[4]. Thus, loss of bone is not uniform, but is located such that it causes loss of cross-sectional moment of inertia. This is at least a partial explanation for exaggerated fragility with age that is independent of bone mass.

A second phenomenon that emerges from this is based on the fact that remodeling occurs in packets with localized, surface-based removal and replacement of bone tissue. The remodeling seems to be particularly aggressive at menopause and beyond in that it penetrates trabeculae, thus removing whole trabecular elements and eliminating connections between trabeculae in the process. This loss of connectivity causes exaggerated weakness and exaggerated increase in the risk of fracture out of proportion to the amount of bone mass loss. Further, remodeling loci that do not penetrate trabeculae result in a localized trabecular thinning and thus a concentration of stress when loaded. This causes a "weak link" in that trabeculae can bear no greater load than what they are capable of bearing at their weakest locations.

Thus, increases in remodeling rates cause, 1) expansion in the remodeling space, 2) removal of endosteal bone, thinning the cortex and reducing the cross-sectional moment of inertia, 3) loss of connectivity, and 4) increases in the numbers of empty resorption lacunae or "notches" present on trabeculae resulting in weakened loci in individual trabeculae.

The reverse happens with cessation or marked reduction in the activation frequency of new remodeling sites, provided bone formation is left undisturbed at those sites where it is occurring at the time of intervention. Thus, closing the remodeling space tends to reverse to some extent all of the above without increasing bone mass very much.

An interesting thought experiment would be to test what would happen to the load-bearing strength of remodeling bone *in vivo* if remodeling were suddenly turned off or markedly reduced in both the resorption and formation phases simultaneously. This experiment (if it could be accomplished) would likely produce no increase in the load-bearing strength of the skeleton, even though there was elimination of remodeling, or marked reduction in the remodeling rate.

The explanation for exaggerated anti-fracture efficacy in patients treated with bisphosphonates may be a combination of the following:

1) Addition of bone mass while closing the remodeling space. Since remodeling is largely occurring at sites distant from the central marrow space, this would cause increases in

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cross-sectional moment inertia.

2) Filling of remodeling sites. This would include replacement of lost bone at empty resorption sites, thus eliminating the concentrations of stress at sites of unfilled resorption lacunae.

3) Cessation of trabecular penetration, or markedly reduced instances of penetration. This would further reduce the risk of fracture compared to placebo controls in which the loss of trabecular connectivity continues.

In this scenario, the increase in bone mineral density with bisphosphonate treatment could be seen as a marker of reduction in bone remodeling.

It is interesting to note that the few anti-fracture studies of bisphosphonates in which there was a failure to demonstrate significant anti-fracture effects were characterized by lesser reductions in the remodeling rates as well as smaller increases in bone mineral density compared to the successful ones.

One of the conclusions that can be made from this experience is that "anti-resorptive" therapy, in order to be successful in reducing fracture risk, must reduce remodeling rates and increase bone mineral density. It is likely that reduction in remodeling rates will have little anti-fracture effect in the absence of increase in bone mineral density.

Perhaps our bone mass (or BMD) paradigm need not be radically altered, but should be refined to accommodate the role of bone remodeling rates in causing variation in bone strength and risk of fracture.

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