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Skeletal fragility and bone quality

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Bone density (bone mineral density, BMD, by dual energy X-ray absorptiometry, DXA) has been the most important measurable determinant of fracture risk since the 1980s when it became feasible to measure it with accuracy in the clinical setting. It has been described as the "bone density paradigm of osteoporosis"[1]. However, there were early clues indicating that BMD was not the only determinant of fracture. The first was a report by Hui et al.[2] showing that age after 50 years was a stronger determinant of fracture risk than forearm bone density. This has been confirmed more recently with DXA[3]. However, the most important event leading to a change in the BMD paradigm is analysis of treatment results from anti-remodeling agents. Among six anti-remodeling agents used successfully to reduce fractures in osteoporosis, the portion of the reduction in fracture risk attributable to the induced BMD change ranged from 4% for calcitonin to 45% for alendronate[4]. Thus, we have begun to evolve changes in the BMD paradigm which, on the one hand, attributes risk of fracture to low BMD, and on the other hand, attributes anti-fracture treatment effects of anti-remodeling agents to an induced rise in BMD.

Bone quality

The foregoing has led to attempts at understanding the concept of *bone quality*. It is difficult to define and includes ideas such as toughness, strength, resistance to failure, load-bearing capacity, etc. Emerging definitions include a number of factors in a single common notion that includes bone intrinsic material properties, bone geometry, bone micro-damage, as well as bone mass.

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Bone remodeling

The function of bone remodeling in skeletal homeostasis is to remove damaged or unused bone tissue and replace it with healthy intact bone distributed appropriate to the loads placed on it. Any remodeling in excess of that required for these purposes can only weaken the skeleton. Thus, we have come to realize that suppression of remodeling by agents such as bisphosphonates or estrogen-like compounds are effective and safe because they reduce excessive remodeling to levels approximating optimal remodeling rates needed for repair and reorganization of bone tissue.

Determining optimal remodeling rates

This has been a difficult problem. When bisphosphonate treatment was first introduced showing as much as 60-70% reduction in remodeling rates, many were alarmed that this degree of suppression would interfere with repair of microdamage, and thus skeletons would become fragile at some time during treatment. The difficulty stemmed from our inability to determine optimal remodeling rates. Biochemical measurements of remodeling (NTx, CTx, etc.) are fraught with a number of difficulties, including analytical and physiological ones. However, more recent data have become available regarding remodeling rates in healthy women. Using dynamic histomorphometry of iliac crest biopsies, we have demonstrated that activation frequency (Ac.f), a tissue-level measure of bone remodeling, is about 0.13 remodeling sites per year on any trabecular surface in healthy premenopausal women[5]. We then demonstrated in these same individuals that Ac.f increased to 0.29/yr in second biopsies performed 12 months after their last menses. Further, in healthy women 13 years past menopause we demonstrated that Ac.f had increased to about 0.44/yr. Thus, healthy premenopausal women are remodeling at a rate only about one-half that at 12 months after menopause. Further, the premenopausal value is only about one-third that of healthy postmenopausal women approximately 13 years later[5]. The value for Ac.f in

untreated patients with postmenopausal osteoporosis tends to be still higher. Thus, high remodeling rates of healthy postmenopausal women may be, in large measure, the cause of skeletal fragility in patients fracturing from postmenopausal osteoporosis. Further, 60-70% suppression of remodeling rates by anti-remodeling agents in patients with postmenopausal osteoporosis results in rates approximately equal to those in healthy pre-menopausal women. Thus, if the anti-remodeling agents suppress only unnecessary remodeling allowing mechanically driven remodeling to continue we have an explanation both for the excessive skeletal fragility in patients with postmenopausal osteoporosis, and a mechanism for the success of treatment with remodeling suppressors.

Excessive remodeling and fragile skeleton

The mechanism whereby excessive remodeling results in a fragile skeleton has not been completely worked out but we may hypothesize several mechanisms.

First, remodeling always weakens the skeleton, at least transiently. However, when appropriate to the repair of microdamage, the transient weakness caused by a remodeling site is compensated by the improvement in strength from the removal and replacement of damaged bone tissue. However, remodeling in excess of that need for maintenance and repair can only contribute weakness to the skeleton. Excess remodeling causes loss of trabecular connectivity and loss of trabecular elements. Further, remodeling sites themselves, Howship's lacunae, weaken trabeculae under load. Finally, the excessive remodeling results in many areas of under-mineralized bone matrix. These areas will not bear load because their stress is shielded by those areas of the skeleton that are stiffer because their osteoid is better mineralized. Thus, there are several mechanisms whereby excessive remodeling weakens the skeleton.

Anti-remodeling agents

The anti-remodeling agents suppress remodeling activation, slow bone loss, and close the remodeling space which results in measurable bone gain. Thus, the anti-remodeling agents reduce the number of resorption sites, stop the cumulative loss of trabecular elements, and result in improvement in mechanical integrity of the skeleton. Most of the improvement in fracture resistance is due to the reduction in remodeling, and less than half is due to the increase in BMD.

Remaining questions

There remains significant uncertainty in the explanation of skeletal fragility and fractures in patients with postmenopausal osteoporosis. Among these are: 1) what is the role of defective bone intrinsic material properties; 2) what is the role of disturbed micro-architecture; and 3) what clinical measures can be developed to characterize bone quality?

Conclusion

While we have advanced our thinking regarding skeletal fragility by understanding that the measurements of bone density explain less than half of the determination of risk of fracture we must devise measures that take into account defective bone quality. The problem of measuring bone quality has become even more important given that we desperately need clinical surrogates of fracture in order to test and develop new drugs that reduce the risk of fracture in patients with osteoporosis.

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