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Bone Remodeling

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The supracellular organization of bone remodeling, aptly referred to by Frost (1) as the skeletal intermediary organization, is the essential link between the macroscopic changes in bone mass and the microscopic changes in bone structure that occur with aging and disease, the adaptations of bone to mechanical loading, and the cell and molecular biology of bone. Since remodeling occurs in temporally and spatially discrete packets or quanta (2), total skeletal remodeling represents the summation of contributions by a large number of focal events, each at a different stage of evolution. In general, the direction of change in bone volume and mass at a surface, whether gain or loss, is determined by the focal balance between the depth of resorption and the thickness of new bone within each individual cycle of remodeling, but the magnitude of change depends mainly on the rate of remodeling activation.

Biochemical Markers of Bone Remodeling

Whole body rates of resorption and formation can be measured by radiocalcium kinetics (3) and estimated by retention of labeled diphosphonate (4) and by the serum levels and urinary excretion rates of a wide variety of biochemical markers. The clinical utility of these markers was reviewed by Marcus (5). Urinary excretion of hydroxyproline in the fasting state remains the most widely used marker of whole body bone resorption rates, but little new information has been learned since our last clinical conference in 1983 (6). A new marker of bone resorption, reflecting the number of resorbing cells rather than the quantity of resorbed bone, is tartrate resistant acid phosphatase (TRAP), an enzyme found only in osteoclasts and in abnormal derivatives of the hematopoietic stem-cell such as the Gaucher cell (5). TRAP correlates well with urinary hydroxyproline but has not yet been compared with bone histomorphometry or evaluated in the management of osteoporosis.

A major recent development has been the discovery of osteocalcin and the measurement of its serum level as an index of bone formation. Marcus (5) reviewed the accumulated evidence in detail and pointed out the precautions that must be taken in interpretation. Serum osteocalcin is relatively insensitive to changes in bone formation rate in Paget disease but identifies with reasonable precision the direction and magnitude of change in bone formation in a wide variety of other disorders. In osteoporosis the data are conflicting, but most groups have found no correlation between serum osteocalcin and histologically determined bone formation rate. Like other markers, osteocalcin is a significant but weak predictor of the subsequent rate of bone loss in perimenopausal women. For physicians and patients who are unconvinced about the cardioprotective effect of estrogen replacement therapy, the combination of a low measurement for bone mass and a high value for some biochemical marker may help select women for such therapy who are at greatest risk of osteoporosis and have most to gain from preventing bone loss (5).

Effects of Age, Sex, and Race on Bone Remodeling

Since most patients with metabolic bone disease, particularly osteoporosis, are white women, most studies of normal bone remodeling have focused on the effects of age in this group. But white men and blacks also experience age-related bone loss and suffer from fractures, albeit less frequently. Studies of bone remodeling in these groups are important not only in themselves but because differences between sexes and between races may provide important clues to fracture pathogenesis. Recker and Heaney (7) reviewed the available data on the demographics of bone remodeling. The main effect of age is a modest increase in remodeling activation in both sexes, which has been shown by histologic, biochemical, and kinetic measurements, but is of smaller magnitude than the effects of estrogen deficiency in women. In addition, there is a decline in the work efficiency of osteoclast and osteoblast teams (7). Bone fragility is increased by the removal of whole trabecular elements and the resultant disruption of architecture, a change more evident in women than in men. Trabecular perforation must result from the cumulative effect of some combination of decreased initial trabecular thickness, increased frequency of remodeling activation, increased resorption depth, or decreased wall thickness, but the relative importance of these factors is unknown.

In the United States, blacks have more bone than whites, both because of higher peak adult bone mass and slower age-related bone loss. The frequency of remodeling activation, estimated both by histologic and biochemical methods, is lower in blacks than in whites and osteoblast work efficiency is reduced (7,8). Reduced remodeling activation has two consequences with opposite effects on fracture risk—conservation of mass and increased bone age. Fracture risk is lower in blacks than in whites so that the former effect predominates. Both increased bone age and slower osteoblast work are postulated to increase bone fragility, the former by increasing the accumulation of fatigue damage and microfractures and the latter by depressing their repair (1). The presence of both of these abnormalities in a group with lower fracture risk is a challenge to those who believe that

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qualitative factors are important (9). It is of particular interest that South African blacks, who differ ethnically from American blacks, have increased rates of bone remodeling and a much lower fracture rate than American blacks (C. Schnitzler, Discussion [see *Clinical Disorders of Bone and Mineral Metabolism*, 1989, Chapter 2]. It seems clear that the study of bone remodeling in different ethnic groups has much more to teach us about the interplay between quantitative and qualitative factors in fracture pathogenesis.

In Vivo Hormonal Effects on Trabecular Bone Remodeling, Osteoid Mineralization, and Skeletal Turnover

Many hormones affect bone remodeling and are implicated in the pathogenesis of metabolic bone diseases, including osteoporosis. The classic endocrinopathies are easily recognized; their effects on bone are complex, and the available information was reviewed by Melsen et al (10). Although not able to distinguish between direct and indirect effects of hormone excess or deficiency, bone histomorphometry is the only way of determining the cumulative long-term summation of all effects. It may be difficult to separate the effects of age-related changes in hormone secretion from the effects of aging alone, but for increases in function the former explanation is more likely and for decreases in function the latter is more likely. Estrogen deficiency increases remodeling activation, and estrogen replacement decreases it; whether these changes result from a direct effect of estrogen on bone lining cells of osteoblast lineage or are mediated indirectly by a different cell type or a different hormone is unknown. Nevertheless, other age-related changes in bone cell function are not corrected by estrogen replacement (10).

One of the most important lessons from bone histomorphometry, superficially paradoxical but important for cell biologists to explain, is that the total quantity of resorption or formation (determined by the frequency of remodeling activation), the amount of work performed by an individual team of osteoclasts or osteoblasts, and the rate at which the work is performed can each vary independently (2). For example, in primary hyperparathyroidism bone formation rate per unit of bone surface is increased, but the mineral apposition rate is decreased. A more surprising finding is that in hypothyroidism osteoblasts work more slowly but eventually make more bone than normal (10). Increased wall-thickness in hypothyroidism must result from some combination of increased osteoblast recruitment and increased lifetime work capacity. Could a profound reduction in the number of teams recruited make more precursor cells available for each team? This and many other unanswered questions arise from the study of bone remodeling in the intact organism. A base is useful only to the extent that it provides support for the superstructure above, and no science can claim to be basic to clinical medicine unless it eventually comes to grips with the questions posed by clinical investigators.

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