

Activation Frequency and Erosion Depth: Meaning and Measurement

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Bone remodeling or turnover is carried out by a battalion of juxtaposed osteoclasts (at the front) and osteoblasts (bringing up the rear), comprising temporary anatomical structures known as basic multicellular units (BMUs). In cortical bone, the BMUs drill tunnels or “cutting cones” through the compact tissue while in spongy, cancellous bone; they usually gouge across the trabecular surface forming a serpentine trench. Bone turnover begins by conversion of a quiescent skeletal surface to a remodeling site, a process referred to as activation. The activation frequency (Ac.f) represents the probability that a new remodeling cycle will be initiated at any point on the cancellous perimeter and is calculated by dividing the bone formation rate (BFR = double-labeled perimeter + $\frac{1}{2}$ single-labeled perimeter x mineral appositional rate) by the average amount of bone formed by a team of osteoblasts per activation event or the wall width (Ac.f = BFR/wall width). The measurement is more than just the rate of BMU origination as it corresponds to the product of the frequency of BMU origination and BMU width, rate of progression and lifespan. Ac.f is the best available 2-dimensional histological index of **the intensity of bone remodeling or turnover** and as such, represents the number of battalions or teams currently in play.

Origination of a BMU involves proliferation of new blood vessels needed to bring recruited resorbing cells to the remodeling site and retraction of the flat, pavement-like cells that cover quiescent perimeters to expose the mineralized bone. The recruited cells become multinucleated osteoclasts, which attach to the newly exposed bone with a ring of contractile proteins sealing off a subosteoclastic resorption compartment. Lysosomal enzymes, hydrogen ions, and collagenase are secreted through the microvilli of the ruffled underside of the osteoclasts and begin to excavate a resorption cavity or bay. Osteoclasts are motile cells, capable of resorbing more than just the cavity within which they are identified. After an osteoclast digs a cavity, it may detach from bone and move on to a new resorption site. When the osteoclasts have moved away, osteoblasts are drafted to reconstitute the previously resorbed cavity with new bone. In any established BMU, both events are happening at the same time; bone formation begins to occur while bone resorption advances. Intermediate between the end of bone resorption and the beginning of bone formation is the reversal phase, when mononuclear phagocytes smooth out the jagged erosion bays. During this phase, the old bone is coated by a thin layer of cement substance, a collagen- and mineral-poor matrix rich in glycosaminoglycans, glycoproteins and acid phosphatase, to which the new osteoblasts attach. During normal bone remodeling, new osteoblasts assemble only at sites where osteoclasts have recently been eroding bone; a phenomenon referred to as coupling. The arrival of the osteoblasts in the right place at the right time and in sufficient numbers is likely due to simultaneous production of osteoblasts and osteoclast in the bone marrow, release of osteotropic substances from resorbed bone and chemotaxis by the cement substance. When

the osteoblasts completely reconstitute previously resorbed cavity, the turnover is referred to as balanced.

Treatment with an antiresorptive drug will reduce the Ac.f, stop the addition of new stress risers caused by erosion cavities, and increase the resistance to fracture long before changes in bone mineral density (BMD) are detectable. With additional administration of antiresorptive therapy, the remodeling space will contract “reversing” some temporary bone loss in a few months and, over years, there will be a substantial reduction in the rate of bone loss. However, the determination of the Ac.f does present some issues. Ac.f is usually calculated from a small sample and single skeletal site (a transilial bone biopsy). Sometimes, fluorescent labels may be missing. In addition, even without an increase in the bone formation rate, the Ac.f will increase if the wall width decreases, as it does with age. Furthermore, interpretation of the Ac.f becomes complicated when an anabolic therapy thickens a trabecular profile by adding bone to a previously completed bone structural unit, as occurs with the intermittent administration of parathyroid hormone.

The concept of erosion depth is more important than the problems associated with its measurement. Erosion depth is cumbersome to measure at best but does represent a clear **index of osteoclast vigor**, which is otherwise only rarely apparent from bone histomorphometry. Erosion cavities have an adverse effect on cancellous bone strength disproportionate to the decrease in bone mass that the cavities represent. Furthermore, loss of bone strength due to perforation of trabecular profiles becomes more likely as the erosion depth increases. The final depth of erosion has a wide frequency of distribution but substantial evidence indicates that it decreases with age more noticeably in women than in men. Difficulty with the measurement occurs when erosion cavities have unusual shapes that defy efforts to reconstruct the original bone perimeter. In addition, erosion cavities may be few and inconspicuous in a specimen obtained from an elderly patient with osteoporosis and selection of only the cavities ideal for measurement may cause considerable bias in the measurement. Additional measurements of bone resorption such as erosion area, depth, width, bottom length, and cavity count should be considered but use of the erosion perimeter (2D) or erosion surface (3D) should be avoided. The eroded surface is composed of the osteoclast surface (about 1% of the bone surface in humans) plus the reversal surface (this histological representation of the reversal phase covers about 9% of the bone surface in humans) and, therefore, is often an unfaithful index of bone resorption. The reversal surface increases with defective or delayed bone formation, as occurs with glucocorticoid excess, and thus has little to do with the current amount of bone resorption. Moreover, most antiresorptive drugs decrease the ability of osteoclasts to erode bone, reduce the BFR, and actually increase the reversal surface, thereby, lengthening the so-called erosion surface.

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