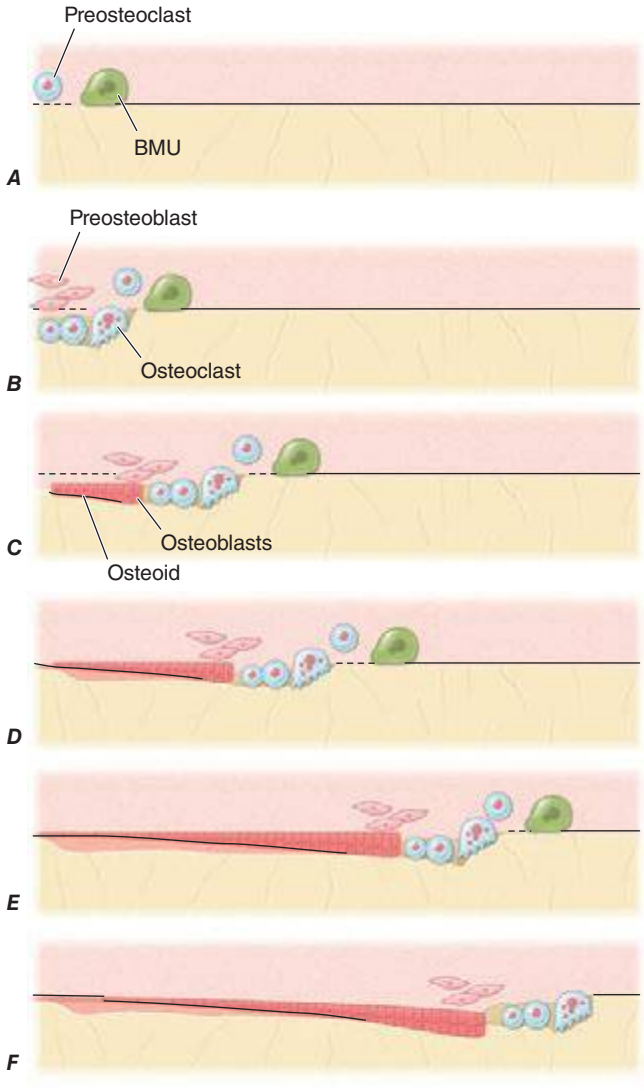

FIGURE 425-4 Mechanism of bone remodeling. The basic molecular unit (BMU) moves along the trabecular surface at a rate of about 10 μm/d. The figure depicts remodeling over ~120 days. ***A.*** Origination of BMU-lining cells contracts to expose collagen and attract preosteoclasts. ***B.*** Osteoclasts fuse into multinucleated cells that resorb a cavity. Mononuclear cells continue resorption, and preosteoblasts are stimulated to proliferate. ***C.*** Osteoblasts align at bottom of cavity and start forming osteoid (*black*). ***D.*** Osteoblasts continue formation and mineralization. Previous osteoid starts to mineralize (*horizontal lines*). ***E.*** Osteoblasts begin to flatten. ***F.*** Osteoblasts turn into lining cells; bone remodeling at initial surface (*left of drawing*) is now complete, but BMU is still advancing (*to the right*). *(Adapted from SM Ott, in JP Bilezikian et al [eds]: Principles of Bone Biology, vol. 18. San Diego, Academic Press, 1996, pp 231–241.)*

CALCIUM NUTRITION

Peak bone mass may be impaired by inadequate calcium intake during growth among other nutritional factors (calories, protein, and other minerals), leading to increased risk of osteoporosis later in life. During the adult phase of life, insufficient calcium intake contributes to relative secondary hyperparathyroidism and an increase in the rate of bone remodeling to maintain normal serum calcium levels. PTH stimulates the hydroxylation of vitamin D in the kidney, leading to increased levels of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] and enhanced gastrointestinal calcium absorption. PTH also reduces renal calcium loss. Although these are all appropriate compensatory homeostatic responses for adjusting calcium economy, the long-term effects are detrimental to the skeleton because the increased remodeling rates and the ongoing imbalance between resorption and formation at remodeling sites combine to accelerate loss of bone tissue.

Total daily calcium intakes <400 mg are detrimental to the skeleton, and intakes in the range of 600–800 mg, which is about the average intake among adults in the United States, are also probably suboptimal. The recommended daily required intake of 1000–1200 mg for adults accommodates population heterogeneity in controlling calcium balance **(Chap. 95e)**. Such intakes should preferentially come from dietary sources, and supplements should be used only when dietary intakes fall short. The supplement should contain enough calcium to bring total intake to about 1200 mg/d.

VITAMIN D

(See also Chap. 423) Severe vitamin D deficiency causes rickets in children and osteomalacia in adults. However, there is accumulating evidence that vitamin D insufficiency may be more prevalent than previously thought, particularly among individuals at increased risk such as the elderly; those living in northern latitudes; and individuals with poor nutrition, malabsorption, or chronic liver or renal disease. Dark-skinned individuals are also at high risk of vitamin D deficiency. There is controversy regarding optimal levels of serum 25-hydroxyvitamin D [25(OH)D], with some advocating levels >20 ng/mL and others advocating optimal targets >75 nmol/L (30 ng/mL). To achieve this level for most adults requires an intake of 800–1000 units/d, particularly in individuals who avoid sunlight or routinely use ultraviolet-blocking lotions. Vitamin D insufficiency leads to compensatory secondary hyperparathyroidism and is an important risk factor for osteoporosis and fractures. Some studies have shown that >50% of inpatients on a general medical service exhibit biochemical features of vitamin D deficiency, including increased levels of PTH and alkaline phosphatase and lower levels of ionized calcium. In women living in northern latitudes, vitamin D levels decline during the winter months. This is associated with seasonal bone loss, reflecting increased bone turnover. Even among healthy ambulatory individuals, mild vitamin D deficiency is increasing in prevalence, in part due to decreased exposure to sunlight coupled with increased use of potent sunscreens. Treatment with vitamin D can return levels to normal and prevent the associated increase in bone remodeling, bone loss, and fractures. Improved muscle function and gait associated with reduced falls and fracture rates also have been documented among individuals in northern latitudes who have greater vitamin D intake and higher 25(OH)D levels (see below). Vitamin D adequacy also may affect risk and/or severity of other diseases, including cancers (colorectal, prostate, and breast), autoimmune diseases, and diabetes; however, many observational studies suggesting these potential extraskeletal benefits have not been confirmed with randomized controlled trials.

ESTROGEN STATUS

Estrogen deficiency probably causes bone loss by two distinct but interrelated mechanisms: (1) activation of new bone remodeling sites and (2) exaggeration of the imbalance between bone formation and resorption. The change in activation frequency causes a transient bone loss until a new steady state between resorption and formation is achieved. The remodeling imbalance, however, results in a permanent decrement in mass. In addition, the very presence of more remodeling sites in the skeleton increases the probability that trabeculae will be penetrated, eliminating the template on which new bone can be formed and accelerating the loss of bony tissue.

The most common estrogen-deficient state is the cessation of ovarian function at the time of menopause, which occurs on average at age 51 **(Chap. 413)**. Thus, with current life expectancy, an average woman will spend about 30 years without an ovarian supply of estrogen. The mechanism by which estrogen deficiency causes bone loss is summarized in Fig. 425-5. Marrow cells (macrophages, monocytes, osteoclast precursors, mast cells) as well as bone cells (osteoblasts, osteocytes, osteoclasts) express ERs α and β. Loss of estrogen increases production of RANKL and may reduce production of OPG, increasing osteoclast recruitment. Estrogen also may play an important role in determining the life span of bone cells by controlling the rate of apoptosis. Thus,