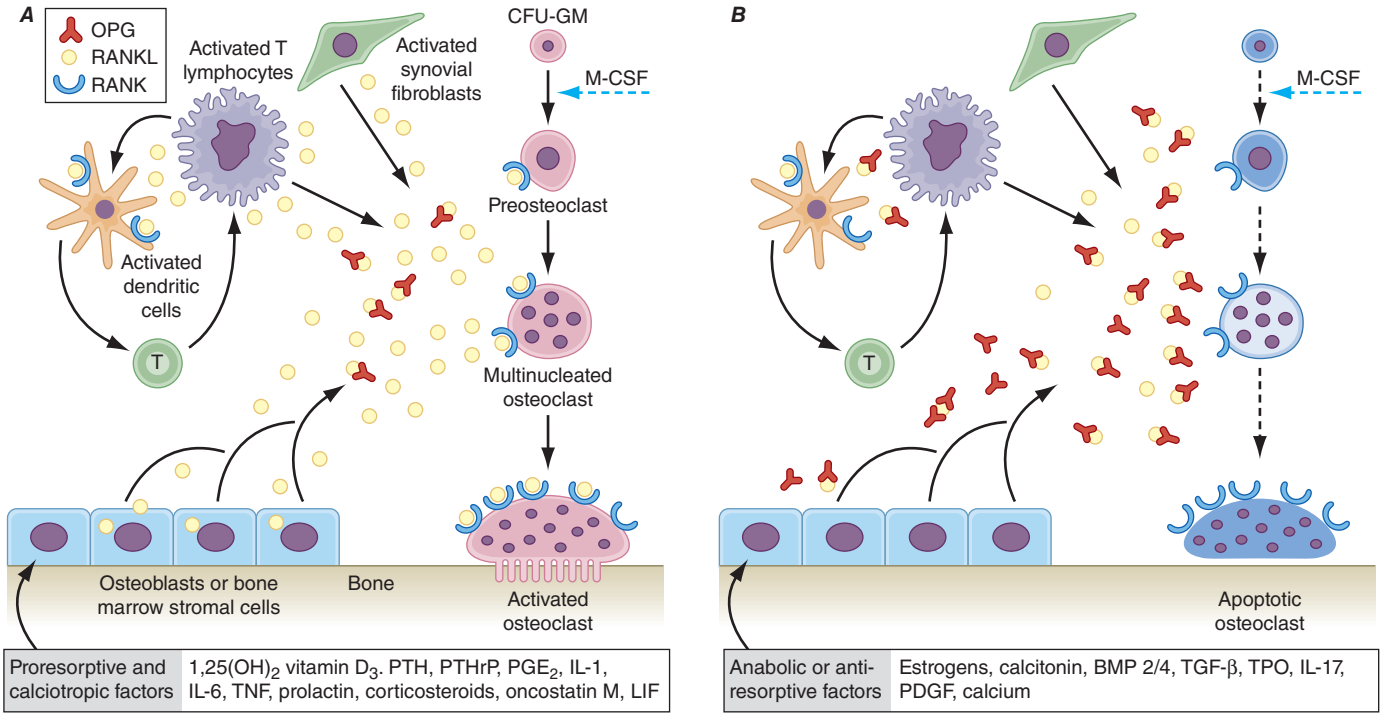

FIGURE 425-5 **Hormonal control of bone resorption.** ***A.*** Proresorptive and calciotropic factors. ***B.*** Anabolic and antiosteoclastic factors. RANK ligand (RANKL) expression is induced in osteoblasts, activated T cells, synovial fibroblasts, and bone marrow stromal cells. It binds to membrane-bound receptor RANK to promote osteoclast differentiation, activation, and survival. Conversely, osteoprotegerin (OPG) expression is induced by factors that block bone catabolism and promote anabolic effects. OPG binds and neutralizes RANKL, leading to a block in osteoclastogenesis and decreased survival of preexisting osteoclasts. CFU-GM, colony-forming units, granulocyte macrophage; IL, interleukin; LIF, leukemia inhibitory factor; M-CSF, macrophage colony-stimulating factor; OPG-L, osteoprotegerin-ligand; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor nuclear factor-κB; TGF-β, transforming growth factor β; TNF, tumor necrosis factor; TPO, thrombospondin. *(From WJ Boyle et al: Nature 423: 337, 2003.)*

in situations of estrogen deprivation, the life span of osteoblasts may be decreased, whereas the longevity and activity of osteoclasts are increased. The rate and duration of bone loss after menopause are heterogeneous and unpredictable. Once surfaces are lost in cancellous bone, the rate of bone loss must decline. In cortical bone, loss is slower but continues for a longer time period.

Because remodeling is initiated at the surface of bone, it follows that trabecular bone—which has a considerably larger surface area (80% of the total) than cortical bone—will be affected preferentially by estrogen deficiency. Fractures occur earliest at sites where trabecular bone contributes most to bone strength; consequently, vertebral fractures are the most common early consequence of estrogen deficiency.

PHYSICAL ACTIVITY

Inactivity, such as prolonged bed rest or paralysis, results in significant bone loss. Concordantly, athletes have higher bone mass than does the general population. These changes in skeletal mass are most marked when the stimulus begins during growth and before the age of puberty. Adults are less capable than children of increasing bone mass after restoration of physical activity. Epidemiologic data support the beneficial effects on the skeleton of chronic high levels of physical activity. Fracture risk is lower in rural communities and in countries where physical activity is maintained into old age. However, when exercise is initiated during adult life, the effects of moderate exercise on the skeleton are modest, with a bone mass increase of 1–2% in short-term studies of <2 years in duration. It is argued that more active individuals are less likely to fall and are more capable of protecting themselves upon falling, thereby reducing fracture risk.

CHRONIC DISEASE

Various genetic and acquired diseases are associated with an increase in the risk of osteoporosis (Table 425-1). Mechanisms that contribute to bone loss are unique for each disease and typically result from multiple factors, including nutrition, reduced physical activity levels, and factors that affect rates of bone remodeling. In most, but not all, circumstances the primary diagnosis is made before osteoporosis presents clinically.

MEDICATIONS

A large number of medications used in clinical practice have potentially detrimental effects on the skeleton (Table 425-1). *Glucocorticoids* are the most common cause of medication-induced osteoporosis. It is often not possible to determine the extent to which osteoporosis is related to glucocorticoids or to other factors, because treatment is superimposed on the effects of the primary disease, which in itself may be associated with bone loss (e.g., rheumatoid arthritis). Excessive doses of thyroid hormone can accelerate bone remodeling and result in bone loss.

Other medications have less detrimental effects on the skeleton than pharmacologic doses of glucocorticoids. *Anticonvulsants* are thought to increase the risk of osteoporosis, although many affected individuals have concomitant insufficiency of 1,25(OH)2D, as some anticonvulsants induce the cytochrome P450 system and vitamin D metabolism. Patients undergoing transplantation are at high risk for rapid bone loss and fracture not only from glucocorticoids but also from treatment with other *immunosuppressants* such as cyclosporine and tacrolimus (FK506). In addition, these patients often have underlying metabolic abnormalities, such as hepatic or renal failure, that predispose to bone loss.

Aromatase inhibitors, which potently block the aromatase enzyme that converts androgens and other adrenal precursors to estrogen, reduce circulating postmenopausal estrogen levels dramatically. These agents, which are used in various stages for breast cancer treatment, also have been shown to have a detrimental effect on bone density and risk of fracture. More recently a variety of agents have been implicated in increased bone loss and fractures. These include selective serotonin reuptake inhibitors, proton pump inhibitors, and thiazolidinediones. It is difficult in some cases to separate the risk