TABLE 425-1 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES

Lifestyle factors		
Alcohol abuse	High salt intake	Falling
Low calcium intake	Inadequate physical activity	Excessive thinness
Vitamin D insufficiency	Immobilization	Prior fractures
Excess vitamin A	Smoking (active or passive)	
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos syndrome	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan's syndrome	Riley-Day syndrome
Hemochromatosis	Menkes' steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Athletic amenorrhea
Anorexia nervosa and bulimia	Premature menopause	Panhypopituitarism
Turner's & Klinefelter's syndromes	Premature ovarian failure	
Endocrine disorders		
Adrenal insufficiency	Cushing's syndrome	Central adiposity
Diabetes mellitus (types 1 and 2)	Hyperparathyroidism	Thyrotoxicosis
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
Gastrointestinal surgery	Pancreatic disease	
Hematologic disorders		
Multiple myeloma	Monoclonal gammopathies	Sickle cell disease
Hemophilia	Leukemia and lymphomas	Systemic mastocytosis
Thalassemia		
Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Other rheumatic and autoimmune diseases		
Central nervous system disorders		
Epilepsy	Parkinson's disease	Stroke
Multiple sclerosis	Spinal cord injury	
Miscellaneous conditions and diseases		
AIDS/HIV	Congestive heart failure	Posttransplant bone disease
Alcoholism	Depression	Sarcoidosis
Amyloidosis	End-stage renal disease	Weight loss
Chronic metabolic acidosis	Hypercalciuria	
Chronic obstructive lung disease	Idiopathic scoliosis	
	Muscular dystrophy	
Medications		
Aluminum (in antacids)	Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 months)	Tamoxifen (premenopausal use)
Anticoagulants (heparin)	Gonadotropin-releasing hormone antagonists and agonists	Thiazolidinediones (such as pioglitazone and rosiglitazone)
Anticonvulsants	Lithium	Thyroid hormones (in excess)
Aromatase inhibitors	Methotrexate	Parenteral nutrition
Barbiturates	Proton pump inhibitors	
Cancer chemotherapeutic drugs	Selective serotonin reuptake inhibitors	
Cyclosporine A and tacrolimus		
Depo-medroxyprogesterone (premenopausal contraception)		

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activated by microdamage to bone as a result of excessive or accumulated stress. Acute demands for calcium involve osteoclast-mediated resorption as well as calcium transport by osteocytes. Chronic demands for calcium result in secondary hyperparathyroidism, increased bone remodeling, and overall loss of bone tissue.

Bone remodeling also is regulated by several circulating hormones, including estrogens, androgens, vitamin D, and parathyroid hormone (PTH), as well as locally produced growth factors such as IGF-I and immunoreactive growth hormone II (IGH-II), transforming growth factor β (TGF-β), parathyroid hormone–related peptide (PTHrP), interleukins (ILs), prostaglandins, and members of the tumor necrosis factor (TNF) superfamily. These factors primarily modulate the rate at which new remodeling sites are activated, a process that results initially in bone resorption by osteoclasts, followed by a period of repair during which new bone tissue is synthesized by osteoblasts. The cytokine responsible for communication between the osteoblasts, other marrow cells, and osteoclasts is RANK ligand (RANKL; receptor activator of nuclear factor-κB [NF-κB]). RANKL, a member of the TNF family, is secreted by osteoblasts and certain cells of the immune system **(Chap. 423)**. The osteoclast receptor for this protein is referred to as *RANK*. Activation of RANK by RANKL is a final common path in osteoclast development, activation, and life span. A humoral decoy for RANKL, also secreted by osteoblasts, is *osteoprotegerin* **(Fig. 425-5)**. Modulation of osteoclast recruitment and activity appears to be related to the interplay among these three factors. It appears that estrogens are pivotal in modulating secretion of osteoprotegerin (OPG) and perhaps also RANKL. Additional influences include nutrition (particularly calcium intake) and physical activity level.

In young adults, resorbed bone is replaced by an equal amount of new bone tissue. Thus, the mass of the skeleton remains constant after peak bone mass is achieved in adulthood. After age 30–45, however, the resorption and formation processes become imbalanced, and resorption exceeds formation. This imbalance may begin at different ages and varies at different skeletal sites; it becomes exaggerated in women after menopause. Excessive bone loss can be due to an increase in osteoclastic activity and/or a decrease in osteoblastic activity. In addition, an increase in remodeling activation frequency, and thus the number of remodeling sites, can magnify the small imbalance seen at each remodeling unit. Increased recruitment of bone remodeling sites produces a reversible reduction in bone tissue but also can result in permanent loss of tissue and disrupted skeletal architecture. In trabecular bone, if the osteoclasts penetrate trabeculae, they leave no template for new bone formation to occur, and, consequently, rapid bone loss ensues and cancellous connectivity becomes impaired. A higher number of remodeling sites increases the likelihood of this event. In cortical bone, increased activation of remodeling creates more porous bone. The effect of this increased porosity on cortical bone strength may be modest if the overall diameter of the bone is not changed. However, decreased apposition of new bone on the periosteal surface coupled with increased endocortical resorption of bone decreases the biomechanical strength of long bones. Even a slight exaggeration in normal bone loss increases the risk of osteoporosis-related fractures because of the architectural changes that occur, and osteoporosis is primarily a disease of disordered skeletal architecture. The main clinically available tool (dual-energy x-ray absorptiometry) measures mass not architecture. Emerging data from high-resolution peripheral quantitative computed tomography (CT) scans suggest that aging is associated with changes in microstructure of bone tissue, including increased cortical porosity and reduced cortical thickness.