Table 26-4 Categories of Generalized Osteoporosis

Primary
Idiopathic
Postmenopausal
Senile
Secondary
Endocrine Disorders
Addison disease
Diabetes, type 1
Hyperparathyroidism
Hyperthyroidism
Hypothyroidism
Pituitary tumors
Neoplasia
Carcinomatosis
Multiple myeloma
Gastrointestinal
Hepatic insufficiency
Malabsorption
Malnutrition
Vitamin C, D deficiencies
Drugs
Alcohol
Anticoagulants
Anticonvulsants
Chemotherapy
Corticosteroids
Miscellaneous
Anemia
Homocystinuria
Immobilization
Osteogenesis imperfecta
Pulmonary disease

metabolic unit. Accordingly, age-related bone loss, which may average 0.7% per year, is a normal and predictable biologic phenomenon. Both sexes are affected equally and whites more so than blacks. Gender and racial differences in peak bone mass may partially explain why certain populations are prone to develop this disorder. Although much remains unknown, discoveries in the molecular biology of bone formation and resorption have provided new insights into the pathogenesis of osteoporosis (Fig. 26-9):

- **Age-related changes** in bone cells and matrix have a strong impact on bone metabolism. Osteoblasts from older individuals have reduced proliferative and biosynthetic potential when compared with osteoblasts from younger individuals. Also, the cellular response to growth factors bound to the extracellular matrix becomes attenuated in older individuals. The net result is a diminished capacity to make bone. This form of osteoporosis, known as *senile osteoporosis*, is categorized as a *low-turnover variant.*
- **Reduced physical activity** increases the rate of bone loss in experimental animals and humans, because mechanical forces stimulate normal bone remodeling. Bone loss in an immobilized or paralyzed extremity, the reduction of skeletal mass in astronauts in a zero gravity environment for prolonged periods, and the higher bone density in athletes exemplify the role of physical activity in preventing bone loss. The type of exercise is important, as load magnitude influences bone density more than the number of load cycles. Because muscle contraction is the dominant source of skeletal loading, resistance exercises such as weight training are more effective stimuli for increasing bone mass than repetitive endurance activities such as bicycling. The decreased physical activity that is associated with normal aging contributes to senile osteoporosis.
- **Genetic factors.** Single gene defects (e.g., *LRP5*, discussed above) account for only a small fraction of cases. Polymorphisms in other genes may account for the variation in peak bone density within a population. In genome-wide association studies, the top associated genes include *RANKL*, *OPG*, and *RANK*, all of which encode key regulators of osteoclasts. Also associated are the HLA locus (perhaps reflecting the effects of inflammation on calcium metabolism) and the estrogen receptor gene (discussed later). Some studies have also implicated genetic variants of the vitamin D receptor and genes involved in Wnt signaling as risk factors.
- **Calcium nutritional state** contributes to peak bone mass. Adolescent girls (more than boys) tend to have insufficient calcium intake in the diet. This calcium deficiency occurs during a period of rapid bone growth, restricting the peak bone mass ultimately achieved. Thus, these individuals are at greater risk of developing osteoporosis. Calcium deficiency, increased PTH concentrations, and reduced levels of vitamin D may also have a role in the development of senile osteoporosis.
- **Hormonal influences.** Postmenopausal osteoporosis is characterized by an acceleration of bone loss. In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone. Women may lose as much as 35% of their cortical bone and 50% of their cancellous bone by 30 to 40 years after menopause. It is thus no surprise that post-menopausal women suffer osteoporotic fractures more commonly than men of the same age. *Estrogen deficiency* plays the major role in this phenomenon and close to 40% of postmenopausal women are affected by

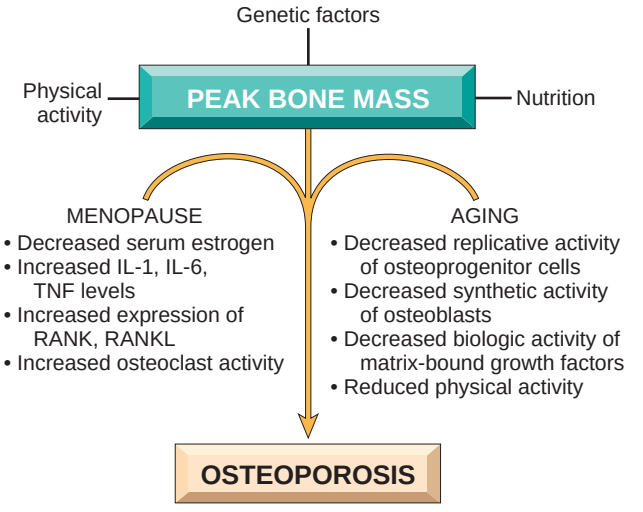

Figure 26-9 Pathophysiology of postmenopausal and senile osteoporosis (see text).