ineffective due to associated abnormalities in vitamin D action. Assays for 25(OH)D can be helpful. Low or low-normal 25(OH)D indicates vitamin D deficiency due to lack of sunlight, inadequate vitamin D intake, or intestinal malabsorption. Recognition that mild hypocalcemia, rickets, and hypophosphatemia are due to anticonvulsant therapy is made by history.

TREATMENT HYPOCALCEMIC STATES

The management of hypoparathyroidism, PHP, chronic renal failure, and hereditary defects in vitamin D metabolism involves the use of vitamin D or vitamin D metabolites and calcium supplementation. Vitamin D itself is the least expensive form of vitamin D replacement and is frequently used in the management of uncomplicated hypoparathyroidism and some disorders associated with ineffective vitamin D action. When vitamin D is used prophylactically, as in the elderly or in those with chronic anticonvulsant therapy, there is a wider margin of safety than with the more potent metabolites. However, most of the conditions in which vitamin D is administered chronically for hypocalcemia require amounts 50–100 times the daily replacement dose because the formation of $1,25(OH)_2D$ is deficient. In such situations, vitamin D is no safer than the active metabolite because intoxication can occur with high-dose therapy (because of storage in fat). Calcitriol is more rapid in onset of action and also has a short biologic half-life.

Vitamin D (at least 1000 U/d [2–3 μg/d] [higher levels required in older persons]) or calcitriol (0.25–1 μg/d) is required to prevent rickets in normal individuals. In contrast, 40,000–120,000 U (1–3 mg) of vitamin D_2 or D_3 is typically required in hypoparathyroidism. The dose of calcitriol is unchanged in hypoparathyroidism, because the defect is in hydroxylation by the 25(OH)D-1α-hydroxylase. Calcitriol is also used in disorders of 25(OH)D-1α-hydroxylase; vitamin D receptor defects are much more difficult to treat.

Patients with hypoparathyroidism should be given 2–3 g of elemental calcium PO each day. The two agents, vitamin D or calcitriol and oral calcium, can be varied independently. Urinary calcium excretion needs to be monitored carefully. If hypocalcemia alternates with episodes of hypercalcemia in high-brittleness patients with hypoparathyroidism, administration of calcitriol and use of thiazides, as discussed above, may make management easier. Clinical trials with PTH(1–34) or PTH(1–84) are promising, but these alternative treatments have not yet been approved.

425 Osteoporosis

Robert Lindsay, Felicia Cosman

Osteoporosis, a condition characterized by decreased bone strength, is prevalent among postmenopausal women but also occurs in men and women with underlying conditions or major risk factors associated with bone demineralization. Its chief clinical manifestations are vertebral and hip fractures, although fractures can occur at almost any skeletal site. Osteoporosis affects almost 10 million individuals in the United States, but only a small proportion are diagnosed and treated.

DEFINITION

Osteoporosis is defined as a reduction in the strength of bone that leads to an increased risk of fractures. Loss of bone tissue is associated with deterioration in skeletal microarchitecture. The World Health Organization (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same sex—also referred to as a *T-score* of –2.5. Postmenopausal women who fall at the lower end of the young normal range (a T-score <–1.0) are defined as having low bone density and are also at increased risk of osteoporosis. Although risk is lower in this group, more than 50% of fractures among postmenopausal women, including hip fractures, occur in this group with low bone density, because the number of individuals in this category is so much larger than that in the osteoporosis range. As a result, there are ongoing attempts to identify individuals within the low bone density range who are at high risk of fracture and might benefit from pharmacologic intervention. Furthermore, some have advocated using fracture risk as the "diagnostic" criterion for osteoporosis.

EPIDEMIOLOGY

In the United States, as many as 9 million adults have osteoporosis (T-score <–2.5 in either spine or hip), and an additional 48 million individuals have bone mass levels that put them at increased risk of developing osteoporosis (e.g., bone mass T-score <–1.0). Osteoporosis occurs more frequently with increasing age as bone tissue is lost progressively. In women, the loss of ovarian function at menopause (typically about age 50) precipitates rapid bone loss so that most women meet the diagnostic criterion for osteoporosis by age 70–80. As the population continues to age, the number of individuals with osteoporosis and fractures will also continue to increase, despite a recognized reduction in age-specific risk. It is estimated that about 2 million fractures occur each year in the United States as a consequence of osteoporosis, and that number is expected to increase as the population continues to age.

The epidemiology of fractures follows the trend for loss of bone density, with exponential increases in both hip and vertebral fractures with age. Fractures of the distal radius have a somewhat different epidemiology, increasing in frequency before age 50 and plateauing by age 60, with only a modest age-related increase thereafter. In contrast, incidence rates for hip fractures double every 5 years after age 70 (Fig. 425-1). This distinct epidemiology may be related to the way the elderly fall as they age, with fewer falls on an outstretched hand and more falls directly on the hip. About 300,000 hip fractures occur each year in the United States, most of which require hospital admission and surgical intervention. The probability that a 50-year-old white individual will have a hip fracture during his or her lifetime is 14% for women and 5% for men; the risk for African Americans is lower (about one-half those rates), and the risk for Asians is roughly equal to that for whites. Hip fractures are associated with a high incidence of deep vein thrombosis and pulmonary embolism (20–50%) and a mortality rate between 5 and 20% during the year after surgery.

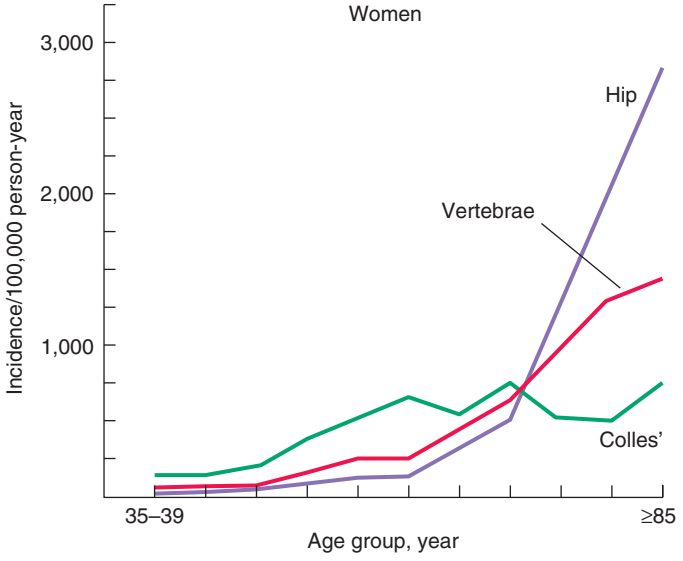

FIGURE 425-1 Epidemiology of vertebral, hip, and Colles' fractures with age. *(Adapted from C Cooper, LJ Melton III: Trends Endocrinol Metab 3:224, 1992; with permission.)*