Overview of Osteoporosis

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Osteoporosis is defined as an absolute decrease in the amount of bone to a level below that required for mechanical support or, as Fuller Albright succinctly put it many years ago, "There is too little bone" (Figure 1). The bone that is present is normal chemically and histologically.

Epidemiology

Osteoporosis is a major public health problem[1,2] In the United States, about 1.5 million fractures are attributable to osteoporosis each year. The sites of these fractures are the vertebrae (650,000), the hip (250,000), the distal forearm (Colles' fracture, 200,000), and other skeletal sites (400,000). One third of women over age 65 at some time will suffer vertebral fractures; the lifetime risk for hip fracture in white women, 15%, approximates that of the combined risks of breast, endometrial, and ovarian cancer. The lifetime risk of hip fracture in men, 5%, approximates that of the risk of prostate cancer. The direct and indirect costs of osteoporosis in the United States have been estimated to be $7 billion to $10 billion annually. Much of this expense relates to hip fracture. This catastrophic type of injury is fatal in 12% to 20% of cases. Half of the survivors are unable to walk unassisted, and 25% are confined to long-term care in a nursing home.

Pathophysiology

Age-Related Bone Loss. It is convenient to divide the skeleton into two compartments consisting of cortical bone and trabecular bone. Cortical bone predominates in the shafts of long bones; trabecular bone is concentrated in the vertebrae, in the pelvis and other flat bones, and at the end of long bones. Trabecular bone is metabolically much more active than cortical bone, probably because of its greater surface area, and is more responsive to changes in mineral homeostasis.

Three distinct phases of changes in bone mass over life can be recognized, two of which occur in both sexes and one third of which occurs only in women[3,4] (Figure 2). The first process leads to attainment of peak bone mass and represents the summation of growth (90% to 95%) and consolidation (5% to 10%).[4] Peak bone mass is attained both by linear growth due to mineralization of the endochondrial growth plates and by radial growth due to a rate of periosteal apposition that exceeds that for endosteal resorption. After closure of the growth plate about age 20, the radial growth continues for another 10 to 15 years.

The second process consists of a slow, age-dependent phase of bone loss. This begins around age 40 for cortical bone and perhaps 5 to 10 years earlier for trabecular bone and continues into extreme old age.[1,3] The rate of slow bone loss due to this process probably is similar in men and women and results in losses of similar amounts of cortical bone and of trabecular bone.[1,3,5] In women, a third process, a transient accelerated postmenopausal phase of bone loss due to estrogen deficiency, is superimposed on the slow phase of bone loss and results in loss of disproportionately more trabecular bone than of cortical bone.[1,3,6,7] The amount of bone that is lost over life with each of these phases is not well defined. However, a reasonable estimate is that the slow phase produces a loss of about 25% from the cortical compartment and about 25% from the trabecular compartment in both sexes. During the accelerated phase, postmenopausal women lose an additional 10% from the cortical compartment and 25% from the trabecular compartment. Thus, overall, women lose about 35% of cortical bone and 50% of trabecular bone during their lifetime, whereas men lose about two thirds of these amounts.[1,5,8]

Age-Related Changes in Bone Remodeling. Bone formation and bone resorption occur at anatomically discrete foci called bone remodeling units.[1,4] At the beginning of each remodeling cycle, through a mechanism yet to be defined, flattened lining cells are activated and retract to expose the underlying bone.[9] Osteoclast precursor cells in marrow are recruited and migrate to the exposed area of bone. These fuse to form osteoclasts and, over a period of 1 to 3 weeks, the osteoclasts construct a tunnel in cortical bone or a lacuna on the surface of trabecular bone. The osteoclasts disappear during a reversal phase and are replaced by osteoblasts, which then fill in the resorption cavity over a period of 3 to 4 months to create a new structural unit of bone (Figure 3).

The main determinant of the rate of bone turnover is the frequency of activation of new bone remodeling units.[4,10] In normal young adults, the processes of bone resorption and bone formation are tightly coupled so that bone balance is maintained. However, during age-related bone loss, there is a remodeling imbalance with a relative or absolute increase in resorption over formation.[4,10] Because of this imbalance at each bone remodeling unit, an increase in bone turnover (i.e., an increase in the number of bone remodeling units) leads to increased bone loss.

The slow and accelerated phases of bone loss are associated with two different abnormalities of bone remodeling (Figure 4). In the slow, age-dependent phase, the osteoclasts construct resorption cavities of normal depth, or even decreased depth, but the osteoblasts fail to refill them completely.[1,4,5] This leads to a gradual thinning of the trabeculae,

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but their connectivity is maintained.[1,11] In contrast, the accelerated, postmenopausal phase of bone loss is associated with a high rate of bone turnover; there is an increase in osteoclast number and the osteoclasts create a resorption cavity of increased depth (Figure 4). These processes lead to trabecular perforation and loss of structural trabeculae and trabecular connectivity.

Age-Related Fractures. When the incidence of fractures is plotted as a function of age, two distinct patterns emerge.[1,12] (Figure 5). The first pattern involves fractures at sites containing large amounts of trabecular bone, such as the distal forearm (Colles' fracture) and vertebrae. These fractures increase in women soon after menopause; for Colles' fracture, the incidence continues to increase until age 65 when it reaches a plateau, whereas the incidence of vertebral fractures continues to rise. The second pattern involves sites containing similar amounts of cortical and trabecular bone. Although the most important fracture of this type involves the hip, a similar pattern is followed by fractures of the proximal humerus, proximal tibia, and pelvis. The incidence of these fractures increases quite slowly with aging until late in life, when an exponential increase leads to a very high incidence of fracture. Fractures of the shafts of the limb bone, which is predominantly cortical bone, do not increase with aging and often are associated with severe trauma; therefore, they do not seem to be directly related to osteoporosis.

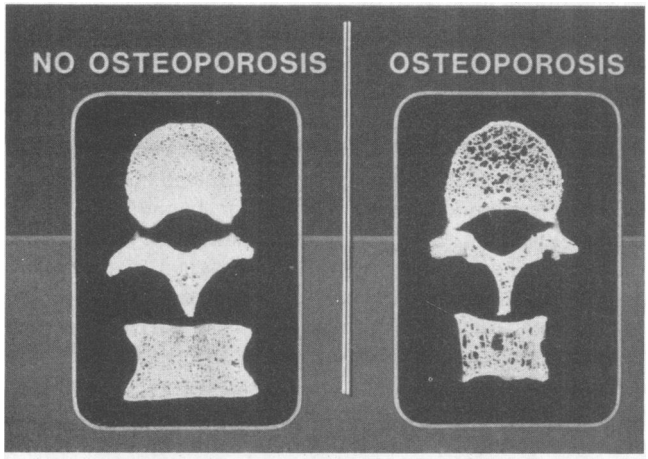

Figure 1.—Transverse and coronal sections or vertebrae from normal and osteoporotic subjects. (From Riggs BL: Osteoporosis. *In* DeGroot LJ et al (Eds): Textbook of Endocrinology. 2nd Ed. Philadelphia, W. B. Saunders Company, 1989, pp 1188-1207.)

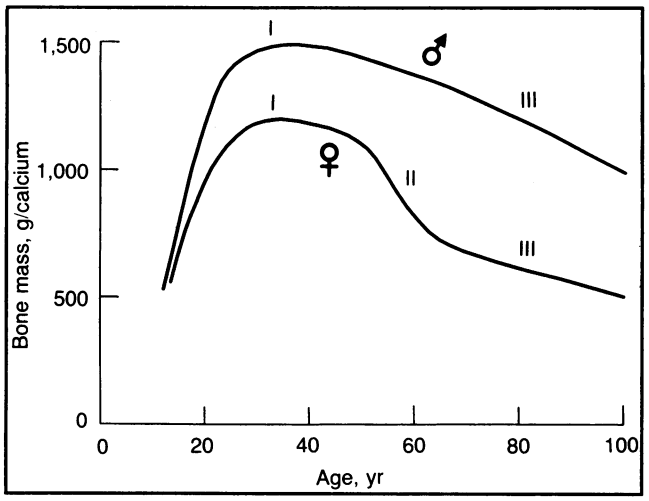

Figure 2.—Changes in bone mass with growth and aging in men and women showing three distinct phases. See text for details. (From Riggs BL: Involutional osteoporosis. *In* Williams TF, Evans JG (Eds): Oxford Textbook of Geriatric Medicine. London, Oxford University Press, in press.)

Etiology

The modern concept is that osteoporosis is a multifactorial disorder. Figure 6 gives a model for the main groups of these factors and how they interact. The morbid event in osteoporosis is fracture. This results from the interaction of low bone density and trauma. Low bone density later in life can occur because the amount of peak bone mass achieved by young adulthood is inadequate or because there is an increased rate of bone loss. The major groups of factors causing increased bone loss can be subsumed under the categories of aging, menopause, local factors regulating bone turnover, and sporadic factors occurring in some but not other members of the population.

Low Bone Density

A decrease in bone mass clearly is the most important cause of fractures in osteoporosis. Eighty per cent of the variance in compressive strength of the trabecular bone and 90% of that in cortical bone can be accounted for by differences in bone density.[3] In the absence of severe trauma, fractures do not occur until bone density has fallen below the

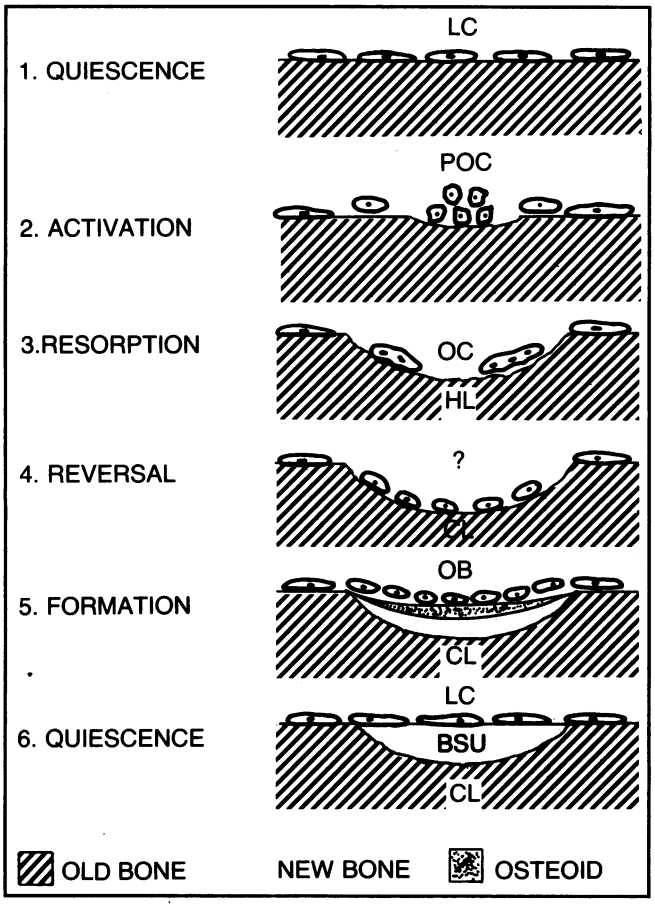

Figure 3.—Illustration of the different stages of bone remodeling. See text for details. (From Parfitt AM: Bone remodeling: Relationship to the amount and structure of bone, and the pathogenesis and prevention of fractures. *In* Riggs BL, Melton LJ III (Eds): Osteoporosis: Etiology, Diagnosis, and Management. New York, Raven Press, 1988, pp 45-94.)

values found in young adults.[5] This fracture threshold has been empirically set at about 1.0 gm per sq cm for the vertebrae, 1.0 gm per sq cm for the proximal femur, and 0.4 gm per sq cm for the ultradistal radius.[13,14] With further decreases in bone density below the fracture threshold, the incidence of hip fractures, vertebral fractures, and Colles' fractures increases. Thus, the lower the level of bone density, the greater the risk of fracture. These increases, however, are not linear, which suggests that osteoporosis may lead to qualitative changes in bone that may weaken the skeleton. Possible qualitative changes include loss of structural elements and trabecular connectivity, accumulation of trabecular microfractures, and, in some elderly subjects, histologic osteomalacia.[15]

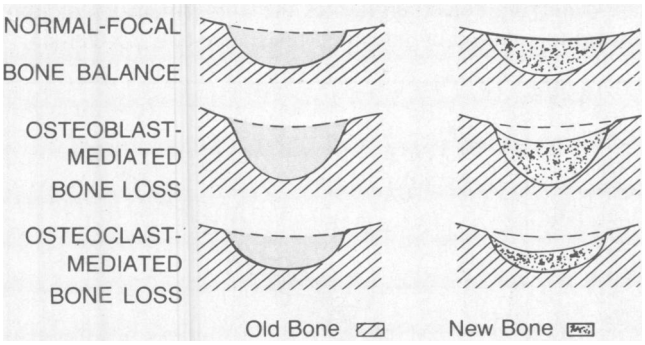

Figure 4.—Two mechanisms for remodeling imbalance in trabecular bone. In healthy young adults **(upper panel)**, the osteoblasts completely refill the resorption cavity constructed by the osteoclasts. In osteoclast-mediated bone loss **(middle panel)**, a resorption cavity of excessive depth is shown that is incompletely refilled by a normal amount of new bone. In osteoblast-mediated bone loss **(lower panel)**, there is a resorption cavity of normal depth that is incompletely filled by a subnormal amount of new bone. (From Parfitt AM: Bone remodeling: Relationship to the amount and structure of bone, and the pathogenesis and prevention of fractures, *In* Riggs BL, Melton LJ III (Eds): Osteoporosis: Etiology, Diagnosis, and Management. New York, Raven Press, 1988, pp 45-94.)

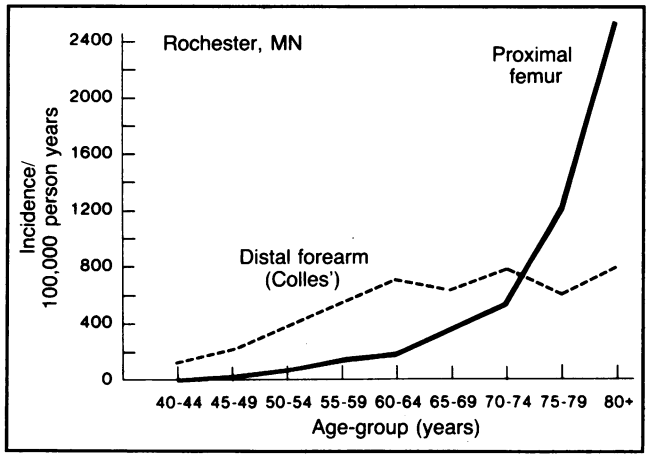

Figure 5.—The two major age-related fracture patterns, as illustrated by the incidence of Colles' fracture and hip fracture as a function of age in women residing in Rochester, MN. (From Riggs BL, Melton LJ III: Evidence for two distinct syndromes of involutional osteoporosis. Am J Med 1983; 75:899.)

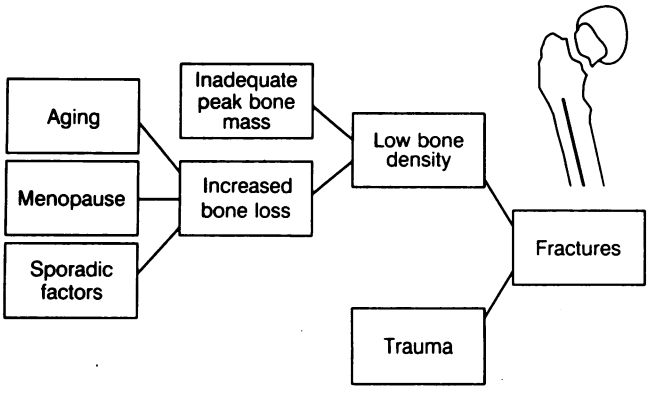

Figure 6.—Model for etiology of osteoporosis showing various groups of factors causing fractures and their interaction.

Trauma

The propensity of the elderly to fall is an independent risk factor for fractures.[16,17] The most common cause of fractures among elderly persons is a simple fall from a standing height or less, although a few hip fractures may be spontaneous and vertebral fractures often result from lifting or straining. The risk of falling increases with aging, and at least one third of community-dwelling elderly persons fall at least once each year. Falls are more frequent in the elderly because of failing vision, neurologic diseases and their sequelae or arthritis of the lower limb joints, and the use of sedatives and other drugs.

Also, the elderly have increased trauma in their falls because impaired coordination and slowed reflexes reduce their ability to break the impact of a fall. In addition, the type of fall may determine the site of fracture.[17,18] Forward falls in which the impact is broken by the outstretched hands are more likely to result in distal forearm (Colles') fracture, and a backward fall landing on the buttocks or with a lateral fall landing on the hip are more likely to result in proximal femur fracture. Although the elderly fall frequently, only 6% of their falls result in fracture.[19]

Inadequate Peak Bone Mass

Insufficient accumulation of bone during skeletal growth and consolidation predisposes to fractures later in life as age-related bone loss ensues. Differences in peak bone mass may explain in part racial and sexual differences in the incidence

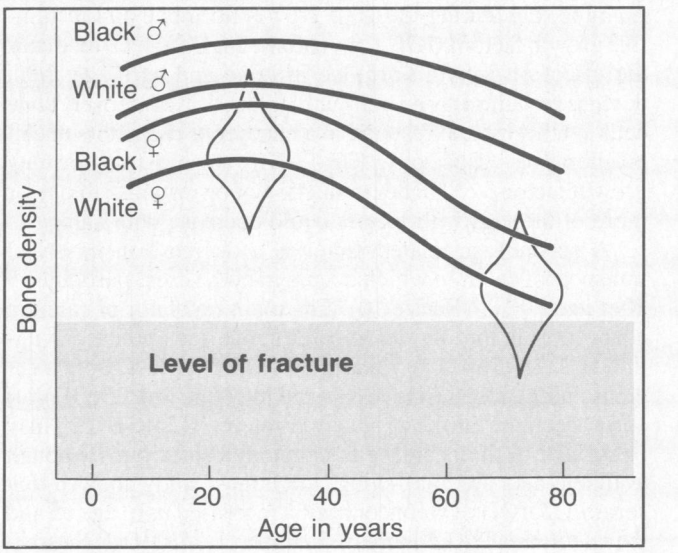

Figure 7.—Effect of sex and race on peak bone mass can explain susceptibility to osteoporosis as age-related bone loss ensues. Individual values about regression lines (for white women this is given by a top-shaped figure). Thus, a white woman in the lower part of the normal distribution in young adult life would be at increased risk for fractures later in life. (From Riggs BL: Osteoporosis, *In* DeGroot LJ, et al (Eds): Textbook of Endocrinology, 2nd Ed. Philadelphia, WB Saunders Company, 1989, pp 1188-1207.)

of osteoporosis.[20] White women have the lightest skeletons and black men have the heaviest; white men and black women have skeletons of intermediate density (Figure 7). This rank order corresponds to the rank order for the occurrence of fractures. Women of short stature and northern European extraction tend toward a more gracile skeleton and also have an increased incidence of osteoporosis later in life. Moreover, if the rate of bone loss with age is constant, those white women with the lowest peak bone mass are at greatest risk for fractures later in life[21] (Figure 7).

Although the determinants of differences in peak bone mass among individuals have not been adequately defined, two important factors appear to be heredity and the level of dietary calcium consumption during growth. Peak bone mass has strong genetic determinants, and studies in monozygotic and dizygotic twins have found a heritability index of about 0.85[22,23] (Figure 8). This may explain the trend for familial aggregation of osteoporosis.[24] It is obvious that insufficient calcium intake will be rate limiting for accumulation of skeletal mass; this is consistent with epidemiologic findings.[25]

Increased Bone Loss

Age-Related Factors. By far the most powerful predictor of bone mass in a given individual is age. For example, if the age of a healthy woman is known, the bone density of her lumbar spine or femoral neck can be predicted with a standard deviation of only 10%[5] (Figure 9). The decrease in bone density with age probably reflects the aggregate effects of a number of age-related factors.

One important factor is decreased osteoblast function. This abnormality, which can be assessed by measurement of wall thickness of trabecular packets, begins in middle life and becomes progressively more severe as age increases.[4,27] Although impaired osteoblast function could be caused by senescence, fracture healing in the elderly is not delayed, indicating that osteoblasts do respond to appropriate stimuli. More likely, the regulation of osteoblast activity is impaired by altered production of systemic or local growth factors. For example, circulating levels of growth hormone and insulin-like growth factor I (IGF-I, somatomedin C), which mediates the effect of growth hormone in bone and cartilage, both decrease by almost one half with aging.[27,28] Moreover, bone cells synthesize and respond to a number of regulators of cell proliferation—especially IGF-I, IGF-II, and transforming growth factor β.[29,30] The production of or response to one or more of these growth factors could decrease with aging.

A second age-related factor is a decrease in intestinal transport of calcium which occurs in both sexes, particularly after age 70[31,32] (Figure 10). The main regulator of calcium absorption is the physiologically active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$]. Both a decrease in the responsiveness of the intestine to 1,25$(OH)_2D_3$ and a decrease in the production rate of 1,25$(OH)_2D_3$ may contribute to the decrease in calcium absorption. Although available data are conflicting, the largest study showed that serum 1,25$(OH)_2D_3$ concentration increased until age 65 and then decreased.[33] An increase in serum 1,25$(OH)_2D_3$ associated with a concomitant decrease in calcium absorption suggests a primary impairment in intestinal responsivess to 1,25$(OH)_2D_3$ action. In experimental animals, the concentration of 1,25$(OH)_2D_3$ receptors in both intestine and bone cells decreases with aging.

The activity of the renal enzyme 25-hydroxyvitamin D [25(OH)D] 1α-hydroxylase, which is responsible for the conversion of 25(OH)D to 1,25$(OH)_2D_3$, is impaired with aging.[34,40] This abnormality may result from atrophy of renal parenchymal tissue with aging and probably decreases the production of 1,25$(OH)_2D_3$ in the elderly, especially in those whose glomerular filtration rate is <40 mL per min. This late-occurring defect aggravates the impairment in calcium absorption caused by intestinal resistance to 1,25$(OH)_2D_3$.

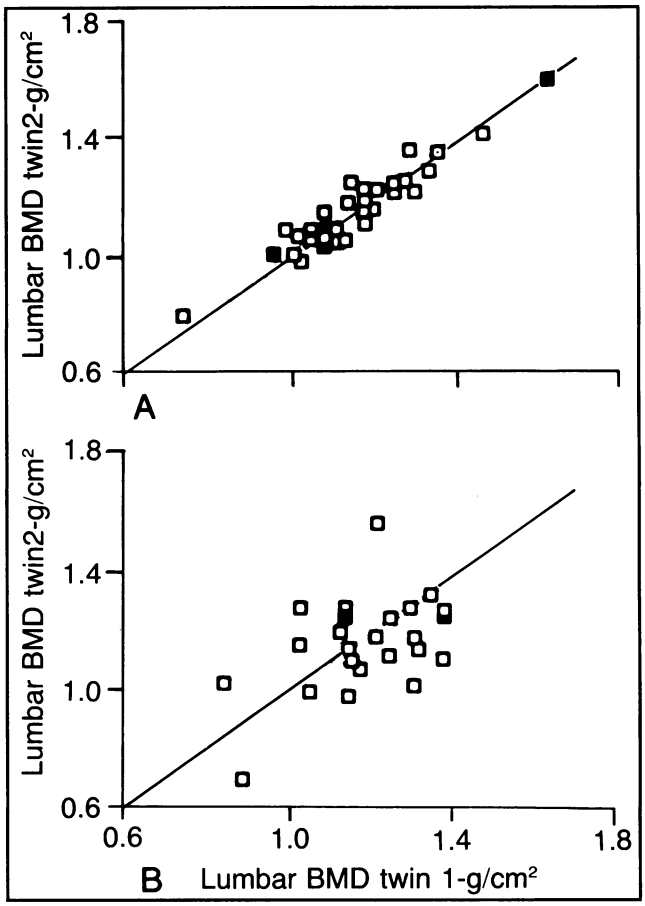

Figure 8.—Relationship between density of lumbar spine in monozygous **(upper panel)** and dizygous **(lower panel)** twin pairs. Diagonal represents line of identity. Note that agreement is much better for the monozygous twins. (From Pocock NA, et al: Genetic determinants of bone mass in adults. A twin study. J Clin Invest 1987; 80:706.)

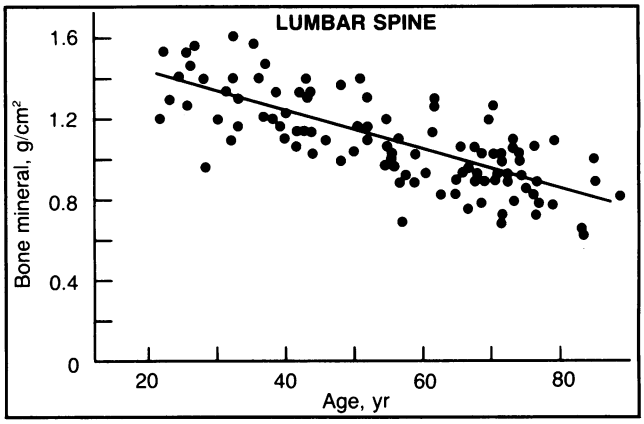

Figure 9.—Relationship between age and density of the lumbar spine in 105 normal women. (From Riggs BL, et al: Differential changes in bone mineral density of the appendicular and axial skeleton with aging: Relationship to spinal osteoporosis. J Clin Invest 1981; 67:328.)

Thus, because they absorb calcium poorly, elderly individuals should consume more calcium to maintain calcium balance, but in fact they consume less. Although the RDA for calcium is 800 mg per day, the recent NHANES survey by the US Public Health Service showed that two thirds of middle-aged and elderly women surveyed had an intake of only 550 mg per day, and one third had an intake of <400 mg per day.[32]

If the decrease in calcium absorption in the elderly is physiologically important, it should induce a compensatory secondary hyperparathyroidism and increased bone loss. There is evidence that both of these events occur. Serum immunoreactive parathyroid hormone (iPTH) increases with aging: increased circulating intact PTH in the elderly has now been convincingly demonstrated by NH_2-terminal-specific radioimmunoassay,[36] by PTH bioassay,[37] and by immunoradiometric assay (unpublished data). Further, in contrast to the older belief that bone turnover decreases with aging, data obtained with biochemical markers for bone turnover, such as serum osteocalcin and serum bone alkaline phosphatase,[38] and with tetracycline-based bone histomorphometry[39] show that it increases. The increase in bone turnover results in an increased number of bone remodeling units, and because of the remodeling imbalance between resorption and formation due to impaired osteoblast function, this leads to increased bone loss.

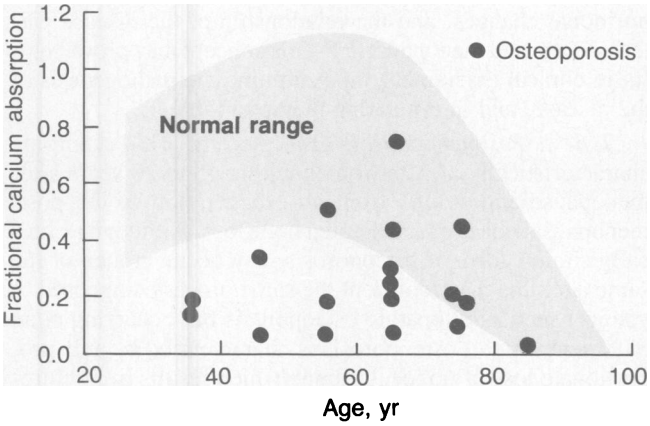

Figure 10.—Shaded area shows age-adjusted normal range for calcium absorption (assessed with ^{45}Ca and 20 mg calcium carrier) in women and closed circles indicate osteoporotic women. Note the striking reduction after age 60 years. (From Nordin BEC: Clinical significance and pathogenesis of osteoporosis. Br Med J 1971; 1:571.)

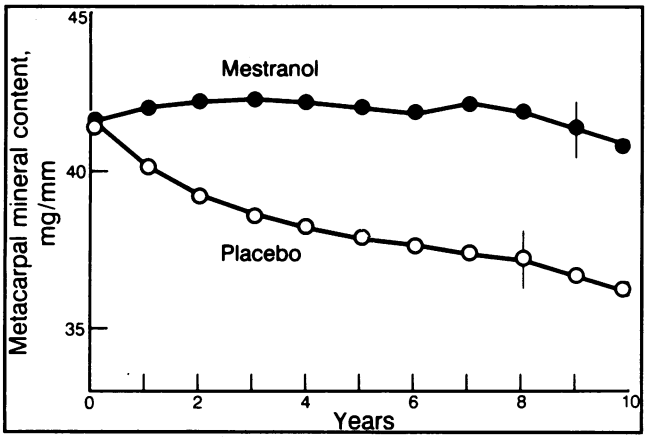

Figure 11.—Effect of estrogen or placebo treatment on bone loss after oophorectomy. (From Lindsay R, et al: Prevention of spinal osteoporosis in oophorectomised women. Lancet 1980; 2:1151.)

A third factor is an age-related decrease in serum 25(OH)D.[40] Aging decreases absorption of vitamin D from the intestine and the dermal synthesis of vitamin D following solar exposure.[41] In addition, many of the elderly are housebound and poorly nourished. A relative or absolute deficiency of vitamin D could contribute to impaired calcium absorption and to bone loss. Indeed, about 10% of elderly American patients having bone biopsy at the time of orthopedic surgery following hip fracture have histologic osteomalacia.[42]

Menopause. Surgical menopause accelerates bone loss, and estrogen replacement prevents or slows this loss in both the appendicular and axial skeletons[6,16] (Figure 11). Postmenopausal administration of estrogen decreases the occurrence of subsequent vertebral or hip fractures by about 50%.[43,44] Women who have undergone oophorectomy in young adulthood have lower bone density in later life than do non-oophorectomized premenopausal women of the same age.[45] Thus, estrogen deficiency at the menopause is an unequivocal cause of bone loss and subsequent fractures in women. Although men do not undergo the equivalent of menopause, male hypogonadism is often associated with osteoporosis.[46]

The accelerated phase of postmenopausal bone loss lasts for about 5 to 10 years,[6] but a component of bone loss up to 20 years after menopause may be related to estrogen deficiency.[47] Normal human bone cells contain sex steroid receptors and respond directly to treatment with these steroids.[48]

Sporadic Factors. A variety of behavioral and environmental factors may increase the rate of bone loss in a given individual. Smoking and high alcohol consumption increase the risk for developing osteoporosis by twofold, and their effects are additive.[49] Ethanol is toxic to osteoblasts.[50] Obesity is protective,[49] possibly because of increased loading stress to the spine and, in postmenopausal women, because of increased conversion (in fat tissue) of adrenal androgens to estrogens.

Skeletal loading from weight bearing and skeletal stresses from muscle contraction stimulate osteoblast function. Muscle mass and bone mass are directly related.[51] Among amen-

TABLE 1.—*Classification of Clinical Types of Osteoporosis*

Primary osteoporosis	Bone marrow disorders
Juvenile	Multiple myeloma and related disorders
Idiopathic (young adults)	Systemic mastocytosis
Involutional osteoporosis	Disseminated carcinoma
Endocrine diseases	Connective tissue diseases
Hypogonadism	Osteogenesis imperfecta
Ovarian agenesis	Homocystinuria
Hyperadrenocorticism	Ehlers-Danlos syndrome
Hyperthyroidism	Marfan's syndrome
Hyperparathyroidism	Miscellaneous causes
Diabetes mellitus (?)	Immobilization
Gastrointestinal diseases	Chronic obstructive pulmonary disease
Subtotal gastrectomy	Chronic alcoholism
Malabsorption syndromes	Chronic heparin administration
Chronic obstructive jaundice	Rheumatoid arthritis (?)
Primary biliary cirrhosis	
Severe malnutrition	
Alactasia	

orrheic anorexic women, those who are more physically active have denser bones than those who are sedentary.[52] Regular exercise programs retard bone loss in postmenopausal women.[53]

Nutritional factors also may be important, although there is considerable controversy regarding this. Inadequate calcium intake may be particularly important during skeletal growth in obtaining the maximal bone mass and, because of inadequate calcium absorption, in maintaining bone mass in the elderly. In a study of older men and women, the level of calcium intake at entry was found to be inversely related to the occurrence of hip fractures when the group was reassessed after 14 years.[54] Nonetheless, a community-based longitudinal study[55] failed to demonstrate a relationship between dietary calcium intake and rates of bone loss. Thus, there is considerable uncertainty whether calcium intake plays much of a role in young or middle-aged adults, except for those with very low intakes (<400 mg per day).

Clinical Spectrum

A classification of the clinical types of osteoporosis is given in Table 1. Osteoporosis can be either primary or secondary, depending on the absence or presence of concurrent medical diseases, surgical procedures, or medications known to be associated with osteoporosis. Such secondary causes can be identified in 20% of women and 40% of men presenting with vertebral fractures[1] and should always be searched for.

Idiopathic Juvenile Osteoporosis

A rare, self-limited primary form of the disease occurs in boys and girls, usually between the ages of 8 and 14 years.[56] The disease runs an acute course, usually over a period of 2 to 4 years, and then remits. During the active phase of the disease, there is growth arrest and multiple axial and appendicular fractures. The clinical severity of the osteoporosis runs the spectrum from mild to severe. The most striking feature of the disease is its almost invariable spontaneous remission with resumption of normal linear and radial bone growth.

The etiology of this condition is obscure. Although the close relationship of the disease to puberty has led some to speculate that hormonal factors are important, there have been documented cases of onset and remission of the disease well before puberty.

Diagnostically, it is important to exclude other causes of osteopenia in children, including Cushing's syndrome, acute leukemia, and osteogenesis imperfecta.

Idiopathic Osteoporosis in Young Adults

This is much more common than idiopathic juvenile osteoporosis but still is much less frequent than involutional osteoporosis. In contrast to involutional osteoporosis, which occurs predominantly in women, idiopathic osteoporosis occurs in both sexes with equal frequency. Undoubtedly, idiopathic osteoporosis represents a composite of several etiologically distinct disorders. The clinical spectrum varies widely: sometimes it is mild and is clinically manifested by a single or only a few vertebral fractures, even in the absence of treatment. More commonly, however, there are multiple vertebral fractures occurring over a period of 5 to 10 years with associated loss of height of up to 6 inches. In contrast to involutional osteoporosis, fractures of the ribs and metatarsals are common. In severely affected patients, there may be unilateral or bilateral hip fractures.

TABLE 2.—*The Two Clinical Types of Involutional Osteoporosis*

	Type I	Type II
Age, yr	51-75	>70
Sex ratio, F:M	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Main fracture sites	Vertebral (crush) and distal radius (Colles')	Vertebral (multiple wedge and hip)
Main causes	Factors related to menopause	Factors related to aging

Serum values for calcium, phosphorus, and alkaline phosphatase are normal. Hypercalciuria is relatively common and is associated with normal values for serum $1,25(OH)_2D_3$.[57] Bone histomorphometry after tetracycline double labeling has shown both high and low bone turnover forms.

Involutional Osteoporosis

Involutional osteoporosis can be divided into two distinctive syndromes on the basis of differences in clinical features, hormonal changes, and the relationship of the disease patterns to age and menopause.[1,58] This concept may prove helpful in clinical assessment, in examining the pathogenesis of the disease, and in evaluating therapy (Table 2).

Type I (Postmenopausal) Osteoporosis. This syndrome characteristically affects women within 15 to 20 years after menopause and results from an exaggeration of the postmenopausal phase of accelerated bone loss. Although a clinically similar form of osteoporosis may occur in men of the same age, this may represent the same process diagnosed in younger men as idiopathic osteoporosis but occurring at an older age. Type I osteoporosis is characterized by a disproportionate loss of trabecular bone which results in fractures at skeletal sites with a high concentration of trabecular bone, especially in the vertebrae, at the distal forearm (Colles' fracture), and at the distal ankle. The vertebral fractures usually are the "crush" type and are associated with considerable deformation and with pain.

The rate of trabecular bone loss in patients with type I osteoporosis is two to four times greater than that of postmenopausal women of the same age without fractures, but the rate of cortical bone loss is only slightly greater. There is some controversy regarding the characteristics of bone turnover, which has variously been reported to be high, normal, or low following analysis of tetracycline-labeled iliac biopsy samples. In a large recent series that employed histomorphometric methods allowing the assessment of both bone formation and bone resorption rate, bone turnover was increased in one third of patients but was normal in the remainder.[59] The increase in bone formation, however, was less than the increase in bone resorption, leading to a remodeling imbalance and bone loss. This remodeling imbalance is consistent with an osteoblast defect, which was demonstrated histologically by a decrease in wall thickness. There was a continuum in changes in bone turnover between the normal and high bone turnover patients rather than a bimodal distribution. Although the possibility of subtypes exists, it is more likely that

some osteoporotic patients have passed through a high turnover stage and have reached a stage of normal bone turnover in which further loss of trabecular bone will be small.

Type I osteoporosis appears to be caused by factors that are closely related to or are exacerbated by menopause. This leads to the following cascade: accelerated bone loss, decreased secretion of parathyroid hormone and increased secretion of calcitonin, and functional impairment in 25-hydroxyvitamin D [25(OH)D] 1α-hydroxylase activity with decreased production of $1,25(OH)_2D_3$, therefore leading to decreased calcium absorption. The defect in calcium absorption may further aggravate bone loss.

All women are estrogen deficient after menopause, however, and serum levels of sex steroids are similar in postmenopausal women with and without type I osteoporosis.[60] Thus, other factors must augment the rate or the duration of the accelerated phase of bone loss: these factors interact with estrogen efficiency to determine individual susceptibility. One possible mechanism is defective regulation of osteoblast function that could account for the impaired bone formation detected by histomorphometry.[59] Thus, when bone turnover increases as a consequence of the menopause, those women who are destined to develop type I osteoporosis compensate less well for the increase in bone resorption by increasing bone formation. Another possible mechanism is local elaboration of a factor that potentiates the effect of estrogen deficiency on increasing bone resorption. Patients with type I osteoporosis and high bone turnover have increased production of interleukin-1 by stimulated monocytes as compared with age-matched controls.[61] This increase can be normalized by treatment with estrogen.[62] On a motor basis, interleukin-1 is the most potent factor known to increase bone resorption. Another possible mechanism is increased sensitivity of bone to circulating PTH, although a recent study infusing PTH into normal and osteoporotic postmenopausal women could not document this.[63] A final possible mechanism is that those persons entering the menopause with low-normal values for bone density may be the first whose values fall below the fracture threshold as postmenopausal bone loss ensues. This is unlikely to be the major mechanism, however, because compared with age-matched postmenopausal controls, most patients with type I osteoporosis have increased rates of bone loss.[64] Obviously, these possibilities are not mutually exclusive.

Type II (Age-Related) Osteoporosis. This syndrome occurs in both men and women age 70 and older but is twice as common in women. It results from slow bone loss operating over a period of several decades. The main manifestations are fractures of the hip and vertebral fractures, although fractures of the proximal humerus, proximal tibia, and pelvis are common. The vertebral fractures are often of the multiple wedge type, leading to dorsal kyphosis ("dowager's hump"). Trabecular thinning associated with slow bone loss is responsible for the gradual and usually painless vertebral deformation. In type II osteoporosis, bone density values for the proximal femur, vertebrae, and sites in the appendicular skeleton are usually in the lower part of the normal range (adjusted for age and sex). This suggests proportionate losses of cortical and trabecular bone and a rate of loss that is only slightly higher than the mean for age-matched peers. Thus, the age-related processes causing type II osteoporosis appear to affect virtually the entire population of aging men and women, and, as the slow phase of bone loss progresses, an increasing number of them will have bone density values below the fracture threshold.[21] The two most important of these age-related factors are decreased osteoblast function and decreased calcium absorption with secondary hyperparathyroidism.

Secondary Osteoporosis

Endocrine Diseases. Osteoporosis may be associated with a number of syndromes of endocrine dysfunction. Hypogonadism in either sex increases the incidence of osteoporosis. Hypogonadism is probably the main cause of osteoporosis associated with ovarian agenesis (Turner's syndrome), although a genetic abnormality of bone maturation probably also is present. Functional hypogonadism in female distance runners may be associated with decreased vertebral density.[65] Endogenous or exogenous hyperadrenocorticism both decreases bone formation and increases bone resorption with rapid bone loss. The decrease in bone formation results from inhibition of collagen biosynthesis. The increase in bone resorption may be indirectly mediated, possibly by an increased sensitivity of bone to parathyroid hormone. Patients with glucocorticoid excess also have impaired calcium absorption, and this can be reversed by administering vitamin D or its active metabolite. An effect of corticosteroids on vitamin D metabolism, however, has not been conclusively established.

Hyperthyroidism consistently increases bone turnover, but in most patients formation and resorption remain coupled. Symptomatic osteoporosis associated with hyperthyroidism, therefore, is relatively unusual and, when present, generally occurs in postmenopausal women. Osteitis fibrosa is the characteristic skeletal abnormality associated with hyperparathyroidism; nevertheless about 5% of patients, mostly postmenopausal women, present with osteopenia and vertebral compression fractures. In contrast, mild hyperparathyroidism in younger subjects is not associated with bone loss.[66] Patients with either juvenile- or adult-onset diabetes mellitus may have an increased risk for osteoporosis, but this has not been clearly established. Osteoporosis associated with acromegaly is believed to be rare and, when present, is the result of concomitant hypogonadism. In fact, because of the anabolic effect of growth hormone excess on the skeleton, most patients with acromegaly have an increase in both trabecular and cortical bone mass.

Gastrointestinal Diseases. These conditions can cause either osteoporosis or osteomalacia, and they generally produce a mixture of both. About 5% of patients with subtotal gastrectomy, particularly those with the Billroth II type, subsequently develop bone disease. Malabsorption syndromes impair absorption of calcium and vitamin D; usually this results in osteomalacia. However, if this is mild, the predominant lesion may be osteoporosis. Chronic obstructive jaundice may be associated with bone disease because the enterohepatic circulation of active vitamin D metabolites is impaired. This mechanism may play a role in the osteomalacia associated with primary biliary cirrhosis. In the United States, however, osteoporosis associated with a profound depression in bone formation is the typical finding.[67] Its etiology is unknown. Severe malnutrition involving both protein and calcium deficiency—as has been observed in prisoners of war—may cause osteoporosis. Women with anorexia nervosa often have osteoporosis, with functional amenorrhea also possibly contributing to the bone loss. Finally, alactasia has

been reported in up to 30% of osteoporotic subjects. This disorder may be a risk factor for osteoporosis because it produces intolerance to milk and thus is associated with a low calcium intake.

Bone Marrow Disorders. Multiple myeloma produces diffuse osteoporosis in about 10% of patients and other myeloproliferative disorders may do so less frequently. This abnormality is mediated by an increased local production of lymphotoxin, interleukin-1, or other cytokines by bone marrow cells. Diffuse osteoporosis also may occur when disseminated carcinoma involves the bone marrow.

Connective Tissue Diseases. An unusually severe form of osteoporosis may occur in osteogenesis imperfecta. This disease is usually inherited as an autosomal dominant trait and is associated with blue sclera, deafness, thin skin, and impaired biosynthesis of type I collagen. Several types of mutations or deletions of the gene for type I procollagen have been described in patients with this phenotype. Although onset usually is in childhood, some patients present with premature spinal osteoporosis in the absence of a history of limb bone fracture. The Marfan and Ehlers-Danlos syndromes also may be associated with spinal osteopenia but less frequently include vertebral fractures. Osteoporosis commonly occurs in patients with homocystinuria, an autosomal recessive disorder caused by deficient cystathionine synthase activity. The resultant increase in homocysteine and other metabolites in the circulation interferes with cross-linking of collagen.

Miscellaneous Causes. Total immobilization, such as occurs in traumatic quadriplegia, results in a loss of up to 1% of bone per month, especially in the trabecular bone of the axial skeleton. After loss of 40% to 50% of bone from the spinal column, a new steady state is reached and bone mass is maintained. Bone loss is associated with both depressed bone formation and enhanced bone resorption. Significant bone loss also occurs during total bed rest among nonparalyzed individuals and in astronauts during gravitational weightlessness. If immobilization is transient, replacement of bone mass occurs on remobilization, provided that there has been only thinning of bone trabeculae rather than loss of trabeculae and other structural elements.

Not infrequently, osteoporosis is associated with chronic obstructive pulmonary disease. Whether this is related to the consumption of tobacco, which is believed to be a bone toxin, or to the pulmonary disease itself is unknown. Young alcoholics also have been shown to have thinner bones than other subjects of similar age. Long-term therapy with heparin has been reported to cause severe loss of bone and spontaneous fractures. Heparin decreases the stability of lysosomes, and release of collagenase and other lysosomal enzymes may be responsible for the bone loss. Whereas it has been suggested that osteoporosis may be a complication of rheumatoid arthritis, most of the bone loss in these patients can probably be accounted for by use of corticosteroids and by immobilization.

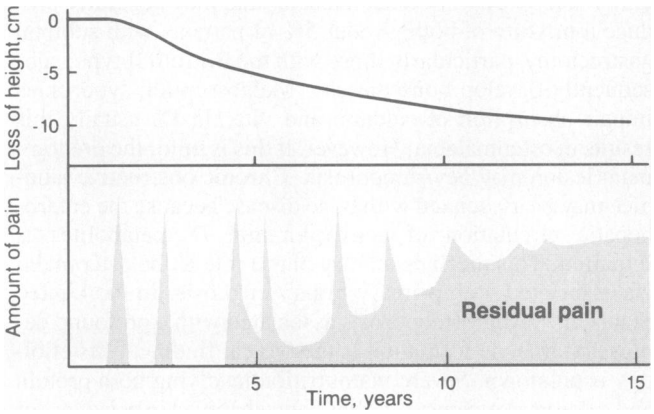

Figure 12.—Clinical course of an untreated or unsuccessfully treated patient with osteoporosis. Upper panel shows continued loss of height. Lower panel shows occurrence of back pain which is at first acute and intermittent but later chronic.

Clinical Presentation

Osteoporosis is manifested by back pain, loss of height, spinal deformity (especially kyphosis), and fractures of the vertebrae, hips, wrists, and, less frequently, other bones. The most characteristic symptom of osteoporosis is back pain caused by vertebral compression. Typically, a woman within 20 years after menopause develops acute lumbar or thoracic back pain after some ordinary activity such as raising a window or lifting a sack of groceries. The pain may be mild or severe, and it may be localized or radiate to the flank. It remits in days or weeks but then recurs with the occurrence of new fractures. After several episodes of acute, intermittent pain, a chronic mechanical backache may develop as a result of spinal deformity (Figure 12). In untreated or unsuccessfully treated patients, severe kyphosis may develop with a loss of 4 to 8 inches in height. In severe cases, the rib cage comes to rest on the pelvic brim, The frequency of occurrence of vertebral fractures and the number of fractures that eventually occur vary widely among patients, but the average is one per year in the initial phase of the disease. In general, progression is slower in elderly women, and commonly substantial dorsal kyphosis and cervical lordosis—the so-called dowager's hump—develops in the absence of significant pain. Half of the hip fractures in elderly men and women are spontaneous and half are associated with falls.

Diagnosis

General Medical Examination

All patients with newly discovered osteoporosis should have a general medical evaluation to assess severity and to exclude secondary diseases that may cause the osteoporosis. There should be historical documentation of the chronology and location of fractures, previous treatment, age at onset and type of menopause (natural or surgical), presence of fractures or osteoporosis in other family members, presence of risk factors such as use of alcohol and tobacco, previous gastrointestinal surgery, and use of corticosteroids. Systemic symptoms of abnormal physical findings suggest the presence of an underlying disease. Even severe osteoporosis generally does not result in weakness or loss of weight.

The physical examination should include an accurate measurement of height and a search for findings suggestive of systemic disease. Blue sclera, thin skin, and lax joints may be indicative of osteogenesis imperfecta or a related collagen disorder. Characteristic physical findings of Cushing's syndrome or hyperthyroidism should be sought for. The presence of splenomegaly or hepatomegaly suggests the presence of lymphoma or other malignancy.

All patients should have a complete blood cell count, determination of erythrocyte sedimentation rate, multichannel serum chemistry analyses, and urinalysis. Serum calcium and phosphorus levels are normal in primary osteoporosis.

Serum alkaline phosphatase levels also are normal except for transient elevations during healing of vertebral fractures. Sustained elevations of the alkaline phosphatase level, in the absence of liver disease, suggest osteomalacia or skeletal metastases.

Multiple myeloma may be present without symptoms and with a normal hematogram and erythrocyte sedimentation rate. Although most cases can be diagnosed by serum and urine protein electrophoresis, bone marrow examination may be required to establish the diagnosis. Bone marrow examination is sometimes also necessary to diagnose the presence of disseminated carcinoma.

Radiologic Findings

Radiographs of the spinal column should be obtained in all patients to diagnose vertebral fracture as a cause of back pain, to evaluate severity of the underlying osteoporosis, to provide a baseline for assessing the effect of therapy on future fracture occurrence, and to search for evidence of secondary diseases that may have produced the osteoporosis. Generalized osteopenia is suggested by the findings of accentuation of the vertebral end plates, prominence of the weight-bearing vertical trabeculae (due to disappearance of the horizontal trabeculae), and loss of contrast in radiodensity between the interior of the vertebral body and the adjacent soft tissue. Vertebral deformity may take the form of collapse (reduction of anterior and posterior height), anterior wedging (reduction in anterior height, usually occurring in the thoracic spinal column), or "ballooning" (by concave compression of the end plates resulting from pressure of the intervetebral disk, usually occurring in the lumbar spinal column). Also, the nucleus pulposus may herniate locally into the vertebral body (Schmorl's nodes). The severity of the osteoporosis may be defined as follows:[68] two Grade I fractures, mild osteoporosis; three to five Grade I or one or two Grade II fractures, moderate osteoporosis; and more than this, severe osteoporosis (Figure 13). A radiograph of the spinal column in a typical patient with osteoporosis is shown in Figure 14B.

Osteoporosis due to glucocorticoid excess should be considered when there is associated osteoporosis of the skull, fractures of the ribs and pelvic rami, and prominent partially mineralized callus at the site of fracture. In the absence of pseudofractures, osteomalacia may be difficult to distinguish from osteoporosis, but it often has a radiographic "ground glass" appearance rather than the characteristic "clear glass" appearance of osteoporosis. Posterior wedging of a vertebra (except for L-5) suggests a destructive lesion rather than osteoporosis.

Bone Densitometry

Recent development of methods that allow precise measurement of bone mineral density in the axial skeleton at sites subject to fracture represents a major advance in the care of osteoporotic patients.[69,70] These measurements have three principal uses: (1) to confirm the diagnosis of osteoporosis, (2) to estimate the severity of bone loss, and (3) to determine whether the patient is responding to treatment. The characteristics of the available three techniques are compared in Table 3. Single-energy quantitative computed tomography (QCT) can be performed using commercially available CT scanners and a calibration phantom. Reproducibility is satisfactory but accuracy is poor (mainly because of a confounding effect of marrow fat), and radiation exposure is relatively high. Better accuracy can be obtained with dual-energy QCT, but at the price of poor reproducibility and higher radiation exposure. Nonetheless, the method is quite sensitive (because of its ability to measure exclusively the metabolically active trabecular bone in the center of the vertebral body) and specific (because distortion by extravertebral artifacts is avoided). Dual-photon absorptiometry (DPA) uses transmission scanning with a ^{153}Gd source that emits two photoelec-

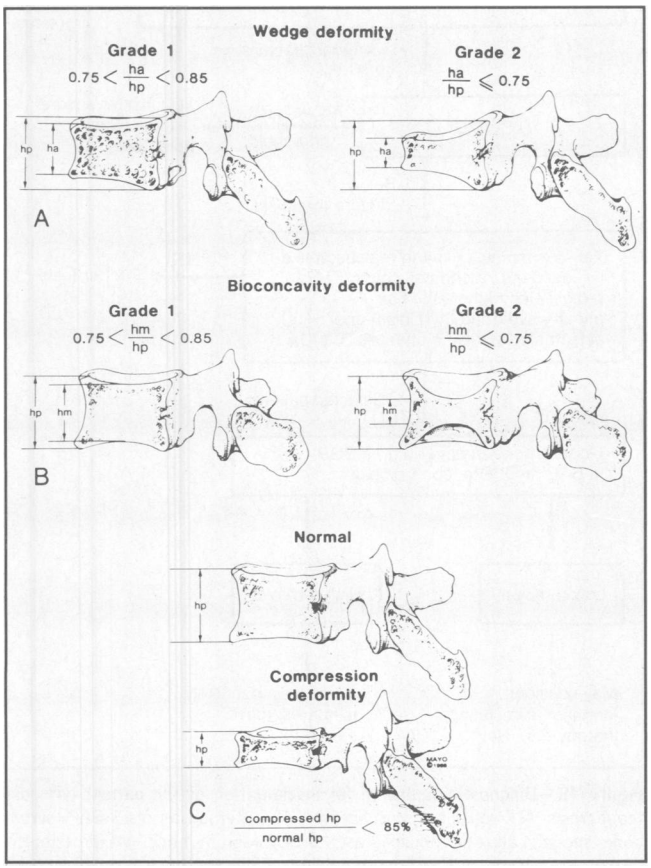

Figure 13.—Method for staging severity of vertebral fractures. See text for details. (From Eastell R, Riggs BL: Diagnostic evaluation of osteoporosis, *In* Young WF, Klee GG (Eds): Endocrinol Metab Clin North Am. Philadelphia, WB Saunders Company, 1988, pp 547-571.)

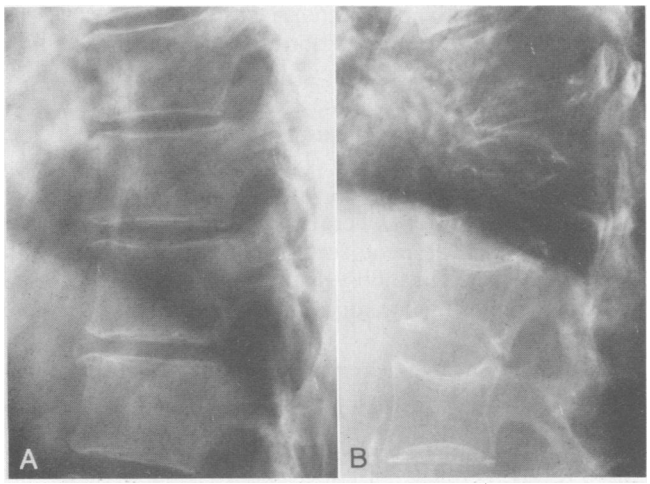

Figure 14.—Radiographs of the spinal column. **A,** Normal bone in a 60-year-old woman. **B,** Vertebral osteoporosis in a 62-year-old woman. There is a decrease in bone density with high-grade collapse fractures of T-12 and L-1 and ballooning (expansion of the intervertebral discs) of L-2 and L-3.

TABLE 3.—*Major Methods for Measuring Bone Mineral Density of the Axial Skeleton*

	QCT	DPA	DEXA
Reproducibility, %	3-5	2-4	1-2
Accuracy, %	5-15	4	4
Radiation, mrems	300-500	5-10	<5
Scan time, min	10-20	30	10

tric peaks, thereby allowing bone density to be measured independently of soft tissue thickness and composition. The method has good reproducibility and accuracy and low radiation exposure, but it measures the entire vertebra, which is only 70% trabecular bone, and results are affected by the presence of dystrophic calcification, osteoarthritis of the spinal column, and vertebral compression fractures within the scanning area. The most recently developed technique is dual-energy x-ray absorptiometry (DEXA), which also utilizes dual-energy transmission scanning but generates photons from an x-ray tube rather than from an isotope source.[71] The new method has several important advantages over DPA, including better reproducibility, shorter scan time, and a scan image approaching that of a standard skeletal radiograph in quality. In contrast to QCT, both DPA and DEXA are capable of measuring mineral density of the proximal femur and of the total skeleton.

Bone density of the appendicular skeleton can be measured by single-photon absorptiometry using transmission scanning with a ^{125}I source. Although the method has good reproducibility (1% to 3%), the correlation between density of the lumbar spine and the radius or os calcis is too low ($r = 0.5$ to 0.8) for vertebral density to be predicted accurately in individual patients. Thus, these older methods gradually are being replaced by QCT, DPA, and DEXA.

Assessment of Bone Turnover

Measurement of bone turnover is helpful in management of the osteoporotic patient in two ways. First, as discussed later, it may be helpful in deciding which type of treatment to employ. Osteoporotic patients with high bone turnover are likely to have a good response to antiresorptive therapy whereas those with low turnover are not. This distinction will become increasingly more important as effective formation-stimulating regimens are developed. Second, it is useful in following the course of therapy.

Iliac trephine biopsy may be useful in selected patients for this purpose and also may be used to exclude osteomalacia.[4] Biopsy specimens should be obtained after the patient has received tetracycline double-labeling. (Tetracycline is selectively deposited in areas where there is bone formation, and it fluoresces when the bone section is transilluminated with ultraviolet light). The biopsy specimen should be processed by an experienced laboratory that will provide quantitative information.

The other way to assess bone turnover is by biochemical markers.[72] Alkaline phosphatase is produced by osteoblasts. Although total serum alkaline phosphatase is relatively insensitive, measurement of the specific isoenzyme of bone may be helpful. Another marker reflecting bone formation is serum bone Gla-protein (BGP, osteocalcin). BGP is a noncollagenous protein found only in bone and dentin. Circulating levels can be measured by radioimmunoassay and correlate well with bone histomorphometry-based measurements of bone formation. Unfortunately, a sensitive measure for bone resorption is not available. Urinary hydroxyproline excretion is relatively insensitive and difficult to measure and requires dietary control to obtain reliable results. Recent reports, however, suggest that urinary excretion of specific pyridinium crosslinks may be a highly specific and sensitive measure of bone collagen breakdown.[73]

A diagnostic algorithm for investigation of the patient with osteoporosis is shown in Figure 15.

Treatment

General Therapeutic Measures

Acute back pain responds to analgesics, heat, and general massage to alleviate muscle spasm. Sometimes a brief period of bed rest is required. Chronic back pain often is caused by spinal deformity and thus is difficult to relieve completely. Instruction in posture and gait training and institution of regular back extension exercises to strengthen the flabby perivertebral muscles are generally beneficial. Occasionally, use of an orthopedic back brace is required. All patients with osteoporosis should have a diet adequate in calcium, proteins, and vitamins, should be reasonably active physically, and should take precautions to prevent falls.

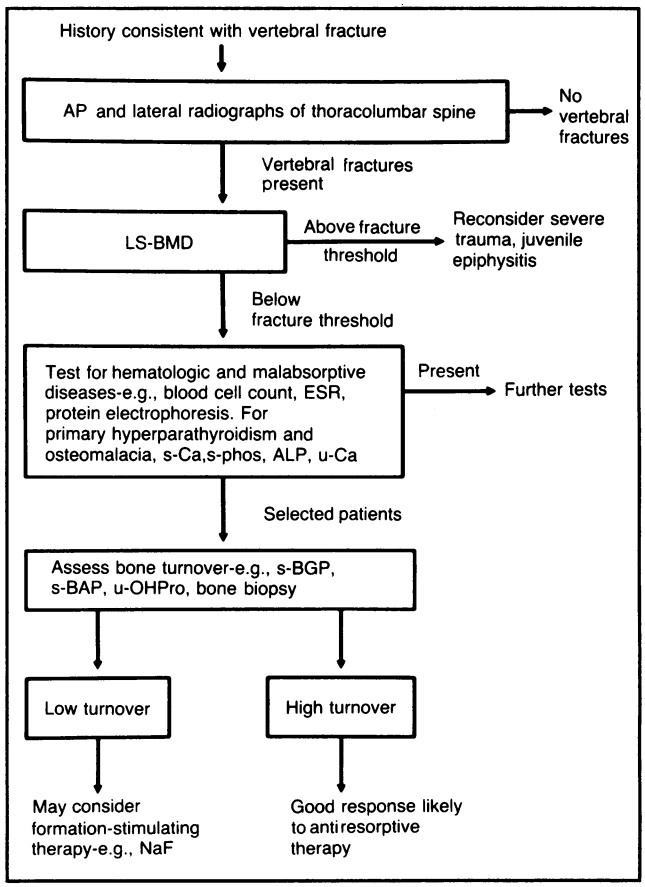

Figure 15.—Diagnostic algorithm for investigation of the patient with osteophorosis. ALP=alkaline phosphatase; AP=anteroposterior; S-BAP=serum bone specific alkaline phosphatase; S-BGP=serum bone Gla-protein; S-Ca=serum calcium; u-Ca=urinary calcium; ESR=erythrocyte sedimentation rate; uOHPro=urinary hydroxyproline; LS-BMD=dual-photon absorptiometry of the lumbar spine. (From Eastell R, Riggs BL: Diagnostic evaluation of osteoporosis, *In* Young WF, Klee GG (Eds): Endocrinol Metabol Clin North Am. Philadelphia, WB Saunders Company, 1988, pp 547-571.)

Drug Therapy

General Considerations. The drugs in the treatment of osteoporosis can be classified as antiresorptive or formation-stimulating (Figure 16). Because of the tight coupling between bone resorption and bone formation, when the new steady state is attained after 3 to 6 months of treatment, there also is a decrease in bone formation that approximates the decrease in bone resorption.[4] Thus, the best result that can be obtained with this class of therapeutic agents is maintenance of existing skeletal mass or slowing of the rate of bone loss. Nonetheless, the rate of new fractures will be decreased by antiresorption therapy because bone structure will be stabilized and thus not subject to further weakening by continued bone loss.[4] In contrast, therapeutic programs that stimulate bone formation more than bone resorption have the potential for increasing bone mass substantially and thus of eliminating the risk of new fractures.

Most of the currently available drug regimens act by inhibiting bone resorption. The antiresorption drugs include calcium, estrogen, calcitonin, vitamin D and 1,25-dihydroxyvitamin D ($1,25[OH]_2D_3$), and, probably, anabolic steroids. The regimens that primarily act by stimulating bone formation include sodium fluoride, low intermittent dosage of parathyroid hormone (PTH), combined phosphate and calcitonin, growth hormone and insulin-like growth factor I, and the AFDR regimen (coherence therapy). Of these various therapeutic regimens, only estrogen and calcitonin have been approved for treatment of established osteoporosis by the United States Food and Drug Administration. Calcium is considered a nutritional supplement and can be sold without prescription. The remaining regimens are investigative and should not be used for the routine treatment of osteoporosis.

Calcium. Calcium supplementation seems to have at least a modest effect on retarding bone loss and reducing fractures in osteoporosis. Relatively large doses may be required, 1,000 to 1,500 mg of supplementary elemental calcium daily; calcium may act by decreasing PTH secretion. Further, it is safe, well tolerated, and inexpensive. Of the various calcium salts, calcium carbonate is most widely used and has the advantage that elemental calcium represents 40% of its total weight. However, calcium carbonate may produce gaseousness and constipation in some patients, and for this reason, calcium citrate or calcium phosphate may be used as alernative preparations. Generally, it is best to give the calcium supplements in divided doses, with meals and at bedtime.

Estrogen. After calcium, estrogen is the most widely prescribed drug for the treatment of established osteoporosis in the United States. As with other antiresorptive drugs, its effectiveness varies directly with the level of bone turnover, being most effective when it is high and least effective when it is low. Estrogen acts directly on bone cells to reduce bone resorption and may oppose the action of PTH. The therapeutic dosage of estrogen in the treatment of osteoporosis is 0.625 to 1.25 mg of conjugated estrogen daily or its equivalent in another estrogen preparation. Estrogen should be given cyclically, such as 25 out of 30 days, and a progestin such as medroxyprogesterone acetate, 5 to 10 mg daily, should be given for the last 14 days of the cycle. This will prevent the development of endometrial hyperplasia and, presumably, endometrial carcinoma, which has a 5- to 10-fold increase in incidence when unaccompanied estrogen is given to postmenopausal women.[74] Because of the high concentration of estrogenic substances in the portal vein following oral administration, the liver produces increased amounts of coagulation factors, renin substrate, and bile cholesterol.[74] These increases probably account for the increased incidence of venous thrombosis and pulmonary embolism, hypertension, and gallstones, respectively, in postmenopausal women receiving estrogen in moderate to high dosages. These complications can be largely avoided by administering estrogen by transdermal patch.[75] Estrogen improves the serum lipid profile in postmenopausal women and may decrease the incidence of coronary artery disease; these favorable effects, however, may be largely offset when a progestin is administered concurrently. Whether estrogen therapy results in a small increase in risk for breast cancer is still uncertain.[76] Nonetheless, annual breast examination and mammography must be done during treatment. Other untoward effects that may occur in some subjects include menorrhagia, metrorrhagia, fluid retention, and edema.

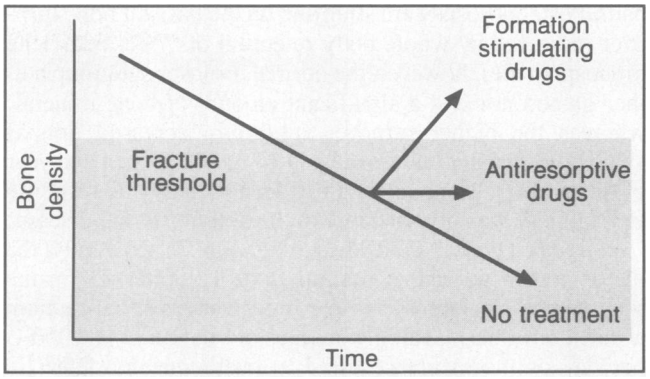

Figure 16.—Effect of two major types of drugs on bone density in a hypothetical patient with osteoporosis.

Calcitonin. Calcitonin, a 32-amino acid polypeptide secreted by the C cells of the thyroid gland in response to an increase in plasma calcium, acts directly on the osteoclasts, which contain calcitonin receptors. Thus, it may substitute for estrogen as an antiresorptive drug. Moreover, in contrast with estrogen, side effects are minor.

Nonetheless, calcitonin has several disadvantages. First, the drug must be made synthetically and is very expensive. Second, it requires parenteral administration. (Recently, however, a transnasal preparation[77] has been developed by several pharmaceutical companies. It is presently available in Europe for treatment of patients and is undergoing clinical testing in the United States.) Third, a substantial proportion of patients treated with salmon calcitonin will develop resistance after one or more years of treatment. Part of this resistance is caused by development of circulating neutralizing antibodies, a complication that is more likely to occur after salmon calcitonin than after human calcitonin administration, but other mechanisms also appear to be operative.

The usual dose is 100 MRC units of salmon calcitonin or 0.5 mg of human calcitonin subcutaneously daily or on alternate days, at bedtime. Calcium supplements should be given as 1 to 2 g of elemental calcium in divided doses to prevent secondary hyperparathyroidism, which may occur when calcitonin is given alone.

Short-term calcitonin therapy increases total body calcium modestly, as assessed by neutron activation analysis. When patients receiving calcitonin treatment for postmeno-

pausal osteoporosis were stratified on the basis of bone turnover (assessed by whole body retention of ^{99m}Te-methylene diphosphonate), however, the normal turnover subgroup neither gained nor lost a significant amount of bone mineral, whereas the higher turnover subgroup increased lumbar spine bone density (assessed by QCT) by 22% with one year of treatment.[78] Thus, as with estrogen therapy, the response to treatment was proportional to the activity of the disease.

Vitamin D and 1,25-Dihydroxyvitamin D. Currently, the major reason for using vitamin D or $1,25(OH)_2D_3$ in the treatment of osteoporosis is to correct low intestinal calcium absorption. Pharmacologic dosages of vitamin D (10,000 U per day or more) are required to overcome the defect in calcium absorption found in patients with osteoporosis. By contrast, only physiologic dosages (0.5 to 0.75 μg per day) of the active metabolite, $1,25(OH)_2D_3$, are required. Thus, osteoporotic patients may have impaired conversion of vitamin D to $1,25(OH)_2D_3$. Also, $1,25(OH)_2D_3$ may have a trophic action on osteoblasts, which contain $1,25(OH)_2D_3$ receptors, but a direct therapeutic effect on osteoblasts has not been established.

Data on the efficacy of $1,25(OH)_2D_3$ in the treatment of osteoporosis have been conflicting, some showing but some failing to show a beneficial effect on bone turnover or on rates of bone loss.[64,79] In general, results have been better when patients with more severe osteoporosis have been treated, particularly when there is evidence of impaired calcium absorption. A recent two-center study showed that patients receiving $1,25(OH)_2D_3$ therapy had a better than 50% reduction in the number of new vertebral fractures as compared with a randomized group receiving placebo.[80]

Because $1,25(OH)_2D_3$ is the final product of vitamin D metabolism and is not subject to feedback control, there are significant risks of hypercalcemia and hypercalciuria when it is used therapeutically. Earlier concerns about renal damage, however, have not been substantiated when patients are carefully followed. Nonetheless, the dosage of $1,25(OH)_2D_3$ probably should be restricted to 0.5 to 0.75 μg per day; although a dietary calcium intake of 800 mg daily should be maintained, additional supplementary or dietary calcium should be interdicted. Low-dose $1,25(OH)_2D_3$ combined with 1,000 mg per day of supplementary calcium has been reported to retard bone loss without problems of hypercalcemia.[81] Serum and urine calcium should be monitored regularly during treatment.

Biphosphonates. These compounds are structurally similar to pyrophosphate (P-O-P) except that the oxygen is replaced by carbon (P-C-P). This chemical modification makes the drugs resistant to degradation by alkaline and acid phosphatases. Biphosphonates are absorbed poorly (< 10%), but once in the circulation, they are taken up avidly by the skeleton or excreted unchanged by the kidney. In bone, they are adsorbed to the surface of hydroxyapatite crystals. Biphosphonates inhibit bone resorption, either by toxic action on the osteoclasts or by rendering hydroxyapatite more resistant to osteoclastic resorption. In addition, one agent in this class, sodium etidronate (EHDP), inhibits bone mineralization and with higher dosages or with prolonged use of low dosage may lead to osteomalacia. Another biphosphonate, dichloromethane diphosphonate (Cl_2MDP), initially showed considerable promise in the treatment of osteoporosis but was withdrawn because of possible hematologic toxicity. A third biphosphonate, amino-hydroxypyropylidine (APD), that is currently undergoing clinical trials in Europe, has been shown to increase bone mass by about 2% to 3% per year in osteoporotic women.[82] Except for transient hyperpyrexia at the initiation of treatment (due to increased production of interleukin-1) and minor gastrointestinal symptoms, the drug is well tolerated. Newer and more potent biphosphonates are currently being developed.

Anabolic Steroids. Because of virilization, androgens should not be used in the treatment of women with osteoporosis. Synthetic 17-methylated heterocyclic steroids have been developed, however, that have equivalent anabolic activity but less androgenicity. These compounds induce a modest increase in skeletal mass.[83] Although anabolic steroids have been thought to act primarily by stimulating bone formation, radiocalcium kinetic studies suggest that they may act mainly by decreasing bone resorption. Nonetheless, they may differ in their effect on bone formation rate from estrogen (which decreases it), as they may have a weak stimulatory effect on the osteoblasts. Although anabolic agents avoid the problem of estrogen stimulation, about one-quarter of women treated develop some side effects related to androgenicity. Moreover, especially when given orally, they may increase plasma cholesterol and low-density lipoprotein concentrations and induce liver dysfunction. Because of substantial side effects, the United States Food and Drug Administration has withdrawn its approval for this class of compounds, although they continue to be used in other countries.

Sodium Fluoride. Of all the formation-stimulating regimens, only therapy with sodium fluoride has been widely evaluated. The drug is a potent osteoblast mitogen and is capable of increasing bone mass substantially (Figure 17). Increases of up to 100% occur mainly in the trabecular bone

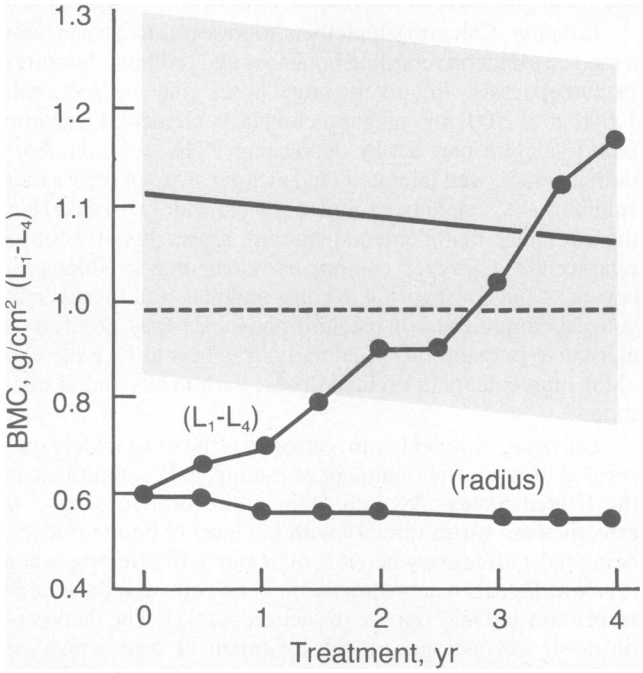

Figure 17.—Effect of sodium fluoride treatment on bone density of a 62-year-old osteoporotic woman. Cross hatched area represents normal range for bone mineral content (BMC) of lumbar spine and horizontal broken line represents fracture threshold. Note dramatic increase in BMC of lumbar spine with treatment but no change in BMC of midradius. (From Riggs et al: The role of sodium fluoride in the treatment of osteoporosis. Proceedings of the Lawrence and Dorothy Fallis Internation Symposium, Detroit, MI, May 8-13, 1988, *In* Kleerekoper M, Krane SM (Eds): Clinical Disorders of Bone and Mineral Metabolism. New York, Mary Ann Liebert, Inc., 1989, pp 605-612.)

of the axial skeleton, whereas cortical bone in the appendicular skeleton remains unchanged or decreases slightly.[84] Concurrent administration of supplementary calcium is required to offset or to minimize the incomplete mineralization that may occur when fluoride alone is given. Bone biopsy studies suggest that fluoride therapy may bypass the normal remodeling sequence and induce osteoblast formation de novo on previously quiescent surfaces.

However, fluoridic bone has increased crystallinity, decreased elasticity, and may be abnormal structurally with decreased bone strength. Recently, a two-center, randomized, controlled and double-blind study failed to demonstrate a decrease in vertebral fracture rate after 4 years of treatment with 75 mg daily of sodium fluoride.[85,86] Thus, the possibility exists that fluoride therapy induces formation of large amounts of bone that is more brittle than normal and does not result in a net increase in bone strength. Because this drug is widely used throughout the world, undoubtedly further evaluation of anti-fracture effects will be made.

Other Formation-Stimulating Regimens. Although PTH increases bone resorption, low dosage, intermittently administered PTH is anabolic and results in substantially increased trabecular bone mass.[87] This anabolic action may be mediated by local production of insulin-like growth factor-I by bone cells.[88] Combination administration of oral phosphate (to increase PTH secretion) and parenteral calcitonin (to decrease bone resorption) has also been effective in inducing moderate increases in trabecular bone short-term.[89] Finally, a theoretical approach to the treatment of osteoporosis, termed ADFR or coherence therapy, has been described in which coherent populations of bone cells are manipulated.[90] An agent such as PTH(1-34) is given to activate (*A*) remodeling cycles and to synchronize the normally asynchronous remodeling activity within the skeleton as a whole. Next, a depressing (*D*) agent such as calcitonin is given that will decrease the activity and duration of the resorption phase. This agent is then withdrawn and a free (*F*) period is allowed so that the formation period will proceed unencumbered, producing a net increase in bone mass. The cycle is then repeated (*R*). Recent studies combining intermittent cyclic etidronate have resulted in increases in bone density in the spine by 6% over 3 years compared with a placebo-treated control.[91]

Treatment of the Individual Patient With Osteoporosis

Type 1 (Postmenopausal) Osteoporosis. Treatment should be begun as early as possible. Thus, in patients with vertebral fractures, even mild, nontraumatic wedge fractures should be treated. Osteopenic patients without vertebral fractures but with bone density values below the age-adjusted normal range should also be treated. Patients with Colles' fracture of the distal forearm should have vertebral densitometry to determine the need for active therapy.

All patients with type I (postmenopausal) osteoporosis should receive supplementary calcium. When there is evidence of impaired calcium absorption on the basis of urinary calcium excretion of 100 mg per day or less, vitamin D or $1,25(OH)_2D_3$ should be employed. Women with more than minimal disease should receive estrogen therapy, especially when high bone turnover can be demonstrated or when patients are within 10 to 15 years past menopause. Calcitonin therapy is an alternative when estrogen therapy is contraindicated or not tolerated.

Type II (Age-Related) Osteoporosis. These patients have already lost most of the bone that they ever will lose and differ little in bone density from peers without fractures. There is no evidence that estrogen or calcitonin therapy is beneficial in such patients. Moreover, because of their age and increased incidence of asymptomatic atherosclerosis, there may be increased risk associated with estrogen therapy. Treatment consists primarily of calcium supplementation (because of impaired calcium absorption) and instruction in measures that decrease the risk of falls. The latter include use of shoes with flat heels, removal of loose floor rugs, avoidance of slippery surfaces (such as recently waxed floors or icy sidewalks), and the use of a light if it is necessary to get up from bed during the night.

Idiopathic Osteoporosis. For idiopathic osteoporosis in juveniles, the basic strategy is to protect the spine until remission occurs. Sex steroids are contraindicated because of the possibility of early closure of the growth plates. Biphosphonates or calcitonin may be useful in retarding bone loss in severely affected cases.

For idiopathic osteoporosis in premenopausal women, there is no reason to prescribe sex steroids because these patients are not estrogen deficient. The mainstay of treatment is calcium supplementation with the addition of vitamin D or its metabolites when there is evidence of impaired calcium absorption. When there is evidence of increased bone turnover, calcitonin can be added as an antiresorptive agent. Cigarettes and excess alcohol should be interdicted.

For idiopathic osteoporosis in men, the treatment is similar to that for idiopathic osteoporosis in premenopausal women. For osteoporosis occurring in older men, a careful search should be made for secondary causes, which will be found in approximately 40% of the patients. Approximately 10% to 20% of men with osteoporosis will be found to have partial or complete hypogonadism of various causes.[49] Those patients with documented low plasma testosterone levels should receive replacement therapy. Calcium supplementation, with or without pharmacologic dosages of vitamin D, is usually given also.

Osteoporosis Associated With Glucocorticoid Excess. Secondary osteoporosis is commonly caused by chronic use of pharmacologic dosages of glucocorticoids. The most important therapeutic measure is to reduce the dosage of glucocorticoids or, if possible, to discontinue it. Administration of the glucocorticoid once daily or on alternate days may maintain a more favorable balance between the anti-inflammatory and immunosuppressive effects and the osteopenic effect in some patients. All patients should receive calcium supplementation and those patients who are postmenopausal women should also be given estrogens. Although glucocorticoids inhibit calcium absorption, the use of vitamin D or its metabolites in treatment is controversial. Finally, thiazide diuretics to antagonize the calciuric effect of glucocorticoids may be useful.

Prevention of Osteoporosis

Considering the magnitude of this enormous problem, prevention is the only cost-effective approach. Dietary calcium, if low, should be increased to at least 1,000 mg per day for adults and possibly more for postmenopausal women. Increased physical activity should be encouraged, and bone toxins, such as cigarettes and heavy alcohol consumption, should be eliminated.

Of all preventive measures, however, the most effective is estrogen replacement therapy begun at menopause. A dosage of 0.625 mg per day of conjugated estrogen or its equivalent will prevent the accelerated phase of bone loss from occurring in nearly all perimenopausal women. It is not known how long estrogen therapy must be continued to be effective. Withdrawal of estrogen therapy, however, results in accelerated bone loss of the same magnitude that occurs following oophorectomy.[91] Thus, it is likely that long-term estrogen therapy will be required to gain maximal benefit.

Because of the potential adverse effects of estrogen and because of the high cost of the necessary surveillance while it is being administered, it will be necessary to develop criteria for selecting those postmenopausal women who are at greatest risk for future fracture. At present, this selection can best be made by obtaining a bone density measurement of the lumbar spine in the perimenopausal period. Those women in the top third of the age-adjusted normal distribution are at relatively low risk and need not be treated unless this is necessary for relief of menopausal symptoms. Those in the lower one third of the distribution are at increased risk, and estrogen replacement therapy should be strongly considered for them. Those in the middle one third of the distribution should have a repeat bone density measurement made after 2 to 3 years and if substantial bone loss has occurred should be reconsidered for treatment. In the future, it is possible that biphosphonate drugs may substitute for estrogen in some subjects.

Summary

Osteoporosis is a common age-related disorder manifested clinically by skeletal fractures, especially fractures of the vertebrae, hip, and distal forearm. The major cause of these fractures is low bone mass, although an increase in trauma due to falls in the elderly also contributes. There are multiple causes for the low bone mass which, in any given individual, may contribute differently to the development of the osteopenia. The most important groups of causes are failure to achieve adequate peak bone mass, slow bone loss due to processes relating to aging, the menopause in women, and a variety of sporadic behavioral, nutritional, and environmental factors that affect bone mass in some but not in other individuals. The most important approach is prevention. Drugs and behavioral factors known to cause bone loss should be eliminated and perimenopausal women should be evaluated for possible preventive administration of estrogen. For patients with fractures due to established osteoporosis, the only drugs approved by the Food and Drug Administration are the antiresorptive agents calcium, estrogen, and calcitonin. Formation-stimulating regimens, however, are being developed and may be available for clinical use in the foreseeable future. These regimens may be capable of increasing bone mass to above the fracture threshold, thereby resulting in a clinical cure of the osteoporosis.

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