Bone is a complex organ. It contains an organic matrix that serves as scaffolding—mineral as calcium distributed in a pattern which provides structure and serves as an ion reservoir for the body. Within this complex tissue reside specialized bone cells, including osteoblasts, osteocytes, and osteoclasts. There are other cells in contact with the inner or endosteal surface of bone, including monocytes, macrophages, and fibroblasts, all of which modulate the activities of the osteoblasts and osteoclasts [1,2]. The organic matrix of bone consists predominantly of type I collagen (about 95% of the organic matrix is this type of collagen) [3]. The primary structure of the type I collagen in bone is similar to that of type I collagen in skin; however, bone type I collagen contains certain secondary posttranslational modifications distinguishing it chemically from that collagen found in skin [4,5].

Bone is a dynamic organ and remodels itself throughout life. This process involves removal or resorption of bone from one surface of bone and the subsequent deposition of new bone on another nearby surface. These two specific actions, bone resorption and formation, are performed by the specialized bone cells, and these events are tightly coupled in time and space. Factors that participate in modulating these processes include systemic hormones and local paracrine factors as well as gravity, physical activity, and weight bearing [1,2].

The specialized cells that perform remodeling include the osteoblasts and the osteoclasts. The osteoblasts are the cells that form bone. They synthesize the organic matrix and subsequently perform the actions leading to mineralization. The organic matrix synthesized by osteoblasts includes other proteins in addition to type I collagen. There are also noncollagenous proteins within the organic structure [3]. These include osteocalcin (also known as bone-GLA protein or BGP) [6]. Osteocalcin contains γ-carboxyglutamic acid and is a vitamin K-dependent protein. The other noncollagenous proteins include osteonectin, thrombospondin, and other sialyted and phosphorylated proteins [3,6–11].
proteins probably have important roles in chemotaxis and cell adherence. Their synthesis is controlled by serum levels of hormones, such as parathyroid hormone (PTH) and 1,25 dihydroxy vitamin D (1,25(OH)2D) [3,7].

The osteoclasts are the bone resorbing cells. Structurally they are polarized cells, multinucleated and characterized by their large size. The cell’s basolateral membrane is closely apposed to the bone marrow and maintains sodium pumps and a bicarbonate/chloride exchanger [12]. The opposite cellular membrane in contact with mineralized bone contains contractile proteins such as actin. The peripheral edge of the cell in contact with the bone surface forms a “sealing zone.” The cell attaches to the matrix osteopontin through an avβ3 integrin (vitronectin) receptor that seals off a compartment [13–16] that is subosteoclastic. In this interface between the osteoclast and bone, bone resorption takes place (Howships lacunae). The plasma membrane is invaginated in this area and forms the typical ruffled border of the cell. Osteoclasts are derived from the same stem cells as monocyte/macrophages [13,17]. Macrophages also participate in the process of bone resorption through phagocytosis of residual debris and by producing cytokines. These cytokines have been demonstrated to participate in increased osteoclast recruitment, differentiation, and function [18–22].

Systemic hormones and local factors regulate the recruitment, replication, and function of the osteoblasts and the osteoclasts. Hormones act on cells directly or indirectly by altering the synthesis, activation, and receptor binding of locally active factors or regulating availability or activity of specific binding proteins modulating the effects of these factors. Locally produced factors include growth factors, cytokines, and prostaglandins and leukotrienes [18,23,24].

Parathyroid hormone is one of the systemic hormones with important effects on bone cell function. It stimulates bone resorption by increasing osteoclast activity; however, no PTH receptors have been demonstrated on these cells. Specific PTH receptors have been identified on cells of the osteoblast lineage or stromal cells. PTH stimulates these cells to produce soluble factors that communicate with and stimulate the osteoclasts to increase bone resorption including a substance termed RANK ligand [23,25,26]. This important molecule interacts with transcription factors that serve to increase osteoblastic development; it is inhibited by another soluble factor, osteoprotegerin. PTH also directly inhibits ostoblastic mediated synthesis of collagen. However, it has been shown that it will also stimulate the local production of insulin-like growth factor (IGF) I, which has the paradoxical effect of increasing matrix synthesis [27]. The inhibitory effects on synthesis of collagen matrix are observed after continuous exposure to the hormone, but intermittent exposure leads to the stimulation of new matrix synthesis [28]. These opposite actions of PTH are mediated through a single receptor coupled to different regulatory (G) proteins.

Calcitonin is another important hormone with specific effects on bone cells. It inhibits osteoclastic bone resorption directly through high-affinity receptors on osteoclasts. There is little evidence to suggest that calcitonin has an effect on osteoblastic function [29,30].
The remodeling process in the adult skeleton is a dynamic process, continuous throughout life to a greater or lesser degree. It is required to maintain the strength of bone and occurs on all bone surfaces, including the periosteal, haversian, cortical, and endosteal surfaces [1,2,23,24,31–34]. Once the bone mass has reached adult proportions, which is probably genetically predetermined, it remains constant with equal rates of bone formation and resorption. This equilibrium is achieved through coupling of packets of interacting cells called “remodeling units” [24,32–34]. Peak bone mass is reached by men and women about in the middle of the third decade of life. A plateau period then ensues during which there is a constant turnover of bone formation, which approximates bone resorption. Following this plateau phase there begins, in men and women, a period of net bone loss equivalent to about 0.3% to 0.5% per year. Beginning with the decrease in estrogen associated with the menopause, women accelerate this net bone loss about 10-fold for approximately 5 to 7 years.

Osteoporosis

Osteoporosis is a heterogeneous group of abnormal processes characterized biologically by the net loss of bone, which results in a decrease in total mineralized bone without a decrease in the ratio of bone mineral to the organic matrix such as seen in osteomalacia [35–41]. Thus there is a decrease in the overall amount of bone. By histomorphometric analysis, the size of the osteoid seams is normal, but there is a decrease in the thickness of the cortex and a decrease in the number and size of the trabeculae in cancellous bone. The trabecular plates have increased perforations, and there is a decrease in trabecular connectivity [41–44]. Trabecular connectivity is probably an important determinant of the extent that bone may be compressible and thus absorb energy, suggesting that connectivity is an important determinant of the tensile strength of bone. Ultimately, osteoporosis leads to bone with less tensile strength and significantly more susceptibility to fracture with less force. At some point, the amount of bone available for mechanical support falls below a certain threshold (the “fracture threshold”) and the patient may sustain a fracture. It is important to remember that there is no absolute fracture threshold for a population of patients; rather, it is different for each individual. The bone loss affects cortical and trabecular bone, with trabecular bone loss more predominant in typical postmenopausal osteoporosis.

Pathophysiology

Peak bone mass is achieved by men and women in the middle of the third decade of life. After a plateau period, during which there is a constant turnover of bone formation approximately equal to bone resorption, there begins a period of
net bone loss equivalent to about 0.3% to 0.5% per year. Beginning with menopause, women sustain an accelerated period of bone loss, which may increase 10-fold, so that for approximately 5 to 7 years they may lose bone at the rate of 3% to 5% per year [35–41]. This same issue of constant bone loss affects men and women over the age of 70. Whereas accelerated bone loss is the dominant effect in postmenopausal osteoporosis, it is likely that a decrease in synthesis of new bone with either stable or accelerated bone loss is the main problem in the older age group in men and women both.

Though the osteoblasts and osteoclasts are under the control of systemic hormones and cytokines as well as other local factors, such as parathyroid hormone (PTH), calcitonin, estrogen, and 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] (see references [19,21,22,25–27,45–47]), estrogen deficiency is a significant cause of accelerated bone loss (see references [20–22,46,47]). Estrogen deficiency is described to affect circulating levels of specific cytokines, such as IL-1, tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony stimulating factor (GM-CSF), and IL-6 [46,47]. With the progressive loss of estrogen, levels of these cytokines rise and enhance bone resorption by increasing the recruitment, differentiation, and activation of osteoclast cells [46–61]. Calcitonin levels are decreased in women compared with men; however, calcitonin deficiency has not been shown to play a role in age-related osteoporosis (see references [35–37,49,62–66]). This increase in activity of cytokines leads to the generation of transcription factors, which lead to increased osteoclastic recruitment and development. The mediator of this activity is RANKL, generated from osteoblasts and other cells, including of the immune system leading to increased bone resorption.

Other factors also affect bone mass (see references [35–37,49,62,67–85]). Physical activity tends to increase bone mass, whereas immobilization leads to increased bone loss. Obesity is associated with higher bone mass. Typical patients with osteoporosis tend to be thin and possess less muscle mass (see references [48,78,86,87]). Low dietary intake of calcium, phosphorous, and vitamin D are associated with age-related bone loss. The body’s acid-base balance is also important; for example, the alkalization of the blood with bicarbonate has been shown to retard bone loss [85]. Late menarche and early menopause, caffeine ingestion, alcohol use and cigarette smoking are also important ingredients determining decreased bone mass (see references [48,71,72,79,86–90]). Race and sex also influence bone mass. Blacks and Hispanics have higher bone mass than Caucasians and Asians, and men have higher bone mass than women [83,84,87]. Genetic factors are probably the most important of these in defining an increased risk of the development of osteoporosis. A family history of fractures in postmenopausal women probably predicts future problems (see references [48,78,91,92]). Some investigators have also demonstrated a correlation with abnormal receptors for vitamin D in some families with osteoporosis in multiple generations [93]. Unfortunately, this seems to be evident in some portions of the world but not in others, and is probably only an important problem in a small number of patients. However, other types of
genetic abnormalities may explain the expression of an osteoporosis phenotype in certain families [48,91,92].

Specific abnormalities in genetic and hormonal factors appear to be important to define two clinical subtypes of age-related osteoporosis (see references [35–37,67,68]). Type I osteoporosis occurs in hypogonadal women or men. Postmenopausal women, women with premature oligo- or amenorrhea (due to anorexia nervosa or obsessive exercise programs), and men after castration or associated with testosterone deficiencies develop net bone loss directly related to the loss of gonadal function (see references [35–37,70–72]). As described, the loss of estrogen leads to increased serum levels of cytokines, which is thought to lead to increased recruitment and responsiveness of osteoclast precursors in trabecular bone, resulting in increased bone resorption [46,47]. As a result, these patients present with fractures of the skeleton where trabecular bone is predominant, such as the distal forearm and vertebral bodies.

Type II osteoporosis, on the other hand, is associated with the normal aging process and is seen in men and women typically after the age of 60 to 70 (see references [35–37,67,68,94]). Normal aging is associated with a progressive decline in the supply of osteoblasts and a decrease in their activity, but not primarily with an increase in osteoclast activity [33,42–44]. However, there remains a net loss of bone, but this time due to decreased formation and not necessarily due to increased resorption. Fractures of cortical bone, such as in the femur, femoral neck, proximal tibia, and pelvis, are more common in this group.

Other pathological circumstances leading to abnormalities of bone metabolism that increase the risk of bone loss include those patients with increased endogenous production of glucocorticoids or those with inflammatory diseases, regardless of whether they are treated with exogenous glucocorticoids. The pathogenesis of glucocorticoid-induced osteoporosis is complex, but is probably due to several induced abnormalities, including changes in gonadal hormone secretion, an induced decrease in calcium absorption, and an increase urinary calcium excretion as well as the direct effects of glucocorticoids on bone cells [45,95–98]. Glucocorticoids have been shown to decrease pituitary gonadotrophin secretion and suppress adrenal androgen production. These powerful anti-inflammatory drugs also decrease intestinal calcium absorption even with normal serum levels of calcitriol. In addition, the other skeletal effects of glucocorticoids include inhibition of osteoblast function, increased sensitivity of the cells to the effects of parathyroid hormone, and possibly transiently increased osteoclast activity. However, long-term use of glucocorticoids decreases osteoclast recruitment and cellular activity. Glucocorticoids also inhibit the generation of osteoprotegerin, a factor that inhibits RANK ligand. Thus, by decreasing inhibition of the inhibitor for RANK ligand there is increased generation of osteoclastic precursors and the generation of more osteoclasts. Bone loss with glucocorticoid therapy is most marked in trabecular bone and appears to be related to the dose and duration of glucocorticoid therapy and can be rapid. A significant amount of this bone loss is due to glucocorticoid-induced secondary changes in calcium balance and can be blunted by adequate use of cal-
Cation supplementation and vitamin D repletion concomitantly with the anti-inflammatory therapy [99–102]. The use of certain diuretics, such as thiazide derivatives, has been shown to decrease the hypercalciuria associated with the use of glucocorticoids [103]. Furthermore, it has been shown that the use of bisphosphonates is clearly beneficial and appropriate when starting systemic glucocorticoid therapy. Those patients with systemic inflammatory diseases are already at increased risk for bone loss, and the use of glucocorticoids to control the inflammation in these clinical circumstances enhances the problem.

Not everyone with low bone mass will fracture. The quantity of bone is measurable as the bone density and is predictive of future fracture; however, without a bone biopsy it is hard to define the quality of bone. The quality of bone, which partially reflects the extent of its connectivity, is also an important component of bone strength. Patient awareness of the potential risks associated with falling down is also important (see references [48,80–82,101]). Many elderly people are at risk for falling as a result of poor coordination, poor vision, muscle weakness, confusion, and the use of hypnotics or other medications that alter the sensorium. Because they are at a higher risk of falling they are also at an increased risk of sustaining a fracture. It has been shown that the use of hip pads by elderly nursing home occupants can reduce the incidence of hip fracture when patients fall.

Differential diagnosis

Osteoporosis can occur as a primary disorder or as a disorder associated with various diseases. Primary osteoporosis is a disease of the elderly, particularly among older women, with most cases occurring in the sixth and later decades of life. This form of osteoporosis is sometimes referred to as “involuntary” osteoporosis.

Secondary osteoporosis is a series of abnormalities and diseases that may manifest with effects in bone. Those disease states associated with osteoporosis include endocrine disorders, systemic inflammatory diseases, bone mineral and metabolic defects, and other chronic illnesses. Some endocrine diseases that commonly effect bone include hyperthyroidism (due to primary thyroid disease or excessive supplemental thyroxine), hyperadrenocortism (primary or iatrogenic), and hyperparathyroidism. Some examples of systemic inflammatory diseases associated with osteoporosis include inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus [37,62]. Osteoporosis may also result from therapeutic interventions, such as with methotrexate drug therapy (decreased osteoblast function), heparin (increased osteoclast activity at doses higher than 15,000 units in 24 h), glucocorticoids at or higher than 7.5 mg/d, or the use of anticonvulsants (which effect vitamin D metabolism and calcium absorption) (see references [45,48,94–96,99,104–106]). Other diseases commonly associated with an increased incidence of osteoporosis in-
include diabetes mellitus, chronic obstructive pulmonary disease, and alcoholism [86–90].

Clinical manifestations

The clinical features of osteoporosis are bone fracture, pain, and deformity. Many patients are surprised to discover they have surreptitiously lost height due to previous asymptomatic vertebral fractures. Pain is the most common of symptoms. The axial skeleton is the most commonly involved area, with fractures occurring frequently in the mid thoracic, lower thoracic, and lumbar spine vertebrae. Spontaneous high thoracic or cervical fractures associated with minimal trauma should raise the suspicion of a malignancy. Osteoporotic fractures are typically sudden in onset and may be caused by a fall, sudden movement, lifting, jumping, or even with innocent traumatic events, such as a cough. Pain may be severe and typically localized to the site of fracture but can radiate to the abdomen or flanks. Activities that increase vertebral pain include valsalva maneuver, bending, or prolonged sitting or standing. Factors that decrease pain include lying on one’s side with knees and hips flexed and arising from the lateral position rather than upright from the supine position. Generalized bone pain is rare and should raise the possibility of other diseases, such as metastatic cancer or osteomalacia.

Pain from an acute fracture usually subsides in a few weeks, and it is typically gone in 3 months. Persistent nagging back pain may continue for years even in the absence of new fracture because of the mechanical changes resulting from the fracture. Classic sciatica or pain characteristic of nerve root impingement is unusual in osteoporosis. Most patients with an osteoporosis related fracture sustain further fractures within the first few years [48,67,107]. Femoral neck fractures occur mainly in people over 65 years of age and increase in incidence as patients age [36,37]. Once a patient fractures a hip, there is a significant increased risk of death within 1 year [69]. This increased mortality is typically the result of complications of the fracture or reparative surgery; however, hip fractures are often sustained by patients who are chronically debilitated for other reasons.

Physical examination typically demonstrates tenderness to palpation over an area of fracture, spinal deformity, loss of height, and, over time, development of a lax abdominal musculature with a protuberant abdomen. Progressive anterior vertebral compression produces an exaggerated kyphosis of the thoracic spine, which leads to a characteristic deformity called a “dowager’s hump.”

Laboratory and radiologic features

Histomorphometry remains the gold standard for determining the state of bone turnover and diagnosing disease; unfortunately, the method is invasive
requiring transiliac bone biopsies obtained with a trephine that has an internal diameter of 7 to 8 mm [43,108,109]. With tissue fixation, the samples are not demineralized, are embedded into plastic, and then thin sections are cut by microtome. Tetracycline labeling may be used as an in vivo marker to determine the rate of bone formation [110,111]. In normal adults, about 1 pmole of bone is deposited daily within active areas of remodeling [110,111]. Although it is a technique providing an enormous amount of information, it is not commonly used in clinical practice because of its invasiveness.

There are now methods to approximate the extent of bone turnover without relying on radiocalcium kinetics or direct measurement by bone biopsy. Biochemical markers can be measured in blood or urine, which define either markers of osteoblastic or osteoclastic function, the amount of new collagen or noncollagenous proteins synthesized, the extent of activity of osteoblasts, or the amount of bone collagen that has been resorbed [112–132]. The degree of elevation of indices of resorption and formation reflects the extent or severity of the abnormal bone turnover. Unfortunately, these markers of bone turnover have not yet been determined to reflect bone mass, quality of bone, or predict risk for fracture alone.

The biochemical markers for new synthesis, which may be clinically useful, include serum alkaline phosphatase, bone specific alkaline phosphatase, type I procollagen carboxyterminal peptide, and osteocalcin (see references [112–114, 116–118,123,132]). As a result of bone resorption, several of the collagen breakdown products are excreted in the urine. These include peptides containing hydroxyproline, hydroxylysine, and glycosylated hydroxylysine that are present in all type I collagens of all sources, or the 3-hydroxy-pyridinium crosslink compounds that are unique to bone type I collagen (see references [112,114,116,119–130,132]).

Elevated levels of serum alkaline phosphatase activity reflect increased activity of the osteoblasts [128]. The available bone specific serum alkaline phosphatase assays have not yet been proven to add more information except in patients with concomitant liver disease [128]. Measurement of bone-specific alkaline phosphatase is more accurate then fractionation of total serum alkaline phosphatase. Another possible marker for bone synthesis includes serum osteocalcin measurements. Osteocalcin contains γ-carboxyglutamic acid, which is a vitamin K-dependent protein, is 49 amino acids, represents about 20% of the noncollagenous component of the organic bone matrix, and undergoes variable processing that can lead to multiple possible immunoreactive peptides circulating in serum, which might profoundly confound the results of some assays. It appears to be a marker associated with osteoblast function, is deposited within the matrix, and thus may be variably released with resorption. There is some evidence that it might be associated with the process of mineralization. This marker appears to be substantially less useful than serum alkaline phosphatase for osteoblast activity and has unpredictable changes associated with it in Paget’s disease (see references [112–114,116,123,132]). In patients suffering from even mild chronic renal failure, the clearance of this peptide is significantly affected.
Serum levels of the type I procollagen carboxyterminal extension peptide have been shown to be highly correlated with trebecular bone formation as determined by histomorphometry [123]. This is particularly true in those patients with osteoporosis whose net loss of bone is associated with increased bone formation, but, unfortunately, their extent of bone resorption is more than their bone formation. It is not as predictive of changes in new bone synthesis in patients with low bone formation. This is probably due to the lack of specificity of this measurement. This assay measures new collagen synthesis from all collagenous tissues, not just bone. At low levels of new bone synthesis, new collagen synthesis in other tissues is probably at a higher rate, which then serves to confound the usefulness of the assay.

Typically, the urinary markers of resorption or osteoclast activity include the hydroxyproline-containing peptides or pyridinium cross-linked peptides, which serve as rapid predictors of changes in osteoclastic activity. The levels of the urinary resorption peptides may fall within hours of exposure to an antiresorptive agent [123]. The newer pyridinium crosslink markers are remarkably reproducible and are predominantly directly related to bone collagen resorption particularly in active disease states (see references [112,119,120,126,127,129,131,132]). Although the extent of absolute values of the individual markers varies when compared one to another, their net change after baseline seems to be useful to monitor therapeutic intervention and responsiveness [129].

There have recently been data evaluating the usefulness of the various available urinary pyridinium markers, either the free deoxypyridinium (Dpd), the N-terminal telopeptide, or C-terminal telopeptide pyridinium peptide. Cummings et al [133] demonstrated that in 410 women 67 years of age or older who were not prescribed hormone replacement therapy, those patients with higher urinary concentrations of the free Dpd marker within the higher quartiles had a higher risk for fracture and were correlated with lower bone density. More directly, a study of 7598 women, 75 years of age or older and followed for 22 months, sustained 109 hip fractures. High urinary levels of the free Dpd and the C-terminal telopeptide pyridinium peptides were correlated with lower bone mass at the hip and more hip fractures [134]. These two studies suggest what is obvious. The patients with high levels of the urinary markers for bone resorption have lower bone densities as determined by densitometry. Low bone mass is associated with an increased risk for fracture. Gannero et al [134] have demonstrated that the relative risk for a hip fracture in elderly women was increased if the patients had low bone mass as determined by standard bone densitometric techniques and high levels of the urinary markers for resorption [femoral neck BMD standard deviation (SD) less than 2.5 = odds ratio (OR) for future hip fracture of 2.7, femoral neck BMD SD less than 2.5 and either elevated levels of the C-terminal telopeptide pyridinium peptide or the free Dpd peptide had an increased risk for future hip fracture of OR, 4.7 and 4.1]. Thus, it is possible with the newer improved assays of urinary pyridinium crosslinks in development that these urinary peptide markers may be useful to predict future fracture risk. Those presently available have been approved for diagnostic use in the United States.
Measurements of skeletal mass

Standard radiologic measurements allow for the definition of skeletal architecture. However, the typical radiograph reveals only a semiquantitative assessment of skeletal mass [135]. In specific epidemiologic studies, the cortex of a specific bone, typically the midshaft of the second metacarpal, is accurately measured using radiogrammetry [136]. Although inexpensive and available, this technique provides little information about trabecular bone, which is the most metabolically active, and as noted, the area of bone most involved in post-menopausal osteoporosis. Instead, methods have been developed for quantization of cortical and trabecular bone mass as well as potential risk for fracture [137–145].

Single-photon densitometry is performed using an iodine [125] absorptiometric technique during which a radiation source with a fixed detector is directed over a bone or bones. This method is best to determine the mineral density of the distal radius. This area is predominantly cortical bone with some trabecular bone, which is considered to be less metabolically active than the trabecular bone found in the vertebral bodies or the femoral neck [137,143,144]. Age-related disease in men and women can be approximated by this measurement; however, as a single photon source, the amount of soft tissue can confound the results.

Dual-photon absorptiometry (DPA) (see references [137,138,143–145]), dual energy x-ray absorptiometry (DXA) [137,142–145], and quantitative computed tomography (QCT) (see references [139,143,145–148]) are used to accurately and reproducibly assess the mineral content of the vertebrae and femoral neck. DPA uses two separate photon energies obtained from a gadolinium [153] source that allows for distinction between the mineral content of bone and soft tissues. Short-term precision is between 1% and 2% [143]. DXA uses x-rays of two separate energies to analyze the distinctions between the mineral content of bone and the density of adjacent soft tissues. DXA is used to examine different skeletal sites and in addition to bone density can provide an estimate of total skeletal mineral. Short-term precision of this technique is between 0.5% and 1.2% [143–145]. QCT is the most expensive technology with a slightly higher dose of radiation per study. As noted, in patients with estrogen-deficient or glucocorticoid-induced osteoporosis, trabecular bone is lost more rapidly than cortical bone. QCT of the forearm or vertebrae is preferred in this setting because QCT is able to measure trabecular bone apart from the surrounding bony cortex. Spinal DXA in the lateral projection is used and appears to be nearly equivalent to spinal QCT. Spinal DXA in the anterior-posterior projection lacks sensitivity because the posterior elements of the spine, which are composed of cortical bone, are included in the measurement. In addition, many patients with osteoporosis are older and may have complicating osteoarthritis of the spine leading to hypertrophic boney changes that can alter the approximation of bone density. For these patients, measurement of the bone mineral density at the hip may be more accurate. For other patients, the most sensitive bone density measurements are made in cortical bone. In these clinical settings, measurement of the shaft of the...
radius, which is composed entirely of cortical bone, can be measured equally well by DXA, DPA, and pQCT (peripheral QCT). The method used depends on time, cost, and the clinical question being asked. In general, DXA is cheaper, faster, and more reproducible than DPA. There is increasing data that demonstrates that ultrasound of the calcaneous may be as predictive of risk for trabecular bone fracture as a spinal DXA [141].

Presently, DXA has become the measurement of choice for osteoporosis, and by using population standards, osteoporosis is defined in a patient with a bone density measurement of the spine that is 2.5 or greater standard deviations from the mean of the standard 35-year-old population in the appropriate gender (T score). Osteopenia is defined as a bone density between 1.0 and 2.5 standard deviations below the bone density of a standard 35-year-old population that is gender appropriate (T score). Thus, patients do not have to sustain a fracture to be diagnosed with this insidious problem. In addition, the Z score provides similar information regarding a patient’s BMD as it relates to age matched controls. Therefore, with this calculation, it is possible to screen for superimposed causes of accelerated bone loss [149].

DXA is used for bone mineral screening because it identifies individuals whose osteoporosis is sufficiently severe that it places them at increased risk for fracture. There is an exponential correlation between the fall in BMD and the rise in fracture risk. For approximately every 1 SD fall in bone mass as measured by a bone densitometer there is a twofold rise in risk for fracture [147]. Perimenopausal and postmenopausal women are at particular risk for osteoporosis (see references [35–44,143,150]). Patients with osteoporotic vertebral compression fractures also develop chronic pain syndromes, which can be hard to diagnose [40,150,151]. Most of these patients suffer from osteoarthritis as well as degenerative disc disease. Some investigators are using single-photon emission computed tomography bone scintigraphy (SPECT) to help differentiate acute vertebral compression fractures from other causes of back pain, such as osteoarthritis [152,153].

**Diagnosis**

The diagnosis of osteoporosis in a postmenopausal woman or older individual who presents with pain and a vertebral compression fracture is uncomplicated; however, before a pathologic fracture occurs the diagnosis of osteoporosis can be more difficult. As noted, radiograph changes are insensitive to early changes of osteoporosis, and clinical symptoms of pain are typically lacking. Additionally, there are no characteristic laboratory abnormalities associated with osteoporosis. The serum calcium, phosphate, and alkaline phosphatase are usually normal for age and sex. There may be hypercalciuria, and urinary hydroxyproline or hydroxyypyridinium excretion may be elevated indicative of increased bone resorption, but not invariably, and therefore these are not yet clinically useful
screening tests for diagnosis. The biochemical markers presently available to determine the extent of bone resorption, such as the hydroxypyridininium (pyridinoline) urinary markers represented by assays for the free pyridinoline peptides (Dpd), the n-terminal telopeptides of type I collagen, and the c-terminal telopeptides of type I collagen, have been useful to determine those patients who are in a state of high bone resorption, as well as to define the response to specific therapy but have not yet been shown to be useful as a screen for diagnosis or to predict fracture risk [101,112,116]. Markers of new bone formation have not been shown to be useful as a measure for osteoblast function in these patients [112,116,123].

Before the diagnosis of osteoporosis is assigned to a patient with risk factors for osteoporosis or a screening radiograph consistent with osteoporosis, it is prudent to exclude other diseases that are associated with osteoporosis. In addition to establishing that there is a normal hematocrit, white blood cell count, platelet count, and erythrocyte sedimentation rate along with normal serum chemistries, renal function, and liver tests, other laboratory tests that are useful in excluding diseases associated with osteoporosis include serum calcium, serum phosphorous, serum alkaline phosphatase, 24-hour urine calcium/creatinine clearance, plasma 25-(OH)D₃, and 1,25-(OH)₂D₃ levels. Elevated serum calcium suggests either carcinomatous skeletal metastases or hyperparathyroidism. Hypophosphatemia is usually present in osteomalacia, although in some circumstances the serum phosphorous levels may be normal; typically, the serum calcium is normal. Low 25-(OH)D₃ serum levels suggest hypovitaminosis D from either inadequate dietary sources, including states of malabsorption or low levels of exposure to sunlight. In the Northeastern part of the United States, it is not unusual for older, homebound people to become depleted of their vitamin D stores over the long winter. Urinary calcium excretion is usually normal or may be elevated in osteoporosis. Normal levels of urinary calcium essentially exclude hypovitaminosis D as a result of intestinal malabsorption but do not rule out a renal calcium or phosphate-leak syndrome. Concentrations of serum 1,25-(OH)₂D₃ should be normal in premenopausal patients with adequate renal function. However, serum 25-(OH)D₃ and 1,25-(OH)₂D₃ levels have been shown to be lower in elderly patients with osteoporotic hip fracture [76,77]. Serum parathyroid hormone may be elevated in states of secondary hyperparathyroidism as found in some patients with glucocorticoid-induced bone loss.

**Management**

The fundamental management goals for patients with osteoporosis are to prevent fractures, decrease pain when present, and maintain function. The drugs available today decrease the risk for further bone loss and reduce the risk of bone fracture when combined with nonpharmaceutical measures. Studies have
shown that women with multiple risk factors and low bone density are at high risk for fracture, and that this risk can be reduced by maintaining body weight, walking for exercise, avoiding long-acting benzodiazepines, minimizing caffeine intake, and treating impaired visual function (see references [42,48, 101,143,154]). It is important to educate patients about the risks of falling [42,101].

The first step to good therapeutic choices is an appropriate diagnosis. As noted, it is not difficult to diagnose a patient who has pain resulting from a vertebral compression fracture. The goal is to diagnose the patient with osteoporosis before they have sustained enough bone loss to be at risk for a fracture. Patients should be identified early who are at risk for future fracture based on their family history and other known risk factors. These patients should undergo a bone densitometry test to determine their bone mass as it relates to an age-matched cohort (Z score) and determines the T score. If the resultant BMD has a standard deviation of 1 or greater, then serious consideration needs to be given to close follow-up and potential therapy.

Once a patient has fractured, therapeutic interventions to decrease the pain include local physical measures, such as warm, moist packs to decrease muscle spasm or occasional cold compresses, gentle physical therapy, appropriate bed rest, and pharmacologic interventions, such as simple analgesics, nonsteroidal anti-inflammatory drugs, muscle relaxants when appropriate, and even the use of calcitonin for its acute analgesic effects.

The pharmacologic treatment strategies for the prevention and treatment of type I and type II osteoporosis include medications that decrease osteoclast-induced bone resorption (antiresorptive therapy) even though increased osteoclastic resorption likely does not play a key role in age-related disease affecting men and women 60 to 70. Therefore, in clinical states associated with decreased osteoblastic activity, an improved bone turnover balance can be restored by decreasing the resorption of bone by drug therapy while new bone formation is decreased naturally due to the aging of the osteoblast lineage of cells. There is also therapy available to increase bone mass by stimulating new osteoblastic activity using parathyroid hormone.

Antiresorptive drugs include calcium and vitamin D supplementation, hormone replacement therapy (HRT), such as estrogen supplementation in women, calcitonin either as parenteral therapy or as an inhaled product, and bisphosphonate therapy. Treatment aimed at stimulating osteoblasts and new bone formation includes sodium fluoride, androgens, and intermittent parenteral parathyroid hormone therapy. Because type II osteoporosis is related to decreased osteoblastic activity, drugs to stimulate osteoblast function would be preferable. Unfortunately, there are significant problems with several of the anabolic therapies, including the potential for virulization and hepatic toxicity because of androgens, or the potential for increased bone pain or the development of bone of poor quality associated with fluoride treatment. PTH treatment has been shown to be successful; however, combination therapy with bisphosphonates and PTH has been a problem [101,102].
Calcium, vitamin D, and calcitriol

Calcium supplementation of the normal diet increases bone mass in adolescents and reduces bone loss associated with advancing age (see references [40,102,107,154–159]). Calcium supplements should be given to all patients with low calcium intake (less than 400 mg/d), postmenopausal women, the elderly, and patients treated with glucocorticoids. Calcium supplements when given alone to women with established osteoporosis have shown variable results in reducing fracture risk in controlled trials [155,157,159]. Recommended total calcium intakes for white women (diet and supplementation) include 1000mg/day for adults, 1500 mg/d for postmenopausal women and women with known osteoporosis, and 1200 mg/d for adolescents [42,160–163].

Relative vitamin D deficiency, like calcium deficiency, is a problem in postmenopausal women, the elderly, and institutionalized people who do not have enough access to the sun. Serum 25-OH vitamin D3 and 1,25-(OH)2vitamin D3 levels are variable and thus not useful as clinical diagnostic tools except in patients with a history compatible with malabsorption; therefore, empiric treatment with vitamin D supplements is preferred [160–166]. Some studies have shown that vitamin D3 plus calcium appears to reduce the risk of hip and other nonvertebral fractures by as much as 43% in elderly institutionalized women [164]. Calcitriol therapy, though safe, requires careful monitoring of serum and urine calcium levels to avoid hypercalcemia and significant hypercalciuria.

Estrogen

Estrogen deficiency is now well established as a major cause of bone loss in postmenopausal women [167]. In young women with amenorrhea or ovulatory disturbances, cyclic medroxyprogesterone has been demonstrated to increase bone density, further demonstrating the central role that female sex hormones play in osteoporosis [168]. Estrogen replacement therapy is associated with increased bone mass, decreased urinary biochemical resorption markers, and reduced fracture rate in many studies [169–172]. Therapeutic regimens that include estrogen are more effective in protecting against osteoporosis than those that contain calcium alone (see references [101,154,155,163,173–187]). Estrogen replacement appears to be most effective at maintaining bone mass when begun soon after menopause and continued. This is due to the accelerated period of bone loss during the early postmenopause during which women may lose bone mass at the rate of up to 3% to 5% per year for approximately 5 to 7 years. Unfortunately, estrogen therapy has significant risks [188–192]. Unopposed estrogen therapy is associated with an increased incidence of uterine cancer, and there is also an increased cumulative risk for breast cancer in women who are treated with estrogen, which may be important in women with a family history of the disease. Furthermore, recent data has demonstrated that use of HRT is associated with an increased risk for acute myocardial infarction and stroke. Thus the use of HRT
has been relegated to only short-term use at low dose for those few patients with significant perimenopausal symptoms. However, there is continued use of the estrogen-like drugs or SERMs. Raloxifene is a commonly used drug for women with postmenopausal osteoporosis, but it does not have preventative effects on perimenopausal symptoms. It has been shown that raloxifene (60 mg/d) decreases the risk of vertebral fracture by 30%. Whether use of this agent prevents the development of breast cancer or heart disease is still not known [193].

Calcitonin

Salmon calcitonin inhibits bone resorption by decreasing osteoclast function by binding to high-affinity receptors [194–197]. Calcitonin is available in the United States as a subcutaneous injection and as an intranasal spray (200 U) for the treatment of osteoporosis [197–206]. In one study it has been shown to be effective in increasing bone mineral content in patients with normal or high bone turnover. Femoral bone mineral content decreased in that study, however, and there was no analysis of the effect of calcitonin on fracture rate [207]. Patients were treated in the standard fashion with calcium (500 to 1000 mg/d) and calcitonin 50 U SQ every other day for 2 years. Common side effects of calcitonin therapy included nausea and flushing, but these were seldom severe enough to warrant discontinuation of therapy. Calcitonin therapy is also hampered by cost and the inconvenience of injections. Though nasal salmon calcitonin appears to reduce spinal bone loss in early postmenopausal woman, it has not been shown to have any effect on the peripheral skeleton [198,199]. There is some evidence that calcitonin has analgesic effects, probably mediated centrally [208].

Bisphosphonates

The bisphosphonates are synthetic analogs of pyrophosphate, a naturally occurring substance that inhibits bone mineralization. The bisphosphonates have been shown to inhibit bone resorption by inhibiting the action of osteoclasts [193,209–220]. These compounds once absorbed orally or by intravenous injection are bound tightly to hydroxyapatite crystals. During the process of bone resorption, the bisphosphonates bound to the hydroxyapatite crystal are released, are taken up by osteoclasts, and inhibit the bone-resorbing function of these cells. Bone surfaces once coated with bisphosphonates also are less able to bind and activate osteoclasts that subsequently arrive.

The bisphosphonates clinically available for the treatment of osteoporosis include etidronate, alendronate, and risedronate. Another choice, pamidronate, is available as a parenteral drug to treat hypercalcemia of malignancy. Some studies have shown that etidronate given in cyclical fashion (400 mg for 2 weeks every 3 months) along with calcium supplementation (500 mg/d) increased spinal bone
density by 4% and reduced the rate of new fracture by 50% to 75% when compared with placebo. Unfortunately, there has been conflicting evidence regarding change in the vertebral fracture rate, and possible protective effects of etidronate on fracture rates in nonvertebral sites were not demonstrated.

Treatment with the next generation of bisphosphonates, such as alendronate or risedronate, has led to decreased fracture rates with years of continuous therapy at vertebral and nonvertebral sites, such as the hip and forearm, with no effect on mineralization. There is some evidence that bone mass continues to improve as measured by densitometry with continuation of these drugs. Other bisphosphonates, such as pamidronate, tiludronate, zolendronate, and ibandronate, are or soon will be available.

Although bisphosphonate therapy has been shown to be of benefit in specific patient populations, there are some risks with these drugs. The complicated intermittent therapy regimen with etidronate was developed because of drug-induced inhibition of mineralization. The intermittent dose decreases that effect. In addition, all bisphosphonates are poorly bioavailable and thus should be taken on an empty stomach to ensure some absorption. For alendronate and residronate, there are further important issues. The major noted toxicity in most clinical studies and in practice has been esophageal irritation. To reduce this effect, a bisphosphonate should be taken fasting first thing in the morning, on an empty stomach, with 8 ounces of water, and the patient should remain upright for 30 to 45 minutes before eating.

**Sodium fluoride**

Sodium fluoride therapy increases trabecular bone mass, but may at the same time decrease cortical bone mass even in the presence of adequate calcium supplementation [221–223]. Though patients receiving sodium fluoride might improve bone mass with a lower dose, confirmation of a benefit from sodium fluoride is lacking. A study employing a new formulation of sodium fluoride has demonstrated better results. When slow release sodium fluoride was used there were similar improvements in BMD at all sites without any one site containing cortical bone losing its content [221]. Although, sodium fluoride therapy clearly increases bone density and increases the activity of osteoblasts, some investigators continue to be concerned about the quality rather than quantity of the bone that is formed.

**Parathyroid hormone**

Traditional therapies for osteoporosis have been aimed at inhibiting bone resorption. Therapies that target increased osteoblast activity, replacing lost bone by increasing new bone formation, are now available. Various forms of parathyroid hormone therapy have been considered for years. One treatment available
now is the use of the synthetic (1–34) amino acid fragment of PTH with or without 1,25 (OH)₂ D [224–232]. Small daily doses of PTH have been shown to stimulate bone formation in osteoporotic patients without increasing bone resorption or causing hypercalcemia. The accumulated evidence shows that there may be large increases in bone density over short periods of time correlated with decreased fracture risk of about 65% after 21 months of treatment. The use of this powerful anabolic therapy when combined with bisphosphonates is still controversial [230].

**Androgens**

Because androgen deficiency likely plays an important role in age-associated bone loss, androgen replacement might stimulate osteoblasts to produce new bone. Androgens have been shown to decrease urinary calcium excretion, increase muscle mass (thereby improving strength and perhaps stability), and perhaps provide an improved sense of well-being [233]. Stanozolol and nandrolone augment bone mass in postmenopausal women, but at the expense of lowering serum HDL concentrations [233,234]. Other concerns include the potential for virulization, alteration in blood lipid levels, which might increase risk for heart disease, and increased risk for hypertension. These concerns, along with the risk of hepatotoxicity when androgens are used for more than 3 months, have limited the usefulness of this form of therapy.

The male patient with osteoporosis presents a unique problem. As in the case of the female hypogonadal patient, the male patient will also benefit from repleting calcium, ensuring adequate vitamin D intake, an appropriate exercise regimen, and the use of antiresorptive agents if applicable. If the patient is hypogonadal, the use of testosterone by injection or patch is appropriate [101].

**Strontium ranelate**

A new agent, strontium ranelate, with a novel mechanism of action acting on bone resorption to reduce the rate of bone growth (as do bisphosphonates) and on bone formation to promote the growth of new bone (as does the parathyroid hormone) has recently been approved for osteoporosis in Europe [235,236]. The recommended dose is 2 g daily. The drug comes in the form of granules to be taken as a suspension in a glass of water. Given the slow absorption, it should be taken at bedtime, preferably at least 2 hours after eating. Food, milk and derivatives, and medicinal products containing calcium may reduce bioavailability by 60% to 70%, so should be avoided for at least 2 hours. Sontium ranelate is reported to reduce the risk of vertebral fractures by 49% after a year, and by 41% over the 3 years of the study. Side effects include an increased frequency of nausea, diarrhea, and headache in the first few months.
of treatment, not usually requiring withdrawal of treatment, and an excess of venous thromboembolism.

In summary, effective therapies are available for the older patient with osteoporosis. The approach is critical to ensure an optimal quality of life in these individuals who suffer a disease that clearly is treatable.

References

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