

# Secondary Osteoporosis

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## Abstract

Secondary osteoporosis occurs as a consequence of various lifestyle factors (eg, eating disorders, smoking, alcoholism), disease processes (eg, endocrinopathies, gastrointestinal tract disease, hepatobiliary disease), and treatment regimens that comprise corticosteroids or chemotherapeutic agents. Some of the disease entities underlying secondary osteoporosis may be clinically silent and identified only during evaluation for documented osteoporosis. The pathogenesis of osteoporosis in these settings is typically multifactorial. The loss of bone may be direct or indirect but ultimately is related to altered osteoblast or osteoclast function. Causes of secondary osteoporosis should especially be investigated in men at all ages and in premenopausal women with atraumatic fractures. In addition, patients with known risk factors should be evaluated. Early recognition and intervention are essential to prevent further loss of bone mass and to prevent fragility fractures.

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Osteoporosis occurs when the normal processes of bone formation and resorption are no longer coupled, leading to a net loss of bone and thus to an increased risk of fracture. Osteoporosis is diagnosed by measuring bone mineral density (BMD) using dual-energy x-ray absorptiometry (DXA). According to the World Health Organization, osteopenia is defined as BMD between 1 and 2.5 standard deviations (SDs) below that of young adults; osteoporosis is defined as BMD >2.5 SDs below this norm.<sup>1</sup> BMD measurements obtained in this manner reflect bone mineral content as well as the size of the bone. Considering the typically larger bone in men than in women, it is important to use gender-specific controls when interpreting results.

Osteoporosis may be primary or secondary. Primary osteoporosis is more common, occurring as a result of menopause or the aging process and accounting for approximately

80% of cases of osteoporosis in women. Although secondary osteoporosis is less common, it is becoming more frequently recognized, especially in men, in whom it accounts for 40% to 60% of all cases of osteoporosis, and in premenopausal women. In addition, although osteoporosis in postmenopausal women is usually linked to their hormonal status, secondary causes are now being identified more often. As is true of the primary disease, secondary osteoporosis is frequently diagnosed after the patient has sustained a fracture.

Secondary osteoporosis can arise as a consequence of many variables, including lifestyle factors, endocrinopathies, systemic disease, organ dysfunction, and neoplastic conditions, or as the result of treatment of these and other conditions (Table 1). Because of improved diagnosis and treatment, patients with chronic and life-threatening conditions are surviving longer. This improved surviv-

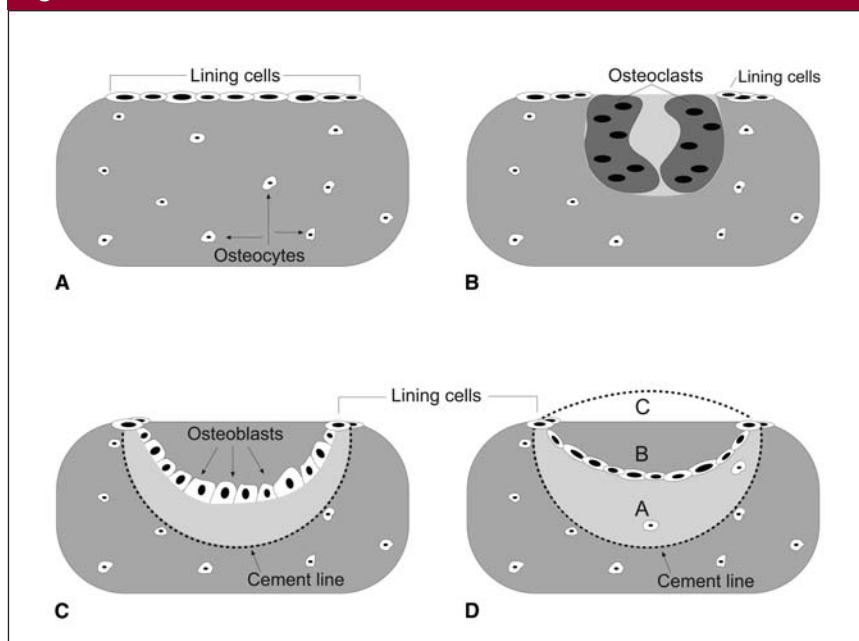
**Table 1**

**Causes of Secondary Osteoporosis**

Lifestyle factors
Anorexia nervosa
Excessive protein intake
Smoking
Excessive alcohol intake
Endocrinopathies
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Type 1 diabetes mellitus
Hypogonadism
Systemic diseases
Gaucher's disease
Mastocytosis
Rheumatoid arthritis
Ankylosing spondylitis
Psoriasis
Organ dysfunction
Cystic fibrosis
Asthma
Chronic obstructive pulmonary disease
Renal failure
Primary biliary cirrhosis
Inflammatory bowel disease
Celiac sprue
Organ transplantation
Medications
Glucocorticoids
Diuretics
Antiepileptics
Methotrexate
Cyclosporin A
Excess thyroid hormone replacement
Alkylating chemotherapeutic agents
Gonadotropin-releasing hormone agonist
Neoplastic conditions
Multiple myeloma

al has led to increased recognition of the long-term effects of these conditions and their treatments on bone. When present in young patients, secondary osteoporosis can interfere with development of peak bone mass, increasing the risk of future

**Figure 1**



The bone remodeling cycle. **A**, Quiescent phase. Inactive bone surface lined with bone-lining cells. Neither bone resorption nor formation is yet occurring on this region of bone surface. **B**, Resorption phase. Osteoclasts remove a discrete packet of bone, creating a lacuna. **C**, Formation phase. Osteoblasts form bone matrix, which fills in the lacuna. The cement line is the boundary between the newly formed bone and the surface of the lacuna. **D**, Quiescent phase. Inactive bone surface demonstrating the completed remodeling cycle. The new surface may be under-filled (A), exactly filled (B), or overfilled (C), reflecting respectively a local decrease in bone mass, no change, or an increase in bone mass. (Adapted with permission from Turner RT: Skeletal response to alcohol. *Alcohol Clin Exp Res* 2000;24:1693-1701.)

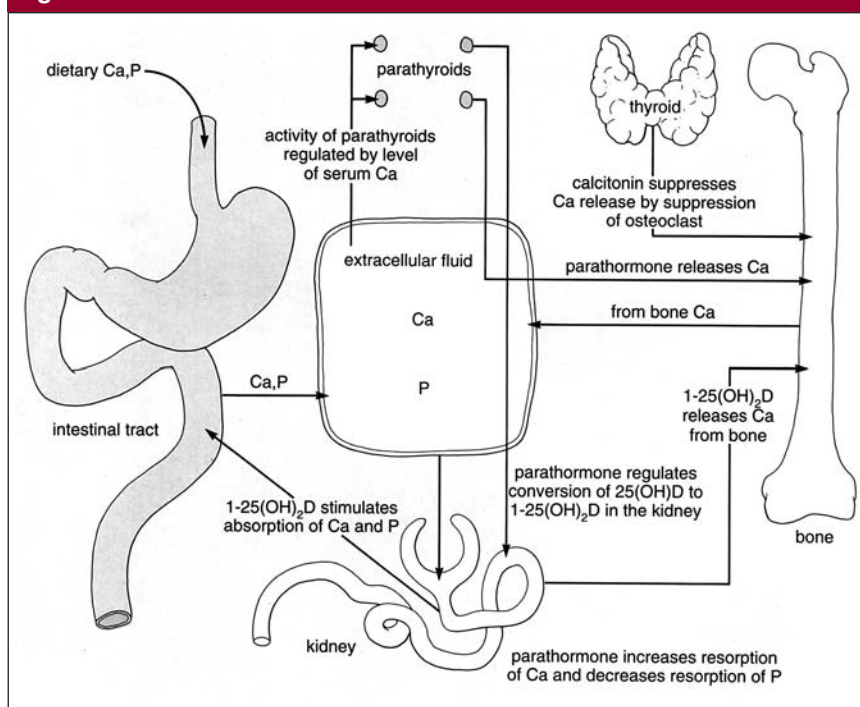
fracture. When present in older adults, the rate of physiologic bone loss is enhanced.

**Regulation of Bone Homeostasis**

Bone remodeling occurs continuously, initiated by resorption by osteoclasts, followed by formation by osteoblasts (Figure 1). Under normal conditions, the structure of bone is maintained by a tight coupling between these two events. Both osteoblasts and osteoclasts originate in the bone marrow: osteoblasts from pluripotential mesenchymal stem cells and osteoclasts from the hematopoietic cell lineage. Circulating endocrine hormones regulate the interaction of these cells. For example,

parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D ( $1,25[\text{OH}]_2\text{D}_3$ ) stimulate production of interleukin-6 by osteoblasts; interleukin-6 in turn stimulates the generation of osteoclasts.<sup>2</sup> The production and release of PTH and of  $1,25[\text{OH}]_2\text{D}_3$ , as well as of calcitonin, is proportional to serum levels of calcium and phosphorus. Successful production and release is dependent on normal functioning of the kidneys, liver, and gastrointestinal tract (Figure 2). Thyroid hormone likewise affects the acquisition and maintenance of bone, in part through regulation of the activation frequency.<sup>3</sup> Bone formation may be indirectly measured by serum osteocalcin; bone resorption may be evaluated by measuring products of collagen breakdown, such as

Figure 2



Calcium (Ca) and phosphorus (P) metabolic pathways associated with the maintenance of normal concentrations of calcium in extracellular fluid. (Reproduced with permission from Bullough PG: *Atlas of Orthopedic Pathology*. Hampshire, UK: Gower Press, 1992, p 75. Copyright Mayo Foundation, Rochester, MN.)

N-terminal telopeptide crosslinked with collagen type I.

Bone remodeling also depends on sex hormones. Estrogen primarily exerts its effect on bone through regulation of osteoclasts. Regulation is achieved by inhibiting osteoclast formation and activity while increasing the apoptotic rate of these cells, perhaps through interaction with interleukin-6. Controversy exists regarding the role of estrogen in osteoblast generation, lifespan, and function. In fact, the effects of estrogen may lead to an increase in all of these areas. Much of the action of testosterone occurs as a result of its aromatization to estrogen.<sup>4</sup> Testosterone exerts an additional effect primarily on osteoblasts by leading to a modest increase in proliferation and a more pronounced decrease in apoptosis. Both estrogen and testosterone may affect bone by modulating the responsiveness of osteoblasts to

PTH.<sup>5</sup> In addition, the effects of both estrogen and testosterone are regulated by sex hormone-binding globulin, the levels of which normally increase with aging. This results in a lowering of the bioavailable fraction of these hormones and a consequent decrease in BMD. In addition, gonadal hormones affect development of bone morphology during growth. Men typically have larger bones, resulting in a lower risk of fracture for a given bone mineral content compared with women.

## Lifestyle Factors

### Diet

The acquisition and maintenance of peak bone mass relies on adequate nutrition, especially intake of calcium, vitamin D, and protein. Calcium requirements vary with age and may be met through normal diet or supplementation. Vitamin D is es-

sential to allow gastrointestinal tract absorption of calcium. This vitamin may be acquired either through exposure to sunlight or through dietary supplementation. Inadequate intake of calcium or lactose intolerance may lead to decreased serum calcium and increased bone resorption.

Adequate intake of dietary protein is essential for the production of hormones that regulate bone formation, and it may be an independent factor in the maintenance of bone mass. However, high-protein, low-carbohydrate diets may result in a subclinical metabolic acidosis, leading to increased renal calcium excretion and thus to elevated PTH levels. Markers of bone resorption in these patients are elevated, whereas markers of bone formation remain unchanged.<sup>6</sup>

Disordered eating also may lead to loss of bone mass, in some patients presenting as the triad of eating disorder, amenorrhea, and osteoporosis ("female athlete triad"). Osteoporosis in this setting is likely secondary to alterations in estrogen production as well as to other factors, such as chronic energy deficit and secondary hypercortisolism. In a study of young women with a variety of eating disorders, Carmichael and Carmichael<sup>7</sup> found that those with bulimia or anorexia-bulimia had BMD measurements close to those of age-adjusted normals. In contrast, patients with anorexia nervosa were found to have substantially lower BMD measurements and a higher incidence of secondary amenorrhea. However, BMD did not vary based on hormonal status, thus implicating factors other than loss of estrogen in the loss of bone mass. Likewise, in a study of female runners, Cobb et al<sup>8</sup> found that among eumenorrheic runners, those with eating disorders were more likely to have reduced BMD. Although runners with eating disorders were more likely to have alteration in their menses, having both conditions led to no further reduction in BMD than did having either one alone.

## Smoking

Smoking results in a diminution of bone formation, presumably a result of the inhibitory effects of nicotine on osteoblast function. No direct nicotine effect appears to occur to osteoclasts, although bone resorption can be secondarily elevated because of lower gastrointestinal tract calcium absorption. The effect of smoking on BMD is more pronounced in men and premenopausal women. This effect appears to be related both to the amount and duration of smoking. However, the impact of smoking on fracture risk is more notable in postmenopausal women, likely a reflection of the duration of smoking as well as confounding risk factors in this group. In a population-based cohort study, Baron et al<sup>9</sup> found an increased risk of hip fracture among current smokers, adjusting for body mass index (BMI) and hormone replacement therapy. In addition, postmenopausal women were found to have an increased risk of hip fracture after a shorter duration of smoking than were premenopausal women.

## Alcohol

Alcohol has both direct and indirect effects on bone. It appears to directly decrease osteoblast differentiation and function while indirectly enhancing bone resorption through effects on the calcium–vitamin D axis and on gonadal hormones. However, the clinical significance of the effect of alcohol is not known, primarily because of limitations in human studies. Most studies of the effect of alcohol involve alcoholic individuals, who have numerous additional risk factors for the development of osteoporosis, such as malnutrition, low BMI, and hepatic disease. In addition, most of the studies have been done in men. The effect of alcohol on bone may be proportional to the amount of alcohol consumed; a moderate intake has been associated with a higher BMD, especially in women.<sup>10</sup>

## Endocrinopathies

### Hyperthyroidism

Secondary osteoporosis can arise in patients with endocrine dysfunction, both idiopathic and iatrogenic. One of the more common causes of osteoporosis is hyperthyroidism, in which there is shortening of both the formation and, more often, the resorption phase of bone turnover.<sup>3</sup> Thus, hyperthyroidism results in an elevated turnover state, with a reduction in trabecular bone thickness. Increasingly negative net calcium balances are seen compared with normal control subjects. In addition to this increased direct effect on bone turnover, Obermayer-Pietsch et al<sup>11</sup> noted a possible indirect effect mediated through vitamin D metabolism. They reported a higher incidence of the genotype BB polymorphism of the vitamin D receptor gene among hyperthyroid patients who were osteoporotic, compared with similar patients with normal or osteopenic BMD.

The overall prevalence of endogenous hyperthyroidism is 2.7% in women<sup>12</sup> and increases with age; this condition is less prevalent in men. Most studies show decreased BMD in patients with hyperthyroidism<sup>11</sup> and increased risk of hip fracture.

The effect of exogenous thyroid hormone administration depends on the disease process for which the hormone is given. Patients who have received suppressive doses of L-thyroxine in the treatment of thyroid carcinoma demonstrate changes in BMD similar to the changes in patients with endogenous hyperthyroidism. However, most hypothyroid patients treated with replacement hormone therapy do not suffer a decrease in BMD or an increased risk of fracture<sup>12</sup> unless the replacement dose is excessive. In a cohort study of women treated with thyroidectomy and subsequent thyroid hormone replacement, an increased rate of hip fracture over time was

noted; however, this increase was related to increasing age and the presence of other risk factors for the development of osteoporosis, rather than to the extent of surgery or the use of hormone replacement therapy.<sup>13</sup>

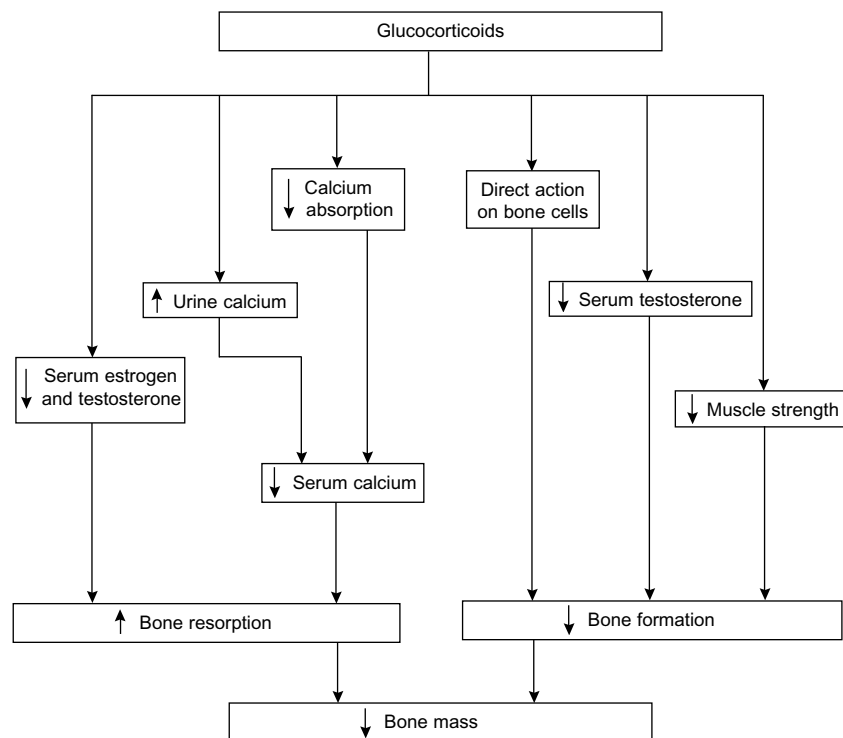
### Hyperparathyroidism

Primary hyperparathyroidism, the third most common type of endocrinopathy, occurs either from increased hormone production from a parathyroid adenoma or as the result of an increased set point for serum calcium. The elevated levels of PTH result in increased bone turnover, with loss of bone more notable at cortical than cancellous bone sites.<sup>14</sup> In spite of the increased turnover, Khosla and Melton<sup>15</sup> found a relative risk of 3.5 for vertebral fracture, of 1.5 for femur fracture, and of 1.9 for forearm fracture in these patients. Being female and increased age were independent risk factors for fracture.

### Type 1 Diabetes Mellitus

Studies using animal models show that insulin stimulates osteoblast cell replication and bone collagen synthesis. Studies in diabetic rats have noted a decrease in the indices of bone formation; administration of insulin corrects these changes.<sup>16</sup> Similarly, clinical studies show lowered levels of serum osteocalcin in some patients with type 1 diabetes mellitus,<sup>17</sup> indicating a decrease in bone formation activity. However, the effect of diabetes mellitus on bone appears to depend on the type of diabetes involved.

Using DXA, an increased incidence of osteopenia or osteoporosis of the femoral neck and lumbar spine has been found in men and women who are insulin-dependent,<sup>17</sup> but with no correlation between BMD and degree of diabetic control.<sup>18</sup> However, Muñoz-Torres et al<sup>18</sup> noted lower BMD in patients with diabetic complications, such as retinopathy, neuropathy, or neph-

**Figure 3**

Model of glucocorticoid-induced osteoporosis. (Reproduced with permission from *Prevention and Treatment of Gluco-corticoid-Induced Osteoporosis*. CME monograph. Atlanta, GA: American College of Rheumatology, 1998.)

ropathy. In a study of the bone density of patients with renal failure, the presence of type 1 diabetes mellitus was found to enhance the risk of lower BMD.<sup>19</sup> Unclear is the impact of age of onset of diabetes mellitus, reflecting both the duration of the effects of the disease as well as a potential effect on the accumulation of peak bone mass. Muñoz-Torres et al<sup>18</sup> noted a weak negative correlation between duration of diabetes and BMD. Overall, a twofold increase in fracture incidence has been noted in patients with type 1 diabetes mellitus.<sup>20</sup>

Changes in BMD in patients with non-insulin-dependent diabetes mellitus are less consistent; authors report increased, decreased, and normal BMD measurements. In a cross-sectional study of patients with type 2 diabetes mellitus, some of whom were not taking hypoglycemic agents,

van Daele et al<sup>21</sup> found increased BMD in men and women, after adjusting for age and BMI, compared with control subjects. The incidence of nonvertebral fractures was equal to or less than that of controls. Patients newly diagnosed with type 2 diabetes mellitus, presumably hyperinsulinemic because of insulin resistance, also demonstrated this increase in BMD. Although the increase in BMD in patients with type 2 diabetes mellitus could be attributed to the protective effects of increased weight in these patients, van Daele et al<sup>21</sup> corrected the BMD for BMI. This indicates that other factors might influence bone density, such as the anabolic effect of insulin on bone.

### Cushing's Syndrome

Endogenous Cushing's syndrome results from excessive adrenal glucocorticoid production, either as the

result of excessive adrenocorticotropic hormone (ACTH) production or from an adrenocortical tumor. Glucocorticoids affect bone metabolism through a variety of mechanisms, including increased sensitivity to PTH, suppressed synthesis of sex hormones, decreased renal resorption of calcium, decreased gastrointestinal tract absorption of calcium, and a decrease in osteoblast number and function<sup>22,23</sup> (Figure 3).

There appear to be sex differences in the presentation of Cushing's syndrome, given that this condition is more common in women yet presents at an earlier age in men. In addition, men are more likely to demonstrate the clinical features of cortisol excess, including osteoporosis.<sup>24</sup> Fragility fractures can be the presenting manifestation in both sexes; cross-sectional studies show that 30% to 50% of patients experience fractures.<sup>22</sup>

### Gonadal Hormone Deficiency

Although physiologic loss of sex hormones occurs during the aging process, pathologic alteration in the production of these hormones can lead to secondary osteoporosis. This alteration may occur through idiopathic disruption of the hypothalamic-pituitary-axis or through gonadal function. However, secondary osteoporosis occurs most commonly as a consequence of iatrogenic manipulation of hormonal status, such as in the management of prostate or breast cancer.

Androgen ablation therapy (surgical or medical) is effective in reducing prostate tumor growth, especially in advanced disease. However, this loss of testosterone can result in an elevated turnover loss of bone mass. Daniell<sup>25</sup> noted that 48% of men with at least 9 years of follow-up after orchiectomy had sustained at least one osteoporotic fracture. Use of gonadotropin-releasing hormone agonists also results in lower levels of serum testosterone and estradiol. Af-

ter an average of 41 months of therapy, Stoch et al<sup>26</sup> found BMD in these patients to be 6.5% to 17.3% lower than in control subjects, depending on the site measured. Markers of bone formation and resorption in these patients were elevated, indicating increased bone turnover. Based on estimates of the rates of bone loss, 48 months of androgen deprivation therapy are required to develop osteopenia in the lumbar spine.<sup>27</sup> The overall incidence of osteoporotic fracture in patients receiving gonadotropin-releasing hormone agonists has been reported as 5%.<sup>28</sup>

In women with breast carcinoma, use of the synthetic antiestrogen, tamoxifen, can impact BMD variably, dependent upon the menopausal status of the patient. Premenopausal women taking tamoxifen have been found to have a significant ( $P < 0.001$ ) loss of BMD compared with age-matched control subjects.<sup>29</sup> The change in lumbar spine BMD was seen initially in the first year of treatment, with a calculated average change of 1.44% per year. Bone loss was also seen in the hip, but this reached significant levels only after 3 years of treatment. Although theoretically the risk of fragility fracture in premenopausal women should appear to be increased after treatment with tamoxifen, this has not been validated clinically.<sup>29</sup> In postmenopausal women, tamoxifen functions as a weak estrogen, resulting in an increase in BMD at both the spine and hip. The clinical significance of this increase has not been established.

### Systemic Disease

Various systemic diseases and their treatments also may affect bone mass. Inflammatory conditions, such as rheumatoid arthritis and ankylosing spondylitis, may increase the risk of a patient's developing osteoporosis because of the impact of inflammatory cytokines on bone. In addition, these patients may

be more sedentary, leading to further bone loss. Treatment for these conditions typically involves corticosteroids and other medications known to affect bone mass.

Mastocytosis is another systemic condition that affects bone. Patients with mastocytosis frequently present with fragility fractures. They also may manifest other symptoms reflecting increased systemic histamine release, such as gastrointestinal tract symptoms.

Gaucher's disease also is a systemic condition that affects bone. It is the most common inherited lysosomal storage disease, resulting from mutations leading to deficiency of glucocerebrosidase, with a prevalence of 1 in 40,000 to 60,000 people.<sup>30</sup> Glucocerebrosidase accumulates in monocytes and macrophages in various organ systems. Bone marrow infiltration resulting in localized cortical thinning is the most obvious finding; however, generalized osteopenia/osteoporosis is also frequently seen. Although not completely understood, bone loss may be a result of the increased production of interleukin-6.<sup>30</sup> In addition, there is a failure of both osteoblast and osteoclast function in patients with Gaucher's disease.

### Organ Dysfunction

#### Pulmonary Disease

Osteoporosis has been noted among patients with chronic pulmonary disease, such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma. As with secondary osteoporosis noted in other disorders, the etiology is multifactorial. Normal bone density, as measured by DXA, has been reported in as few as 7% of patients with cystic fibrosis.<sup>31</sup> Patients with cystic fibrosis have been noted to have lower 25(OH)D<sub>3</sub> levels, a lower BMI, and a history of corticosteroid therapy, all independent risk factors for the development of osteoporosis. Low serum levels of 25(OH)D<sub>3</sub> result from

changes in the gastrointestinal tract, leading to malabsorption. These low levels are noted even in patients receiving oral vitamin D supplementation, with<sup>32</sup> or without<sup>33</sup> pancreatic enzyme replacement. Donovan et al<sup>33</sup> found that serum 25(OH)D<sub>3</sub> levels and BMI more strongly correlate with BMI than a history of corticosteroid therapy. As a result of low levels of vitamin D and consequent secondary hyperparathyroidism, bone resorption markers have been found to be elevated in patients with cystic fibrosis, compared with control subjects,<sup>31</sup> especially in patients with more severe pulmonary disease. However, markers of formation were not significantly increased, indicating that formation is unable to compensate for increased rate of bone resorption. Donovan et al<sup>33</sup> noted a 19% incidence of vertebral fractures and 41% incidence of fracture, overall, in adults with cystic fibrosis.

Patients with COPD also exhibit osteoporosis as a result of multiple factors. These patients frequently have a history of smoking. In addition, patients with COPD typically have a low BMI, as a result of poor nutrition and increased metabolic demand as the disease progresses. In a comparison of COPD patients, with or without osteoporosis, Incalzi et al<sup>34</sup> found that the nutritional status of the former, as measured by BMI, was notably worse. In addition to overall nutritional status, patients with COPD have low serum vitamin D levels, either as a result of poor dietary intake or lack of sun exposure as their functional ability deteriorates. As with most chronically ill patients, patients with COPD are hypogonadal. Treatment of COPD is based on the administration of oral and/or inhaled corticosteroids, an independent risk factor for the development of osteoporosis.

Similarly, patients with asthma have a variety of risk factors for the development of osteoporosis, including decreased physical activity and use of corticosteroids. Although oral

corticosteroids have been found to contribute to osteoporosis, results for inhaled corticosteroids are ambiguous, most likely because of confounding factors such as intermittent use of oral corticosteroids and variable drug penetration. A negative association has been reported between cumulative inhaled corticosteroid dose and BMD, with doubling of the corticosteroid dose associated with a decrease in lumbar spine BMD of 0.16 SDs.<sup>35</sup>

### Renal Disease

Metabolic bone disease is a frequent consequence of renal dysfunction, usually taking the form of a high-turnover state (typically a result of secondary hyperparathyroidism) but may also be low turnover bone disease (adynamic or osteomalacia). The pattern of bone response is influenced by the age of the patient, degree of renal disease, and management of hyperparathyroidism. Osteomalacia is primarily the result of a deficiency in  $1,25(\text{OH})_2\text{D}_3$  and is seen less frequently as an isolated finding. The development of adynamic bone disease is associated with excessive suppression of PTH by exposure to calcium.<sup>36</sup> The etiology of osteoporosis in renal failure is multifactorial and may be the result of alterations in calcium-phosphorus-vitamin D metabolism, secondary hyperparathyroidism,<sup>19</sup> decreased physical activity levels, and decreased sex hormone formation.<sup>37</sup> Uremia may also lead to decreased bone formation, as high levels of urea inhibit osteoblast function.

Changes in BMD may begin during the early, asymptomatic phases of renal failure. In a cross-sectional study of predialysis renal failure patients, Rix et al<sup>19</sup> found a prevalence of osteoporosis of 30%, compared with 10% among a group of age-, sex-, and BMI-matched controls. The reduction in BMD was significantly ( $P < 0.05$ ) related to the degree of renal failure and the early onset of renal failure, possibly reflecting the

impact of renal failure on the acquisition of peak bone mass. The effect of duration of hemodialysis on bone density is not clear-cut. Stein et al<sup>38</sup> found no relationship, indicating that much of the loss of BMD occurred before the initiation of dialysis.

### Gastrointestinal Tract Disease

Secondary osteoporosis may be seen in patients with gastrointestinal tract disorders, including celiac disease and inflammatory bowel disease. Osteoporosis can be secondary to calcium and vitamin D malabsorption by involved areas of bowel, systemic effects from the primary inflammatory process, or treatment regimens.

Celiac disease, characterized by changes in the mucosa of the small intestine after ingestion of gluten or gluten-related proteins, may result in impaired absorption of vitamin D and calcium, with prolonged malabsorption, secondary hyperparathyroidism may develop.<sup>39,40</sup> Low bone density is noted in nearly all patients with untreated celiac disease, with osteoporosis found in more than a quarter of the patients.<sup>41,42</sup> The clinical manifestations of this disorder are highly variable, with overt, subclinical, and silent forms. Although onset in childhood typically presents with gastrointestinal tract symptoms, approximately half of adults with celiac disease have no such history.<sup>41</sup> Osteopenia has been reported in up to one third of adults who present without gastrointestinal tract symptoms. Thus, celiac sprue may be first diagnosed during an evaluation for osteoporosis. The impact of celiac disease on BMD has been reported to be more significant in men than in premenopausal women, suggesting a protective effect of estrogen.<sup>42</sup>

The effect of other types of inflammatory bowel disease on BMD is less consistent than that of celiac disease. Cross-sectional studies have

reported a prevalence of reduced BMD in more than 40% of patients with inflammatory bowel disease,<sup>43</sup> with an annual mean loss of BMD of between 1% and 2%. Although there is no consensus, most studies have noted no impact of disease type (Crohn's disease versus ulcerative colitis) on bone density, which, at diagnosis, is frequently normal.<sup>44</sup> However, Dresner-Pollak et al<sup>45</sup> reported that the greatest rate of bone loss during the course of inflammatory bowel disease was in patients with the most active bone resorption at the time of diagnosis, as measured by serum bone resorption markers. Ardizzone et al<sup>46</sup> reported that the rate of BMD loss was related to disease duration in Crohn's disease and to cumulative lifetime corticosteroid dose in ulcerative colitis. Thus, loss of BMD may be related to the disease process in Crohn's disease and to the use of corticosteroids in ulcerative colitis.

This conclusion was further demonstrated by Ulivieri et al,<sup>47</sup> who evaluated BMD in 38 patients with mild ulcerative colitis that was treated with only low doses of corticosteroids. For women at both baseline and 6-year follow-up, there was a statistically significant negative correlation between the use of corticosteroids and lumbar spine BMD (baseline,  $P = 0.0006$ ; follow-up,  $P = 0.003$ ). The rate of fracture in patients with inflammatory bowel disease, both Crohn's disease and ulcerative colitis, was found in one study to be 40% greater than that in the general population.<sup>43</sup> The incidence of fractures was highest in the wrist/forearm compared with incidence in the hip, spine, and rib. Finally, the incidence of fractures increased with advancing age at all anatomic sites.

### Hepatobiliary Disease

Secondary osteoporosis is frequently found in patients with cholestatic liver disease, including primary biliary cirrhosis and primary sclerosing cholangitis, and in

nearly all patients with end-stage liver disease. Osteoporosis is found more commonly in patients with primary biliary cirrhosis than in those with primary sclerosing cholangitis. As in other forms of secondary osteoporosis, the pathogenesis in cases associated with hepatobiliary disease is multifactorial. An increased incidence of inflammatory bowel disease exists among patients with primary sclerosing cholangitis, which, as noted earlier, is a risk factor for the development of osteoporosis. Patients with hepatobiliary disease display abnormalities in vitamin D metabolism, such as malabsorption of vitamin D, as well as decreased cutaneous synthesis of vitamin D, resulting from jaundice, with consequent secondary hyperparathyroidism. Hydroxylation of vitamin D is also diminished in patients who have progressed to liver cirrhosis. In addition, bilirubin was found to diminish osteoblast function *in vitro*.<sup>48</sup> Bone loss may be exacerbated by the use of corticosteroids in the treatment of these diseases. In a study of patients with primary biliary cirrhosis, Menon et al<sup>48</sup> found that 87% had BMD in the range of osteopenia or osteoporosis. BMD was inversely correlated to the severity of the disease; patients with more severe disease at baseline also were found to have the highest rates of subsequent bone loss.

### Organ Transplantation

Although organ dysfunction may result in loss of BMD, transplantation of these organs, while improving clinical and most indices of metabolic function, may lead to further loss of bone mass as a result of immunosuppressive therapy, especially corticosteroids and cyclosporine A. Sheiner et al<sup>49</sup> noted a 9.4% incidence of osteoporosis in liver transplant patients at a median of 2.1 months after liver transplant; 13.8% of patients had osteoporotic fractures, with a female-to-male ratio of 14:5.

However, BMD in these patients may improve with increased time from transplantation as liver function improves. Conversely, BMD after kidney transplantation shows no such improvement.

Although the production of  $1,25(\text{OH})_2\text{D}_3$  may improve following kidney transplantation, the secondary hyperparathyroidism that occurs with renal failure may persist. Patel et al<sup>50</sup> reported that up to 44.3% of all kidney transplant patients had osteoporosis on evaluation at a mean of 5.1 years since transplantation. The incidence of osteoporosis varied by the site measured and was consistently lower in male patients; 16.4% were found to have a low-impact appendicular fracture. Serum parathyroid hormone level and bone resorption markers were higher in the group of patients that had sustained fracture. This persistence of hyperparathyroidism and bone turnover has been confirmed by others.<sup>51</sup>

When the corticosteroid dose is decreased or eliminated in the immunosuppressive regimen after transplantation, there is a subsequent increase in BMD, suggesting that the other immunosuppressive drugs have a lesser effect on BMD.<sup>52</sup>

## Medications

### Glucocorticoids

Glucocorticoids are the most frequent cause of medication-induced osteoporosis. The effect of corticosteroids on BMD and fracture is related to dose and duration of treatment. An increased risk of fracture, especially at the spine and hip, has been reported for patients taking  $>2.5$  mg/d of glucocorticoids.<sup>53</sup> In male COPD patients, incidence of both single and multiple vertebral fractures was greater in patients who received systemic corticosteroids than in those who used inhaled corticosteroids.<sup>54</sup> It has been reported that the likelihood of vertebral fracture increases by 35% for every 1 SD in cumulative cortico-

steroid dose. Approximately 30% to 50% of patients taking systemic glucocorticoids on a long-term basis will have a fracture.<sup>55</sup> Although inhaled corticosteroids may have an effect on bone mass, there may be a dosage threshold below which inhaled corticosteroids do not significantly affect bone mass.<sup>56</sup>

### Diuretic Agents

Diuretic agents affect bone through their alteration of renal calcium resorption. Thiazide diuretic agents lead to a net increase in renal calcium resorption, which in turn leads to an increase in BMD, according to most studies. In a study of older patients using thiazide diuretics, there was a notably lower risk of hip fracture than was seen in control subjects.<sup>57</sup> However, the duration of usage of this medication to realize the lower fracture risk has not been identified. Unlike thiazide diuretic agents, loop diuretic agents lead to a net loss of calcium. This loss can potentially lead to hyperparathyroidism and bone loss. However, there are only limited, contradictory data available on the effect of nonthiazide diuretic agents on BMD.<sup>58</sup>

## Neoplastic States

Patients with malignancies may present initially with decreased bone mass, as a result of factors such as decreased physical activity, impaired nutrition, and low BMI, as well as systemic effects of the tumor, such as the effects in patients with multiple myeloma. Although focal lytic lesions are common in multiple myeloma, patients may also present with diffuse osteoporosis. Sixty percent of patients have diffuse bone loss; 5% of these are without evidence of focal lytic lesions.<sup>59</sup> Bone loss is a result of the diffuse spread of myeloma cells as well as the production of osteoclast-activating factors by these cells.<sup>60</sup>

Treatment of malignancies may lead to bone loss through a variety of

**Table 2****Malignant Tumors in Which Osteoporosis May Occur as a Result of Therapy**

Tumor	Mechanism
Breast carcinoma	Hypogonadism
Prostate carcinoma	Hypogonadism
Testicular carcinoma	Hypogonadism
Hodgkin's and non-Hodgkin's lymphoma	Hypogonadism
Acute lymphatic leukemia	Chemotherapy (methotrexate) Tumor osteopathy Posttransplantation osteopathy
Osteosarcoma	Methotrexate/ifosfamide
Brain tumor	Methotrexate/growth hormone deficiency after cranial radiation therapy
Thyroid carcinoma	Suppressive therapy with L-thyroxine
Gastric carcinoma	Malnutrition/malabsorption
Hepatocellular carcinoma	Post-transplantation osteopathy
Myeloma	Tumor osteopathy

Adapted with permission from Pfeilschifter J, Diel IJ: Osteoporosis due to cancer treatment: Pathogenesis and management. *J Clin Oncol* 2000;18:1570-1593.

pathways, both indirect and direct (Table 2). One such indirect effect is through induction of hypogonadism; however, treatment regimens containing alkylating agents may also result in hypogonadism because of direct toxicity to the gonads. In women, these treatment regimens frequently result in ovarian failure and the onset of premature menopause. Seventy-one percent of premenopausal women who received adjuvant chemotherapy became amenorrheic, all within 1 year of the initiation of therapy. These women were reported to have mean BMD values 10% lower than the women who had not received chemotherapy.<sup>61</sup> In a study of breast cancer patients who had received chemotherapy at least 2 years previously, Headley et al<sup>62</sup> noted that the patients who became amenorrheic had a mean spinal BMD 14% lower than that of women who either had not become amenorrheic or had resumed menses. This finding implies that the impact on BMD from chemotherapeutic agents resulted from

the loss of ovarian function, not as a direct influence of these agents on bone. The gonadotoxic effect of chemotherapeutic agents in men is less pronounced because of the slower proliferative activity of testicular cells.

Chemotherapeutic agents, such as methotrexate, doxorubicin, and cyclophosphamide, may affect bone through nonhormonal pathways because those agents have been found to inhibit osteoblast replication as well as production and mineralization of bone matrix.<sup>63</sup>

Researchers have noted an effect on bone mass in patients treated with hematopoietic cell transplant, either autogenous peripheral stem cells or allogeneic bone marrow. As a result of pretransplant chemotherapy, there is a dose-dependent toxicity to bone marrow osteoprogenitor cells.<sup>64</sup> After transplantation, the bone marrow stromal cells (osteoblast precursors) are of recipient origin (ie, exposed to chemotherapeutic toxicity), but the peripheral mononuclear cells, the source of os-

teoclasts, are of donor origin. Thus, osteoblast replication and matrix production may be diminished compared with osteoclast activity, leading to progressive uncoupling of bone remodeling. In these patients, the greatest bone loss has been found to occur in the first year after transplantation, although Ebeling et al<sup>65</sup> reported continued bone loss in some patients up to the median follow-up (30 months) in their study. A fracture incidence of 10.6% has been reported during the first 3 years after transplantation, with half of these fractures occurring during the first year.<sup>66</sup>

Finally, as a result of cancer treatment during childhood, patients may not attain peak bone mass, thus entering the period of normal senescent bone loss with lower bone reserve. This diminished reserve accentuates the normal loss of bone mass with aging. In adult survivors of pediatric malignancies, BMD may be reduced, although markers of bone formation and resorption are within normal limits. The combination of these values would indicate that bone remodeling returned to normal during adulthood, but that peak bone mass was not attained.<sup>67</sup>

## Evaluation

Unfortunately, many patients with osteoporosis are identified only after they have sustained a fracture. Once a fragility fracture has occurred, an evaluation for osteoporosis should be initiated by the treating orthopaedic surgeon, the primary care physician, or an internist with a special interest in osteoporosis. A thorough history should include information regarding prior fractures, family history of fractures, smoking history, amount of alcohol use, and current or previous illnesses and treatments. Evaluation also should address symptoms of possible endocrinopathies, such as weight loss associated with hyperthyroidism, hot flashes or menstrual irregularities

(seen in low-estrogen states), or fatigue, change in libido, and loss of endurance (associated with low testosterone levels). A history of gastrointestinal tract complaints (eg, diarrhea, food intolerances) should be obtained to address the possibility of conditions such as lactose intolerance, inflammatory bowel disease, or celiac sprue. General complaints, such as chronic anemia or new onset of fatigue, may point to a bone marrow disorder, such as multiple myeloma. Physical examination may reveal other manifestations of primary disease processes, such as striae or muscle-wasting in hypercortisolism and signs of hypercalcemia, suggesting possible hyperparathyroidism.

The diagnosis of osteoporosis should be established with a DXA scan. This also allows documentation of a baseline BMD and, in addition, indicates whether changes in BMD are normal for the patient's age or whether an underlying disease process exists. When the degree of bone loss is greater than expected for the patient's age, sex, or race, it is especially important to search for secondary causes. Frequently, these causes are subtle and difficult to identify. Initial studies may include a complete blood count and chemistry panel. Serum chemistries allow identification of renal or hepatic dysfunction, hypercalcemia, or hypophosphatemia.

Tannenbaum et al<sup>68</sup> found that among healthy, osteoporotic women, 32% had an underlying condition leading to secondary osteoporosis, the most common being hypercalciuria, malabsorption, hyperparathyroidism, vitamin D deficiency, and exogenous hyperthyroidism. Eighty-six percent of these women could be identified by obtaining a serum calcium and PTH level, a 24-hour urine calcium level, and, for women on thyroid-replacement medication, thyroid-stimulating hormone level. The sensitivity increased to 98% when a serum 1,25(OH)<sub>2</sub>D<sub>3</sub> level

was added, although this added marked expense to the evaluation. Similarly, evaluation of otherwise healthy men with osteoporosis showed that the most common causes of secondary osteoporosis were hypogonadism, use of corticosteroids, and alcoholism.<sup>69</sup>

Additional laboratory tests should be obtained to confirm a diagnosis when the history, physical examination, or initial studies point to a particular disease process. These laboratory tests may include 1,25(OH)<sub>2</sub>D<sub>3</sub>, serum intact parathyroid hormone, thyroid function tests, luteinizing hormone, follicle-stimulating hormone, testosterone, estrogen, serum hormone binding globulin, and serum immunoelectrophoresis (to identify multiple myeloma). More specific investigations, such as a low-dose dexamethasone suppression test, may be used to evaluate patients suspected of having Cushing's syndrome.

## Management

Treatment of secondary osteoporosis entails education and attempts at modification of lifestyle factors, such as ensuring an adequate diet (including calcium and vitamin D), discontinuing smoking, limiting alcohol intake, and including appropriate exercise. Specific interventions for individual disease processes include avoiding excessive replacement of thyroid hormone, performing parathyroidectomy for hyperparathyroidism, and administering the lowest dose of corticosteroids effective in disease control. The use of corticosteroids for inflammatory diseases may lead to improved bone mass by decreasing the production of cytokines and limiting the effect of these on osteoclasts. However, this needs to be balanced with the detrimental effects of corticosteroids on bone. For disease processes for which there is not a specific intervention, bisphosphonates have been found to be effective in

improving BMD and decreasing fracture risk.

## Summary

Secondary osteoporosis may occur as a result of numerous disease entities. Some of these conditions may be clinically silent and identified only during evaluation for documented osteoporosis. In addition, loss of bone mass may occur consequent to established disease processes or related treatment protocols, such as organ transplantation or chemotherapy. The pathogenesis of osteoporosis in these settings is typically multifactorial, including poor nutrition, alteration in the calcium-vitamin D axis, or induction of hypogonadism.

For atraumatic fractures, especially those occurring in men and premenopausal women, a workup for osteoporosis should include evaluation of underlying disease processes that could contribute to decreased bone mass. To lower the risk of additional fractures and preserve quality of life in these patients, interventions should be targeted toward limiting further bone loss and decreasing the risk of falls.

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