



Secondary osteoporosis

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Bone loss occurs during the normal aging process. The term “primary” osteoporosis refers to osteoporosis that results from the involutional losses associated with aging and, in women, additional losses related to natural menopause. Osteoporosis that is caused or exacerbated by other disorders or medication exposures is referred to as “secondary” osteoporosis [1–3]. The prevalence of secondary causes of osteoporosis varies according to the population studied. Secondary causes are most commonly found in premenopausal women and in men with osteoporosis, with the reported prevalence among men as high as 64% [4]. Secondary causes are not limited to these groups, however. As many as 30% of postmenopausal women with osteoporosis have been found to have other conditions that may have contributed to their bone loss [3]. There are many causes of secondary osteoporosis (Box 1), including hypogonadism, endocrine disorders, gastrointestinal (GI) diseases, transplantation, genetic disorders, and medications [5]. This article describes the major etiologies and provides a framework for the diagnostic investigation of patients suspected of having secondary osteoporosis.

Premenopausal estrogen deficiency and hypogonadism

Gonadal hormones play a vital role in achieving and maintaining bone mass. Estrogen deficiency during adolescence is associated with decreased bone acquisition, which leads to low peak bone mass. Estrogen deficiency, which develops later in life after peak bone mass is reached, is associated with increased bone resorption, which results from increased secretion of osteoclastogenic cytokines. Increased bone resorption leads to more rapid bone loss than occurs in estrogen-replete subjects [5]. Several conditions in

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Box 1. Secondary causes of osteoporosis

Genetic disorders

- Ehlers-Danlos
- Glycogen storage diseases
- Gaucher disease
- Hemochromatosis
- Homocystinuria
- Hypophosphatasia
- Marfan syndrome
- Menkes steely hair syndrome
- Osteogenesis imperfecta
- Porphyria
- Riley-Day syndrome
- Hypogonadal states

Hypogonadal states

- Androgen insensitivity
- Anorexia nervosa/bulimia
- Athletic amenorrhea
- Hyperprolactinemia
- Panhypopituitarism
- Premature menopause
- Turner and Klinefelter syndromes

Endocrine disorders

- Acromegaly
- Adrenal insufficiency
- Cushing syndrome
- Diabetes mellitus
- Hyperparathyroidism (1° and 2°)
- Thyroid disease

Gastrointestinal diseases

- Gastrectomy
- Inflammatory bowel disease
- Malabsorption
- Celiac disease
- Primary biliary cirrhosis

Hematologic disorders

- Sickle cell disease
- Thalassemia
- Hemophilia
- Multiple myeloma
- Leukemias and lymphomas
- Systemic mastocytosis

Rheumatologic diseases

Ankylosing spondylitis

Rheumatoid arthritis

Nutritional deficiencies

Calcium

Magnesium

Vitamin D

Drugs

Anticoagulants (heparin and warfarin)

Anticonvulsants

Cyclosporines and tacrolimus

Cytotoxic drugs

Glucocorticoids (and adrenocorticotrophic hormone)

Gonadotropin-releasing hormone agonists

Methotrexate

Thyroxine

Miscellaneous

Alcoholism

Amyloidosis

Chronic metabolic acidosis

Congestive heart failure

Cystic fibrosis

Emphysema

End stage renal disease

Idiopathic hypercalciuria

Idiopathic scoliosis

Immobilization

Multiple sclerosis

Organ transplantation

Parenteral nutrition

Sarcoidosis

which deficiency of gonadal hormones contributes to decreased bone acquisition or increased bone loss are discussed below.

Turner syndrome

Turner syndrome is characterized by diminished or absent ovarian estrogen production due to total or partial X chromosome monosomy that leads to gonadal dysgenesis. Patients with Turner syndrome frequently have osteoporosis and other skeletal abnormalities, including short stature, cubitus valgus, and delayed skeletal maturation [5]. Longitudinal studies demonstrate failure to achieve age-appropriate increases in BMD once puberty begins in their age-matched counterparts. Adults with Turner

syndrome have decreased bone mineral density (BMD), ranging from 19% to 27% below age-matched control subjects, regardless of corrections for small body habitus [5]. Similar reductions in BMD have been found in women with other causes of primary amenorrhea, suggesting that lack of estrogen, rather than chromosomal abnormalities, is the cause for low BMD seen in Turner syndrome [6]. BMD may increase significantly with estrogen replacement therapy, but it usually does not normalize, probably because the deficit is the result of decreased bone acquisition rather than increased bone loss [5].

Athletes with amenorrhea

The effects of exercise on the growing skeleton are complex and influenced by many factors, including the nature and intensity of the activity, area of skeleton primarily involved, body weight, and dietary calcium intake. Although increased physical activity is usually associated with higher BMD, women who exercise excessively may develop hypothalamic amenorrhea. Weight loss, low caloric intake, and previous history of irregular menses increase the risk of developing exercise-induced amenorrhea. Low BMD is a consequence of exercise-induced amenorrhea [5]. The syndrome of disordered eating, amenorrhea, and bone loss in athletes is often referred to as the “female athlete triad.” In one study, women athletes with amenorrhea had BMD that was on average 14% below eumenorrheic women athletes [7]. Significant reductions in BMD have been found in women who have missed 50% of their expected menses by 20 years of age. The most severe losses occur at the lumbar spine, a site characterized by relatively large amounts of metabolically active cancellous bone [5,7].

Eating disorders

The association between anorexia nervosa and osteoporosis has been clearly demonstrated by many studies. Patients with anorexia may be at increased risk for osteoporosis because of several associated endocrine abnormalities, including estrogen deficiency, secondary hyperparathyroidism related to low dietary calcium and vitamin D, excess endogenous cortisol production, low levels of IGF-1, and malnutrition [7]. Those in whom the disease developed during adolescence, which is the time of peak bone acquisition, may be more severely osteoporotic. The decrease in BMD is prominent in sites high in cancellous bone. Most biopsy studies suggest that osteoporosis rather than osteomalacia is the histologic lesion [5]. Some studies have demonstrated improvement of BMD with recovery from anorexia, defined as restoration of weight and resumption of menses. However, several studies have found that BMD deficits persist after recovery. A recent cross-sectional study by Hartman et al [8] found that BMD had not fully returned to normal in patients who had been recovered

from anorexia for an average of 21 years. This group found that the largest deficits in BMD were at the femur and not the lumbar spine, in contrast to previous studies. No correlation was observed between BMD and duration of anorexia or age at onset of the illness [8].

Hyperprolactinemia

Patients with hyperprolactinemia and hypogonadotropic hypogonadism have decreased BMD compared with control subjects. An inverse relationship exists between duration of hyperprolactinemia and BMD. The crucial role of estrogen deficiency in the development of osteoporosis in patients with hyperprolactinemia has been demonstrated by several studies in which serum estradiol rather than serum prolactin levels correlate with BMD. Moreover, hyperprolactinemic women with oligomenorrhea or normal menses have higher BMD than their amenorrheic counterparts [5,7].

Dopamine agonist therapy usually restores menses and may improve BMD in some patients with hyperprolactinemia [9]. In one study, an improvement in BMD was seen in only 56% of patients who had restoration of menses [5]. Another possible contributing factor is elevated levels of parathyroid hormone (PTH)-related peptide (PTHrP), which have been reported in patients with hyperprolactinemia. A significant negative correlation has been demonstrated between serum concentrations of PTHrP and BMD Z-scores in hyperprolactinemic patients [10].

Klinefelter syndrome

Men with Klinefelter syndrome have an XXY karyotype, hypogonadism, and may have osteoporosis. An inverse relationship has been reported between serum testosterone level and BMD, suggesting that the bone loss in Klinefelter syndrome is related to hypogonadism rather than to a genetic defect. A recent study found increased markers of bone resorption and decreased markers of bone formation and significantly decreased forearm BMD in patients with Klinefelter syndrome [11].

Androgen insensitivity

In androgen insensitivity syndrome (AIS), partial or complete lack of response to androgens is caused by mutations in the androgen receptor. Patients with AIS have 46, XY genotypes and variable degrees of virilization and sexual ambiguity. Expression of AIS may range from complete AIS characterized by a female phenotype that lacks axillary and pubic hair to normal masculinization with variable androgen resistance. Marcus et al found that individuals with complete AIS had significantly reduced lumbar spine BMD, whereas those with partial AIS did not [12]. After adjustment for the tall stature of these patients, the deficits in BMD were more

pronounced. Compliance with estrogen replacement therapy was associated with significantly higher BMD, although even patients with excellent compliance had significant deficits in BMD. Thus, osteopenia in patients with AIS seems to be exacerbated by inadequate estrogen replacement [12].

Endocrine disorders

Thyroid disease

Thyroid hormone excess is associated with enhanced osteoclast and osteoblast activity [3]. With chronically elevated serum T4 levels, bone resorption is increased to a greater extent than formation, resulting in net negative bone balance and increased rates of bone loss [5]. Histomorphometric studies show an increased surface area of unmineralized bone matrix, increased numbers of osteoclasts, resorption pits, and an increased ratio of resorption to formation surfaces. The bone remodeling cycle is shortened, primarily because of a decrease in formation period with subsequent failure to completely replace bone that has been resorbed [13].

Deleterious skeletal effects of thyroid hormones have been demonstrated in patients with endogenous and exogenous thyroid hormone excess. These effects are influenced by gender, menopausal status, other risk factors for osteoporosis, and severity of thyroid disease [5]. In premenopausal and postmenopausal women with thyrotoxicosis, BMD has been reported to be decreased by 10% to 30% [5]. Epidemiologic studies suggest that thyrotoxic patients are at increased risk for fracture and that fractures occur at earlier ages [13]. Most studies have found that BMD improves, but does not completely recover, with successful therapy of thyrotoxicosis. The etiology of thyrotoxicosis does not seem to affect the skeleton to as great an extent as the degree of thyroid hormone excess [14]. Studies of BMD in men with thyrotoxicosis have been too few to yield conclusive results [5].

Common metabolic abnormalities in hyperthyroid patients are related to the primary increase in bone resorption. These include suppressed serum levels of PTH and 1,25-dihydroxyvitamin D and elevated calcium levels. Hypercalciuria, hyperphosphaturia, and impaired intestinal absorption of calcium have also been reported [3].

Women with endogenous subclinical hyperthyroidism due to toxic multinodular goiter, Grave disease, or solitary autonomous nodule may or may not have decreased BMD [5]. Similarly, the effect of exogenous subclinical hyperthyroidism resulting from suppressive therapy for thyroid cancer or goiter on BMD is variable. The literature suggests that thyroid hormone excess from any source that is associated with suppressed serum thyroid stimulating hormone (TSH) concentrations should be viewed as a risk factor for osteoporosis, and patients should receive appropriate evaluation and treatment [5]. Thyroid hormone replacement that is not

associated with TSH suppression is also not associated with substantial detrimental effects on BMD [13].

Diabetes

Several factors could contribute to bone loss associated with type 1 diabetes, including excessive renal calcium losses, secondary hyperparathyroidism related to osmotic diuresis, and deficiency of insulin and IGF-1, which are important trophic factors for bone growth and formation [2]. The relationship between diabetes and osteoporosis is controversial [2]. Patients with type 1 diabetes mellitus on average have reductions in appendicular BMD of approximately 8%. Studies of the axial skeletons of patients with type 1 diabetes have yielded discrepant results. The effects of gender or duration on BMD are also uncertain.

The literature concerning the effects of type 2 diabetes on BMD is similarly inconsistent. BMD has been reported as decreased, unchanged, and even increased in these patients [15,16]. The obesity common in type 2 diabetics may protect against osteoporosis. Stress fractures of the tarsal and metatarsal bones are common in diabetic patients. Whereas some epidemiologic studies have found an increased rate of femoral neck fracture in diabetic patients, recent studies have found no difference in risk of fracture between diabetic patients and control subjects [2].

Hemochromatosis

Hemochromatosis is a genetic disease in which there is excessive intestinal iron absorption and subsequent intracellular iron accumulation. An acquired form of the disorder exists in patients with thalassemia, sideroblastic anemia, or any condition requiring multiple blood transfusions. Organ dysfunction and multiple endocrinopathies can occur as a result of the excess iron deposition. Hypogonadism, diabetes, and anterior pituitary dysfunction are seen in hemochromatosis and may contribute to bone loss. In addition, hepatic fibrosis commonly develops and may interfere with 25-hydroxylation of vitamin D [2]. Studies evaluating BMD and fracture risk in patients with hemochromatosis are few but suggest that patients with this disease often have decreased BMD and increased propensity to fracture [17,18]. A recent study of 31 patients with genetic hemochromatosis found reduced BMD in 22 patients and osteoporosis in 9 patients. Osteoporosis was found to correlate with degree of iron overload in these patients [19].

Acromegaly

The association between acromegaly and osteoporosis is unclear. In children, growth hormone (GH) stimulates IGF-1 production and linear bone growth. However, the effects of GH on the adult skeleton, particularly when secreted in excess, are uncertain. Although studies have found decreased BMD

in acromegalic patients, this reduction is likely related to the hypogonadism that often accompanies this disorder [2]. Recent studies of eugonadal patients with acromegaly have not found deficits in BMD [20]. In eugonadal acromegalic patients, GH may have anabolic effects on the skeleton [21]. These data are supported by histomorphometric studies that have found increased cancellous bone volume and trabecular plate thickness. An increased risk of fracture has not been demonstrated in acromegalic patients [2].

Hyperparathyroidism

The classic bone disease of primary hyperparathyroidism, osteitis fibrosa cystica, is rarely seen today. However, skeletal demineralization may occur [22], most commonly at sites with a high proportion of cortical bone. Spine BMD is usually preserved in mild forms of primary hyperparathyroidism [22], although a subgroup of patients with preferential loss of spinal bone density has been identified [23,24]. There has been considerable controversy regarding the risk of fractures in patients with primary hyperparathyroidism. However, a recent study by Vestergaard et al found an increased risk of fracture of the forearm, vertebrae, and lower extremities in patients with primary hyperparathyroidism. The increased fracture risk was seen as early as 10 years before parathyroid surgery, and fracture risk normalized within 1 year of parathyroidectomy [25].

Glucocorticoid excess

For a detailed discussion of glucocorticoid excess, see the article by Saag in this issue. Exogenous glucocorticoid excess is the most common cause of secondary osteoporosis. Cushing syndrome (ie, endogenous glucocorticoid excess) is much less common but can lead to rapidly progressive severe osteoporosis when it does occur [3].

GI disease

Adequate dietary supplies of calcium, phosphorous, and vitamin D are crucial for proper bone growth and maintenance [26]. Conditions that interfere with normal intestinal absorption of these essential skeletal building blocks can cause profound bone disease. In addition, patients suffering from chronic GI or other illnesses may be homebound and may have minimal exposure to sunlight and high rates of malnutrition. Moreover, a number of GI diseases are treated with glucocorticoids, which contribute to bone loss.

Celiac disease

Celiac disease, or gluten-sensitive enteropathy, is a disorder in which the ingestion of gluten and related proteins causes inflammatory injury to the mucosa of the small intestine and resultant malabsorption. The most

common features of celiac disease are diarrhea, steatorrhea in severe cases, and iron deficiency. Children may present only with failure to thrive or with diarrhea and abdominal distention. The prevalence of celiac disease is difficult to determine because many patients have atypical symptoms or are completely asymptomatic. Celiac disease can be diagnosed from serologic tests for antiendomysial and antigliadin and tissue transglutaminase antibodies. However, the gold standard remains small bowel biopsy. The treatment is a gluten-free diet [27].

Celiac disease is an important but commonly overlooked cause of secondary osteoporosis. In one study of patients with postmenopausal osteoporosis, 12% were found to have antigliadin antibodies [4]. Although osteomalacia and osteoporosis have been reported in association with celiac disease, osteoporosis is the most common lesion [28]. The prevalence of low bone mass in patients with celiac disease varies according to age at diagnosis and age when treatment with a gluten-free diet was initiated. At diagnosis, as many as 80% of adults have reduced BMD and 60% of children have growth retardation. BMD often improves after institution of a gluten-free diet [26], although some patients have persistent osteopenia despite treatment [26]. Lumbar spine osteoporosis has been reported in 26% to 34% of patients with celiac disease; femoral osteoporosis is less common [29,30]. Patients with celiac disease have an increased risk of fracture that is higher among patients who are not following a gluten-free diet [31]. Reduced BMD may be seen in patients who have few or no GI symptoms. The initiation of a gluten-free diet may be associated with improvements in BMD. A recent study of patients who had been treated for celiac disease found significantly reduced distal forearm BMD and much less severe deficits at lumbar and femoral sites. Serum PTH and $1,25(\text{OH})_2\text{D}$ were also elevated in these patients. PTH correlated negatively with forearm BMD, suggesting that secondary hyperparathyroidism related to malabsorption may contribute to bone loss in patients with celiac disease [32].

Postgastrectomy bone disease

Osteoporosis and osteomalacia have been found in patients after total gastrectomy and Bilroth II procedures [33]. Studies of postgastrectomy patients have found an increased prevalence of osteopenia and fracture. The bone disease in these patients is likely related to reduced absorption of calcium and vitamin D and to mild degrees of fat malabsorption [26]. However, increased fracture risk also may be related to associated conditions common in this population, such as advanced age, glucocorticoid use, thyroid disease, and chronic anticoagulation. Low BMD is more common in women after gastrectomy, with observed prevalence rates ranging from 24% to 86%. The rates in men were lower (22% to 41%) but still significantly higher than in control subjects. Several investigators have found increased rates of fracture of the spine and hip in postgastrectomy patients. A recent study of women 5

years or more after gastrectomy reported a vertebral fracture prevalence of 20% [16].

Inflammatory bowel disease

Increased prevalence rates of osteopenia and fractures have been reported in association with Crohn disease and ulcerative colitis [26]. Studies suggest that the association between low BMD in Crohn disease is at least in part related to glucocorticoid therapy. However, malabsorption and ileal resection with resultant disruption of the enterohepatic circulation also contribute to bone loss. In ulcerative colitis, bone loss may be solely the result of steroid treatment [33].

Pancreatic insufficiency

Patients with isolated pancreatic insufficiency rarely have clinically significant bone disease. When bone disease does occur in such patients, other contributing factors, such as associated cholestasis and alcohol abuse, should be considered [26]. Haaber et al recently reported decreased bone mass in 62% of patients with chronic pancreatitis [34]. However, in 79% of the patients in their study, the pancreatic disease was associated with alcohol abuse. Thus, it was not possible to distinguish between the effects of alcohol and pancreatic insufficiency.

Children and adults with cystic fibrosis (CF) commonly develop exocrine pancreatic insufficiency. Markedly decreased BMD and extremely high fracture rates are also frequent complications of CF. However, patients with CF have many additional risk factors for osteoporosis, including calcium and vitamin D malabsorption, delayed puberty, reduced sex steroid production, and increased serum concentrations of cytokines secondary to chronic pulmonary infections. The reduction in BMD compared with age-matched control subjects increases as patients with CF progress through puberty, most likely related to reduced sex steroid production [26], resulting in low peak bone mass in many patients.

Hepatic disease

Liver function affects bone physiology through several mechanisms: hepatic conversion of parent vitamin D to 25-OHD, synthesis of vitamin D transport proteins, enterohepatic circulation of vitamin D metabolites, and promotion of intestinal vitamin D and calcium absorption by bile. The potential for bone disease is increased when any of these mechanisms is disrupted.

Although primary biliary cirrhosis (PBC) is associated with osteoporosis and osteomalacia, osteoporosis is a more common result. The bone disease of PBC is multifactorial and may result from malabsorption of calcium, phosphorus, and vitamin D and from increased urinary losses of vitamin D conjugates. Serum concentrations of 25-OHD tend to be low. Bone biopsies

are consistent with low turnover osteoporosis. Moreover, because PBC is predominantly a disease of middle-aged women, its skeletal effects may be superimposed upon losses related to postmenopausal estrogen deficiency. BMD is low, and the prevalence of fractures is increased [26]. The prevalence of vertebral fracture is 20% [16]. BMD is more profoundly decreased in the axial than the appendicular skeleton and is lower than in patients with other chronic liver diseases, such as chronic hepatitis and alcoholic or postnecrotic cirrhosis.

Chronic active hepatitis (CAH) is associated with an increased incidence of fracture and reduced BMD. Glucocorticoids are commonly used in the management of CAH, and whether CAH affects bone in the absence of steroid therapy has not been well studied [32,35]. Low BMD has been reported in patients with cirrhosis due to hepatitis B and C and correlates with severity of hepatic disease. Biochemical data in these patients suggest that bone turnover is increased [36], possibly related to liver inflammation and increased circulating cytokines [26].

Osteopenia and fractures are common among patients with alcoholic liver disease. Osteopenia has been reported in 50% of male alcoholics. Vertebral and rib fractures have been reported in as many as 30%. The prevalence of fractures is higher in patients with alcoholic cirrhosis than with any other type of liver disease. However, this may be in part related to an increased propensity for falls and violence. Bone disease in these patients is likely multifactorial and related to malnutrition, dietary calcium and vitamin D deficiency, increased urinary calcium and magnesium losses caused by ethanol, and direct toxic effects of alcohol or one of its metabolites on bone-forming osteoblasts. Abstinence from alcohol seems to halt the progression of bone disease and may cause some degree of reversal.

Transplantation osteoporosis

Organ transplantation has become an increasingly common treatment for end-stage renal, hepatic, cardiac, and pulmonary disease. Survival rates after transplantation have dramatically improved over the past several years. As a result, the long-term complications of organ transplantation, such as osteoporosis, are attracting more attention [37]. The pathogenesis of osteoporosis in transplantation patients is complex. Candidates for organ transplantation often have the accepted risk factors for osteoporosis, including older age, Caucasian race, vitamin D deficiency, postmenopausal status, physical inactivity, and excessive tobacco and alcohol use. They are often exposed to medications that cause bone loss, such as glucocorticoids, loop diuretics, and heparin. In addition, particularly in the instance of renal or hepatic failure, end-stage organ failure may influence mineral homeostasis and cause bone loss before transplantation. However, the main factor contributing to bone loss and fracture in transplant recipients is thought to be immunosuppressive therapy with glucocorticoids and with cyclosporine

A and tacrolimus (FK506). Glucocorticoids, used in virtually all post-transplant regimens, are well known to cause osteoporosis [37]. Cyclosporine A and tacrolimus cause significant bone loss in animal models. However, their effects in human subjects are controversial, in part because they are usually given in combination with glucocorticoids [38].

Kidney transplantation is the most common type of solid organ transplantation [37]. In addition to the usual pre-transplant risk factors, patients undergoing kidney transplantation often have some form of renal osteodystrophy, including hyperparathyroidism, osteomalacia, osteosclerosis, and adynamic or aplastic bone disease. After transplantation and restoration of renal function, serum phosphate and 1,25(OH)₂D normalize, and parathyroid hormone levels decline. However, some degree of elevation may persist for years after transplantation, and, in many patients, PTH may never normalize.

Many cross-sectional studies have found diminished bone mass in patients after kidney transplantation. Longitudinal studies demonstrate rapid lumbar spine loss during the first 3 to 18 months after transplantation ranging from 3% to 9%, with the greatest losses during the first 6 months. However, significant ongoing vertebral losses may occur as long as 8 to 10 years after transplant. Fracture prevalence in renal transplant recipients is above normal [39]. In nondiabetic patients, fracture prevalence ranges from 7% to 11%. In contrast, those transplanted for diabetic nephropathy have much higher fracture prevalence—as high as 45%. Fractures involve the long bones and metatarsals more often than vertebrae or ribs, possibly because of PTH-related catabolic effects on cortical bone [37].

Patients with end-stage heart disease have been found to have low BMD before transplantation. Vitamin D deficiency and secondary hyperparathyroidism related to prerenal azotemia are also common. After cardiac transplantation, osteoporosis and fractures are common. The prevalence of vertebral fracture in cardiac transplant recipients ranges from 18% to 50%. The most rapid bone loss occurs during the first 6 to 12 months after cardiac transplantation. Fracture incidence is also highest during this period, ranging from 10% to 35% [37]. In more recent years, lower glucocorticoid doses have been associated with lower rates of bone loss and fracture.

The rates of bone loss and fracture may be very high after liver transplantation. The incidence of fracture is greatest during the first year and has been reported to range from 24% to 65%. Patients with primary biliary cirrhosis seem to have higher rates of fracture post-transplant than patients with other types of hepatic disease. The most common sites of fracture are the ribs and vertebrae [37]. After the first 6 to 12 months, BMD often improves and may increase to pre-transplant levels [35].

Patients with end-stage pulmonary disease are at extremely high risk for osteoporosis due to chronic hypoxemia and hypercapnia, glucocorticoid use, malnutrition, inactivity, vitamin D deficiency, and tobacco use. Low BMD has been documented in 45% to 75% of patients before lung

transplantation. Fracture prevalence is also high. On average, lumbar spine and hip BMD fall by 5% during the first year despite calcium and vitamin D supplementation. One study found that 37% of lung transplant recipients suffer fractures during the first year after lung transplantation despite receiving anti-resorptive therapy [37].

Bone marrow transplant recipients have similarly been found to have decreased BMD. These patients may have pre-transplant bone loss related to myeloablation with alkylating agents, whole body radiation, or a combination of the these therapies that often cause severe and permanent hypogonadism. In addition, significant bone loss occurs during therapy with prednisone and cyclosporine A for graft-versus-host disease [37].

The management of transplantation osteoporosis should include strategies directed at transplant candidates and recipients. BMD measurements should be obtained in all patients before transplantation, and any patient with osteopenia or osteoporosis should be referred for further management. Patients should be prescribed adequate calcium (1500 mg/d) and vitamin D (400 to 1000 IU or enough to maintain levels of 25-OHD in the upper normal range). Gonadal steroids should be replaced in men and women with hypogonadism if there are no contraindications. Patients should participate in physical rehabilitation programs if possible. In patients with low BMD or osteoporosis at initial assessment, anti-resorptive therapy, usually bisphosphonates, should be considered before and continued after transplantation. Transplant physicians should prescribe the lowest possible doses of glucocorticoids and use alternative agents if possible. In patients with normal pre-transplant BMD, anti-resorptive therapy should be initiated as soon as possible after transplantation and continued for at least 1 year. BMD should be measured every 6 months for the first 2 years after transplant and then annually [38]. A decision regarding the advisability of continuing anti-resorptive therapy can be made at the end of the first year based on the BMD at that time and should be re-evaluated annually.

Inherited disorders of skeletal development

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a genetic disorder characterized by fragile bones and recurrent fractures that can lead to skeletal deformities. Patients with OI have variable mutations involving genes that encode for type I procollagen, COL1A1, and COL1A2 [40]. The inheritance pattern is heterogeneous. Patients are classified as Type I through IV on the basis of phenotype and disease severity. There is considerable overlap between the types. In addition to bone disease, patients with OI may have blue sclera, short stature, dentinogenesis imperfecta, adult-onset hearing loss, and joint laxity.

Homocystinuria

Homocystinuria, a disorder that can result from several different genetic mutations, is associated with premature osteoporosis, skeletal abnormalities, mental retardation, ectopia lentis, Marfanoid habitus, and thrombovascular disease. Approximately 50% of patients with this disorder have clinically apparent osteoporosis by the time they reach 30 years of age. The vertebral bodies appear flattened and elongated in the antero-posterior orientation. The relationship between elevated plasma homocystine levels and osteoporosis is not well understood but is thought to involve defects in collagen synthesis from elevated homocystine levels [40].

Marfan syndrome

Marfan syndrome is an autosomal dominant disorder caused by one of two mutations in the genes coding for fibrillin, a glycoprotein associated with elastin and extracellular matrix. Patients with this disorder have skeletal, cardiovascular, and ocular abnormalities and commonly have scoliosis. Significant deficits in BMD have been found even after corrections for bone size in these patients. Nontraumatic fractures have not been observed in these patients [40].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome refers to a group of connective tissue disorders characterized by joint and skin laxity and fragile skin that bruises easily. These disorders vary according to mode of inheritance, degree of joint laxity, and whether they have an associated characteristic phenotype. Patients with Ehlers-Danlos syndrome may have vertebral abnormalities, including spondylolisthesis and wedge deformities. In one study of four patients aged 16 to 25, lumbar spine BMD was 1 standard deviation (SD) below age- and gender-matched norms [40].

Rheumatic diseases

Two forms of osteoporosis have been associated with rheumatoid arthritis. Juxta-articular osteoporosis, observed early in the course of the disease, has been hypothesized to be related to local release of inflammatory cytokines, which cause increased bone turnover in adjacent bony structures. Generalized osteoporosis has also been reported in patients with rheumatoid arthritis, as have increased rates of vertebral and hip fractures. Glucocorticoid therapy and decreased mobility are thought to contribute to the development of osteoporosis in these patients. A recent study of physically active patients with rheumatoid arthritis found the largest reduction in BMD at the distal radius, whereas decreases at the radial diaphysis and lumbar spine were not significant [16]. Thus, juxta-articular osteoporosis

may occur even in active patients, whereas generalized osteoporosis may require a component of immobility. Other rheumatic diseases, such as ankylosing spondylitis, systemic lupus erythematosus, and polymyalgia rheumatica, have been associated with osteoporosis. BMD reductions may be related to the associated immobility, malnutrition, and chronic steroid therapy or to the underlying diseases [3,41].

Disorders of bone marrow malignancy and proliferation

Multiple myeloma

Multiple myeloma is most commonly associated with localized lytic bone lesions. However, generalized osteoporosis may also occur [41]. Osteoclast-activating factors and cytokines released by myeloma cells that inhibit osteoblasts are thought to contribute to the skeletal disease [3]. Biochemical markers of resorption are increased in this disorder, whereas markers of formation are decreased. Bisphosphonates prevent the development of lytic lesions, vertebral fractures, and bone pain [41].

Leukemias and lymphomas

Patients with chronic lymphoproliferative disorders often have associated osteoporosis. Bone-resorbing cytokines are produced in association with many of these conditions, including acute and chronic leukemia, Burkitt lymphoma, and non-Hodgkin lymphoma. Hypercalcemia, related to cytokine production and excess unregulated synthesis of 1,25(OH)₂D by the transformed cells, is common [3].

Gaucher disease

Gaucher disease is a lipidosis in which there is a proliferation of fat cells in the bone marrow. Bone loss, bone pain, and pathologic fractures have been observed in this disorder. The pathophysiology of the bone disease in this disorder is not well understood but seems to involve inflammatory cytokines that cause lytic lesions. The replacement of osteoblasts by Gaucher cells may also play a role in bone loss [3].

Systemic mastocytosis

Systemic mastocytosis is a condition associated with mast cell proliferation. Clinical manifestations of this disease include urticaria pigmentosa, hepatomegaly, splenomegaly, bleeding diabetes, and diarrhea. Skeletal symptoms may be found in up to 75% of patients; osteoporosis and osteosclerosis have been reported [3,41]. Factors secreted by the mast cells, including heparin, fibroblast growth factor, and prostaglandins, are thought to cause the bone-related changes in this disorder. Mastocytosis may present

with osteoporosis as the sole finding. Bisphosphonates and interferon α -2b are effective in the treatment of this disorder [41].

Pregnancy-related osteoporosis

Pregnancy-related osteoporosis was first described in 1955, and several cases have subsequently been reported. This disorder usually presents with back pain, loss of height, and vertebral fractures during the third trimester or postpartum period. Pregnancy-related osteoporosis is most commonly seen in the first pregnancy and may not recur. The pathogenesis is unknown. Bone biopsies suggest osteoblast failure. An increased prevalence of fractures has been observed in the mothers of patients with this disorder, signifying a possible familial component. There is rapid symptomatic improvement after delivery. Approximately 15% to 20% of patients with this disorder have a pre-existing diagnosis that is a known cause of secondary osteoporosis [42].

Medications and osteoporosis

Anticonvulsants

Bone disease has been reported in association with several frequently prescribed anticonvulsants, including diphenylhydantoin, phenobarbital, sodium valproate, and carbamazepine. Risk factors for anticonvulsant bone disease include long-term therapy, high medication doses, multiple drug regimens, low vitamin D intake, chronic illness, old age, institutionalization, restricted sun exposure, and simultaneous therapy with other medications that induce hepatic enzymes [5]. Most commonly, patients with anticonvulsant bone disease present with asymptomatic reductions in BMD. However, osteomalacia (rickets), proximal muscle weakness, hypocalcemia, and hypophosphatemia may be seen in severe cases. The mechanisms by which diphenylhydantoin, phenobarbital, and carbamazepine affect bone and mineral metabolism are likely related to their stimulatory effects on hepatic mixed function oxidase with subsequent increased degradation of vitamin D metabolites. Sodium valproate, which is not known to have direct effects on vitamin D metabolism, may affect bone through its toxic effects on the kidney. Several studies have reported decreased serum levels of 25-OHD in patients taking anticonvulsants, particularly in patients residing in northern latitudes. Increased disappearance of vitamin D and 25-OHD from the circulation and increased appearance of inactive polar metabolites in bile and urine have also been demonstrated. Direct effects of anticonvulsants on cellular metabolism have been described, including inhibition of intestinal calcium transport. Inhibition of parathyroid hormone-mediated bone resorption has been observed *in vitro*; if this occurs in humans, secondary increases in circulating PTH could result. In addition, diphenylhydantoin directly inhibits collagen synthesis. Bone histomorphometric data indicate that patients receiving

anticonvulsants have increased bone turnover and normal bone mineralization. Patients on chronic anticonvulsant therapy should receive supplementation with at least 400 IU of vitamin D. Those with known bone disease should receive doses (2000 to 4000 IU/d) sufficient to maintain serum 25-OHD concentrations in the normal range.

Heparin

In vitro, heparin has been shown to stimulate bone resorption and suppress osteoblast function [3]. Heparin-induced osteoporosis has been reported in patients receiving chronic heparin therapy at doses of 15,000 U or greater for at least 6 months [22]. The bone loss may be reversible with cessation of heparin treatment [22].

In recent years, the use of low-molecular-weight heparin has become increasingly common. Few data are available regarding its effects on bone. In one study, osteopenia was less in rats treated with low-molecular-weight than unfractionated heparin, and osteoclast surface was increased only by unfractionated heparin. There is one case report, however, of a woman who developed lumbar vertebral fractures after being treated with low-molecular-weight heparin for 3 months. Although warfarin has been shown to inhibit bone formation in vitro, there is no direct evidence that this drug causes osteoporosis [2].

Methotrexate

Methotrexate, a folate antagonist, is used in high doses to treat malignancies and in lower doses to treat inflammatory diseases such as rheumatoid arthritis. The results of cross-sectional studies on the effects of methotrexate on bone have been inconsistent, although some studies found bone loss. In rat models, little change was seen with short-term, low-dose therapy; however, prolonged courses similar to those used for malignancies were associated with decreased formation, increased resorption, and decreased bone mass [38].

Diagnostic evaluation for secondary causes of osteoporosis

In any patient being evaluated for osteoporosis, secondary causes may have contributed to the situation. In cases where bone loss is greater than expected for the patient's age, gender, race, and menopausal status, it is even more important to consider and search for secondary causes. Several causes of osteoporosis may be clinically subtle, such as mild asymptomatic hyperparathyroidism, celiac disease, and Cushing syndrome [3]. An intensive investigation is indicated particularly in all pre-menopausal or peri-menopausal women and in men with atraumatic fractures or BMD that is more than 1 SD below age-matched control subjects. A complete history and physical examination may reveal one of the many causes of premature bone

Box 2. Laboratory evaluation for secondary osteoporosis

Routine laboratory testing

Complete blood count

Renal function

Chemistry panel (calcium, phosphorous, alkaline phosphatase, albumin, liver function)

Thyroid function tests (total T4 and sensitive thyrotropin)

24-hour urinary calcium and creatinine excretion

25-hydroxyvitamin D

Gonadal function (in men)

Specialized laboratory testing^a

Intact parathyroid hormone (if serum calcium is borderline or frankly high or low)

Urine free cortisol or overnight dexamethasone suppression test (if suspect Cushing syndrome)

Serum and urine protein electrophoresis and immunoelectrophoresis (if anemia, increased erythrocyte sedimentation rate)

Antigliadin antibodies and small bowel biopsy (if evidence of malabsorption, such as iron or vitamin D deficiency, or suggestive history)

Serum iron and ferritin (if malabsorption or hemochromatosis is suspected)

Transiliac bone biopsy (in selected cases)

^a Selected tests may be performed in patients in whom history, physical examination, or routine tests suggest a secondary etiology.

loss. Because routine laboratory data are usually normal in patients with postmenopausal osteoporosis, the presence of laboratory abnormalities can suggest certain etiologies and guide further diagnostic investigation. All patients with osteoporosis should have the following routine laboratory tests: a complete blood count, chemistry profile, erythrocyte sedimentation rate or C-reactive protein, liver function panel, thyroid function tests, and 24-hour urine calcium and creatinine. In men with low bone densities, serum testosterone and gonadotropins should be included in the initial assessment [43–46]. Specialized laboratory testing can be performed based on information gleaned from the history and physical and initial laboratory tests (Box 2). In patients with conditions or taking medications known to be associated with osteoporosis, physicians should routinely measure BMD and maintain a high level of vigilance for the development of osteoporosis as a complication of their underlying disease.

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