Secondary osteoporosis: Pathophysiology & diagnosis

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Osteoporosis is a skeletal disease characterized by decreased bone mass and microarchitectural changes in bone tissue that increase the susceptibility to fracture. Secondary osteoporosis is loosely defined as low bone mineral density or increased risk of fragility fracture caused by any factor other than aging or post-menopausal status. The purpose of this review is to discuss the current understanding of the pathophysiology and contribution to fracture risk of many of the more common causes of secondary osteoporosis, as well as diagnostic considerations, outlined by organ system. While not comprehensive, included are a wide array of diseases, conditions, and medications that have been associated with bone loss and susceptibility to fractures. The hope is to highlight the importance to the general clinician of screening for and treating the osteoporosis in these patients, so to limit the resultant increased morbidity associated with fractures.

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* The authors realize that this mini review is not complete but space does not allow coverage of the extensive number of conditions which predispose to bone loss and osteoporosis but have attempted to highlight those diseases which may be very interesting to most clinicians.

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Introduction

Osteoporosis is a skeletal disease characterized by decreased bone mass and microarchitectural changes in bone tissue that increase the susceptibility to fracture. It is estimated that 10 million Americans over the age of 50 have osteoporosis, and tens of millions more are at risk. Bone mineral density testing has been the accepted standard for screening for this disease, and is routinely targeted at postmenopausal females by general clinicians. A growing understanding of other factors that contribute to the susceptibility of fragility fractures, many of which are not reflected in BMD testing, has expanded the spectrum of patients considered at risk and in need of a workup.

Secondary osteoporosis is loosely defined as low bone mineral density or increased risk of fragility fracture caused by any factor other than aging or postmenopausal status. A wide array of diseases, treatments, and medications can affect bone quality in men and women of all ages. In light of the significant public health burden caused by osteoporosis, a recognition and understanding of these factors is of utmost importance. The following is an organ-system based review of the pathogenesis and diagnostic considerations of the more common causes of secondary osteoporosis. Please note that genetic bone diseases, male osteoporosis, renal osteodystrophy, and treatment considerations are not included in this review.

Endocrinology

Glucocorticoid excess

Endogenous overproduction or systemic administration of glucocorticoids is a well-known cause of bone loss, and is the most common iatrogenic cause of osteoporosis seen in clinical practice [1]. The pathogenesis includes diverse effects on three main cell types in bone biology, changes in calcium handling, as well as increased falls related to steroid-induced myopathy [2,3]. As many as 30%—50% of patients receiving chronic glucocorticoid therapy will experience a fracture, making this a major contributor to the morbidity and mortality associated with steroid-responsive chronic diseases such as lupus, rheumatoid arthritis, giant cell arteritis, transplant recipients, inflammatory bowel disease, and COPD [4,5].

Glucocorticoids cause decreased production of osteoblast precursors and increased apoptosis of mature osteoblasts [6,7]. Histomorphometric studies have confirmed decreased numbers of osteoblasts on cancellous bone in patients with glucocorticoid-induced osteoporosis (GIO) with associated thinning wall width. Decreased osteoblast differentiation is in part mediated through inhibition of wingless (Wnt)/β-catenin signaling, as the expression of Dickkopf-1 and sclerostin, both antagonists of Wnt signaling, can be enhanced by glucocorticoids [8,9]. Enhanced apoptosis of osteocytes is also seen, which are the main mechanosensing cells of bone that contribute to the ability to withstand significant compressive forces. Glucocorticoid excess can increase the expression of 11B-hydroxysteroid dehydrogenase type 1 at the bone, which converts inactive adrenal hormones to active metabolite, leading to deleterious effects on osteocytes and osteoblasts including decreased vascularity, interstitial fluid, and strength [10].

While glucocorticoid therapy can decrease osteoclast production, the lifespan and activity of osteoclasts are increased, thereby maintaining their effect relative to the decreased osteoblastic number and activity. Studies have shown increased production of receptor activator of NF-κB ligand (RANKL) which promotes osteoclastic activity and survival, and suppression of osteoprotegerin (OPG), a natural decoy receptor for RANKL [11,12]. Additionally, glucocorticoids have been shown to confer a pro-survival effect directly to osteoclasts, independent of alterations in RANKL and OPG, in the early stages of steroid exposure in mice [13]. The bone abnormalities may also be enhanced by the decreased sex hormone secretion because of suppressed hypothalamic-pituitary function.

Bone loss occurs quickly with glucocorticoid therapy and appears to be biphasic, with as much as a 6%—12% loss in BMD within the first year, followed by a continued annual loss with ongoing therapy [14]. Biochemical markers of bone turnover are affected as early as 1—2 months following initiation of therapy, and the bulk of bone loss is seen within the first 6 months [15]. Addressing the deleterious effects of steroid therapy on bone is imperative early on in the course, particularly if long term use (ie,
90 days or longer) or moderate to high dose (>7.5 mg/day) is planned. Risk factors associated with GIO include advanced age, low BMI, dose and duration of glucocorticoid, as well as other traditional factors [16]. Bone density testing is recommended at the onset of therapy as a general screening, though changes in the mechanical qualities of bone may occur prior to any changes reflected in BMD testing thus predisposing to fractures at a higher BMD.

Primary hyperparathyroidism

Parathyroid hormone (PTH) is critically involved in calcium and phosphorus homeostasis, and continuous exposure to elevated levels in primary hyperparathyroidism (PHPT) are known to be catabolic to the skeleton. The contribution to osteoporosis is so well established that in patients with PHPT significant metabolic bone disease is generally considered an indication for parathyroidectomy [17]. The majority of patients with PHPT are postmenopausal females, with an incidence as high as 1 in 500 reported in this population [17]. PHPT preferentially affects areas rich in cortical bone more so than cancellous bone, therefore evaluating distal forearm and femoral neck BMD is recommended [18].

The precise mechanism of bone loss in PHPT is not completely understood. Histomorphometrically, persistently elevated levels of PTH induce a state of high bone turnover and have been associated not only with a low BMD but also with alterations in the mineralization density distribution and collagen crosslinks affecting bone stiffness and quality [19,20]. At the cellular level, compared with healthy controls, patients with PHPT had a low OPG/RANKL ratio favoring a state of bone resorption, which improves following parathyroid surgery [21]. Variable effects on mediators of the Wnt signaling pathway have been found in PHPT, with elevated levels of Dkk-1 and suppressed levels of sclerostin described [22,23]. Further studies are needed to expand on the clinical implications of these differential effects on the Wnt pathway. Taken together, the finding of increased bone turnover, low BMD and reduced bone quality appear to confer an increased risk of fracture in PHPT.

Hyperthyroidism

Thyrotoxicosis is an established cause of high-turnover osteoporosis, and many studies have shown a consistent decrease in BMD and increase in fracture risk in patients with untreated hyperthyroidism [24,25]. While bone loss has been documented at all skeletal sites, there is preferential involvement of cortical bone, suggesting the need to screen distal forearm BMD [26,27]. While the cause of the hyperthyroidism may not matter, the severity is an important factor, as a TSH of <0.1 mU/L was associated with a threefold increase risk of hip fracture and a fourfold increase risk of vertebral fracture in a cohort of postmenopausal females [28].

The effect of thyrotoxicosis on bone was felt to be mediated by the effects of T3 through it’s interaction with nuclear receptors TR-alpha and TR-beta. Excessive stimulation of TR-alpha-1, the primary receptor located in bone, accelerated bone remodeling leading to osteoporosis. In addition to the direct catabolic effects of excess thyroid hormone on bone, recent evidence has shown that thyroid stimulating hormone (TSH) may be a negative regulator of bone turnover. Decreased expression of TSH-receptor leads to a high turnover state and low BMD, despite normal T3 and T4 levels, suggesting reduced TSH signaling in the pathogenesis of hyperthyroid related bone loss [29]. This is important implications for other situations with low TSH such as subclinical hyperthyroidism and use of thyroid replacement medications. In hypothyroidism the use of highly sensitive TSH measurements has allowed a more accurate control of patients on replacement therapy and it is recommended that values be kept in mid normal range to avoid bone sequelae [30]. In thyroid cancer patients the level of TSH will be kept lower than in non-malignant hypothyroid disease.

Growth hormone deficiency

Growth hormone (GH) is an important determinant of longitudinal bone growth and development of skeletal maturity, and children with GH deficiency exhibit short stature and reduced peak bone mass [31]. The anabolic effect of GH on osteoblasts appears to be dependent upon insulin-like growth factor 1 (IGF-1), whose production by the liver and osteoblasts is stimulated by GH [32].The interaction of
IGF-1 and its binding proteins regulate GH receptor (GHR) on osteoblasts. GHR-deficient mice exhibit growth retardation and osteoporosis, which can be rescued by overexpression of IGF-1 [33]. A marked reduction in bone turnover is seen histomorphometrically in adult-onset GH deficiency, primarily affecting cortical bone [34]. This is associated with a lower BMD, and a non-vertebral fracture risk 2–3 times that of osteoporotic patients without GH deficiency [35].

**Acromegaly**

Acromegaly is associated with significant increase in markers of bone turnover due to the effect of excess GH and IGF-1 on osteoblasts and osteoclasts [36]. Studies on the effect of acromegaly on BMD are nuanced due to the structural changes in bone influencing the accuracy of testing, as well as the common finding of concurrent hypogonadism. Overall, the BMD in acromegals is generally preserved, with some showing a relative decrease in trabecular bone density [37,38]. Despite a preserved BMD, several studies document an increased incidence of vertebral fractures compared with a control populations, influenced by factors such as the duration of active acromegaly, serum IGF-1 levels, and postmenopausal status [39,40].

**Male hypogonadism**

Androgens are important for developing and maintaining skeletal health in men [41]. Serum testosterone levels decline with aging starting around the 5th decade of life in men, a time after which approximately 85% of cortical bone loss occurs [42,43]. In addition to aging, medications such as androgen deprivation therapy (ADT) cause an abrupt decline in androgen levels. In vitro studies have shown that androgens, via the androgen receptor, can stimulate osteoblastic cell proliferation, up-regulate TGF-b and IGF-1 (involved in bone formation), and down-regulate IL-6 (involved in bone resorption [44,45]. Estrogens are also involved in male skeletal health, and their levels can fall with aging as they are produced predominantly in men by conversion of testosterone to estrogen by aromatase in peripheral tissues, including osteoblasts and osteocytes [46–48]. Estrogens play a role in both bone resorption and bone formation in men. Several large studies have shown a relationship between low serum estradiol levels in men and low BMD [49,50].

Measurement of sex hormone levels can be valuable in the workup and prognostication of bone health in men with hypogonadism. While low testosterone levels are associated with decreased bone mass and muscle strength, a much stronger correlation with fracture risk is seen with low bioavailable estradiol levels or high sex hormone binding globulin (SHBG) levels [51,52]. The highest correlation with fracture was when both the bioavailable estradiol level was low and the SHBG level was high. Hypogonadism, whether from aging, surgery, or a medication, is a major cause of osteoporosis in men, and the relative contributions of alterations in estradiol, testosterone, and SHBG need to be better defined.

**Diabetes mellitus**

Both type 1 (T1DM) and 2 diabetes mellitus (T2DM) are associated with deleterious effects on the skeleton [53,54]. Compared with healthy controls, there was a 12-fold increased risk of hip fracture in T1DM and a 1.7-fold increase in T2DM seen in the Iowa Women’s Health Study [55]. A similar increase in fracture risk was seen in the Women’s Health Initiative in those with T2DM, even after adjusting for frequent falls and BMD changes [56]. T1DM is associated with decreased BMD and failure to achieve peak bone mass [57]. In T2DM, however, there is often a normal or elevated BMD, implicating a decline in the quality of the bone as a contributor to fracture risk [58]. In a small study using high resolution peripheral quantitative computed tomography (HR-pQCT) in elderly female patients with T2DM, there was an increased intracortical porosity despite dense trabecular bone, which is known to be an important determinant of bone strength and fracture propagation under bending loads and is associated with increased fracture risk [59]. A recent report utilizing in vivo micro-indentation testing showed decreased bone material strength in the tibia of postmenopausal females with T2DM compared with age-matched non-diabetic controls [60].
The osteoporosis associated with DM is one of low bone turnover, with decreased markers of osteoblastic activity [61]. Insulin and amylin have anabolic effects on bone, and their decrease in T1DM may lead to impaired bone formation likely through decreased IGF-1 [62,63]. Additionally, mouse models of insulin-dependent diabetic osteopathy have shown an increased expression of Dkk1 and SOST, both antagonists of Wnt signaling and osteoblastogenesis [64]. The accumulation of advanced glycation endproducts and lower enzymatic collagen crosslinks contribute to altered biomechanical features of diabetic bone [65].

In diabetes there is increased bone marrow adiposity which has been linked with osteoporosis [66]. Peroxisome proliferator activator receptors (PPARs), especially PPAR-gamma, are transcription factors and nuclear receptors involved in glucose metabolism, and have been shown to be potent regulators of adipogenesis. The mesenchymal stem cells in the bone marrow microenvironment can experience an adipogenic or osteogenic fate, and PPARs and their ligands rosiglitazone and pioglitazone appear to drive the differentiation toward adipocytes and away from osteoblasts [67]. This has important implications as these agonists are commonly used in the treatment of T2DM (see below under drugs). In addition to the above cellular mechanisms of bone compromise in DM, other factors such as retinopathy-induced visual impairment, neuropathy-induced balance problems, renal osteodystrophy from dialysis, and renal transplantation all add to the fracture burden. In addition, sarcopenia contributes to an increased risk for falls and fractures in this population [68].

**Vitamin D deficiency**

Deficiency of vitamin D is characterized by reduced intestinal absorption of calcium and phosphorus, hypocalcemia, secondary hyperparathyroidism, and demineralization of bone [69]. The main sources of vitamin D are diet and sunlight exposure; lack of fortification of foods and increased appreciation of the harmful skin effects of excessive sunlight exposure have contributed to the amount of vitamin D deficiency seen in clinical practice. Serum 25(OH)D is best indicator for vitamin D status in clinical practice, and while 20 ng/mL is generally considered the threshold for defining insufficiency with regards to bone health, optimal calcium absorption and control of secondary hyperparathyroidism have been seen closer to 30 ng/mL [69,70]. Extreme examples of the skeletal effects of vitamin D deficiency are seen in cases of osteomalacia, or rickets in children, where there is a softening of the bones caused by an increase in the unmineralized osteoid component of the bone matrix. Vitamin D receptor (VDR)-mediated intestinal absorption plays a large role in the pathophysiology, as animal studies with null VDR mutations can have their osteomalacia phenotype reversed with treatments of parenteral calcium [71].

Due to the difficulty involved in isolating the effect of vitamin D on clinical outcomes, and the heterogeneity of the investigations, the magnitude of its effect on bone loss is debated, but most studies agree that levels of 25(OH)D below 20 ng/mL are associated lower BMD [72,73]. For similar reasons, the effect of vitamin D deficiency on fracture risk is difficult to quantify, but large population studies of both men and women agree that hip fracture risk is higher in those with a 25(OH)D level below 20–25 ng/mL [74–76]. Decreased physical function in a study of 4100 older subjects in the NHANES study was seen in those with the lowest 25(OH)D levels, potentially from sarcopenia and weakness, increasing the risk of falls [77]. While there is debate about the definition of optimal vitamin D level for bone health, there is agreement that levels below 20 ng/mL are associated with lower BMD, increased fracture risk, and decreased efficacy of pharmacologic and non-pharmacologic interventions for osteoporosis.

**Rheumatologic & inflammatory**

**Systemic lupus erythematosus**

Low BMD is described in up to 50% of female patients with systemic lupus erythematosus (SLE) [78]. In addition to traditional risk factors, bones of SLE patients are affected by use of corticosteroids and other immunosuppressive drugs, physical inactivity, and vitamin D deficiency on the basis of sun avoidance [78–80]. While HR-pQCT studies have documented increased cortical
porosity and decreased bone strength in SLE patients on glucocorticoids, a recent study saw similar changes in SLE patients without steroid exposure implicating effects of the disease rather than medications [81]. Osteoclast-inducing inflammatory cytokines are known to be elevated in SLE and contribute to bone loss [82]. An elevated risk of fracture is seen, some citing as high as 12.5% of patient experiencing fractures, with age at diagnosis, duration of disease, and glucocorticoid use increasing that risk [83,84]. As SLE commonly affects premenopausal females, heightened awareness of the deleterious skeletal effects and fracture risk is important to prompt early screening.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis associated with several forms of skeletal remodeling including marginal joint erosions, periarticular osteopenia, and systemic osteoporosis. Low BMD and an increased risk for fracture have been seen in RA patients compared with control populations, though confounding variables make the underlying mechanism of bone loss somewhat difficult to elucidate. These include age, female sex, physical inactivity, disease severity, and use of medications such as glucocorticoids. An association between disease severity and bone loss has been observed, though there has been no consistent correlation between joint erosions and low BMD [85,86]. Many of the cytokines and growth factors known to be involved in RA-associated inflammation, such as IL-1, IL-6, TNFα, can promote osteoclastic activity themselves or modulate the expression of the osteoclastogenic factor RANKL and its inhibitor OPG [87].

Further insights into the control of bone turnover in RA have come from studies of RANKL and OPG. In early, active, untreated RA patients, an increased RANKL:OPG ratio, as well as increased CTX levels, were predictors of rapid and persistent bone damage over an 11 year follow up [88,89]. Consistent with these findings, TNFα blockade, an effective treatment of the inflammatory process, has been associated with decreased systemic bone loss, and these effects correlate with a fall in serum RANKL levels [90]. In addition to an increased RANKL:OPG ratio, increased levels of Dkk-1 and sclerostin, inhibitors of bone formation, have been found in the serum of RA patients [91]. Treatment with tocilizumab, an inhibitor of IL-6, was associated with a favorable decrease in the RANKL:OPG ratio as well as a drop in the Dkk-1 and sclerostin levels [91]. Further studies will aid in expanding our knowledge of the roles of these mediators in the deleterious skeletal effects of RA. Clearly, monitoring for bone loss and instituting timely therapy is of utmost importance in RA.

**Ankylosing spondylitis**

Ankylosing spondylitis (AS) is a chronic arthritis characterized by inflammation in synovial joints as well as the entheses. In contrast to RA, the inflammation can be accompanied by increased bone formation, particularly at areas of enthesal inflammation such as at ligament insertion sites in the spine. Osteoporosis is a known complication of AS, which can often go undiagnosed because of the young, mostly male population affected. Osteoporosis is seen in up to 25% of patients with AS, with osteopenia seen up to 50% of the time, and is usually associated with disease activity and duration [92]. The fact that bone loss can be seen early in the disease process argue that immobility is not the primary cause [93]. Vertebral fractures are seen in 16–18% of patients with AS contributing to the morbidity of the disease, and are associated with advanced age, longer disease duration, and degree of structural changes [92,94]. Chronic systemic inflammation is apparent, as is progressive immobility, which both are thought to contribute to the bone loss. Studies of various mediators of osteoblast and osteoclast function show an increase RANKL:OPG ratio, though measuring Wnt signaling pathway inhibitors such as Dkk-1 levels have been inconsistent [95,96]. It is likely that further clarification of the expression of these mediators in different stages of the disease process, as well as in response to various therapies, will aid in our understanding of the differential effects of AS on bone formation at sites of inflammation compared with generalized bone loss.
Neurologic

Spinal cord injury/immobilization

Spinal cord injury (SCI), or any situation that results in prolonged immobilization and skeletal unloading, is associated with bone loss and an increased risk of fracture [97,98]. While DEXA is an important tool for screening for low BMD, the most affected areas of the skeleton in SCI patients appear to be the distal femur and proximal tibia, areas not routinely accessible, limiting the value of the test. Initially following SCI there is massive mobilization of calcium from the mineral phase of bone, which can lead to complications such as hypercalcemia and hypercalciuria. Animal studies have shown an increase in osteoclasts and bone resorption surfaces after only 72 h of rat leg immobilization, and decreased trabecular bone volume at 10 days [99]. In human SCI patients, there is a minor initial increase in markers of bone formation with a profound and sustained increase in bone resorption markers that peaks at 10–16 weeks after immobilization [100,101]. Isolated osteoblasts from rats with SCI exhibit downregulation of several anabolic signaling pathways such as Wnt and GH/IGF-1 [102]. The exact cause of these findings is unknown, though in a recent series of 40 immobilized human patients following a stroke, serum levels of the Wnt pathway antagonist sclerostin were elevated compared to controls, and negatively correlated with bone formation markers [103]. These findings could implicate a role for sclerostin in the skeletal response to mechanical unloading. Some what related to immobilization is the effect of loading or weight bearing on the skeleton. This particularly applies to space travel especially for prolonged periods where bone loss can be severe [104].

Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurologic disorder associated with reduced mobility and an increased risk of falling [105]. Compared to age and sex-matched controls, there is a decrease in femoral neck and lumbar spine BMD, 25-OH vitamin D levels, and an increase in bone turnover markers in patients with PD [106]. There is a significantly increased risk of bone fracture in PD, particularly at the proximal femur, which is likely affected by disease duration and severity and propensity for falls [107,108]. In addition to traditional risk factors affecting this population, such as advanced age and female gender, contribution to bone loss by reduced mobility, low BMI, poor nutrition, and vitamin D deficiency appear to increase the risk of osteoporosis [109]. Screening BMD and vitamin D levels are recommended at the onset of disease as appropriate therapy may prevent progression of bone loss and risk of fracture.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating neurologic condition often leading to profound disability and functional limitation. Low BMD, particularly at the hip, has been consistently shown in MS compared to a control population in both male and female patients [110,111]. While factors such as vitamin D deficiency, frequent courses of glucocorticoid therapy, and female gender are considered risk factors, the most important determinants of bone loss are degree of functional impairment, advanced age, and duration of disease [112]. In a large multinational longitudinal cohort of women (GLOW), MS was one of the comorbidities that appeared to contribute significantly to fracture risk, though quantifying the specific contribution of MS to fracture risk has yet to be done [113]. Vitamin D deficiency is very prevalent in MS, though the extent of it’s role in the pathogenesis of bone loss in MS is unclear [114].

Hematologic/oncologic

Multiple myeloma/monoclonal gammopathy of undetermined significance

Hematologic malignancies can directly and indirectly affect bone contributing to generalized osteoporosis and pathologic fractures, bone pain, and hypercalcemia. Multiple myeloma (MM) has the
highest incidence of bone involvement of all malignant diseases. It is estimated that 70% of patients present with bone pain in MM, and up to 60% of patients will develop a pathologic fracture during their course [115]. The skeletal involvement of MM is a major contributor to the morbidity and mortality associated with MM, and up to 90% of patients will develop generalized osteoporosis or lytic bone lesions [116].

The bone loss in MM is driven by the uncoupling of bone turnover, with marked increase in osteoclastic bone resorption and a decrease in the rate of bone formation, leading to generalized osteolysis. In the bone marrow microenvironment, MM cells produce multiple factors that increase osteoclast production, activity, and survival. By binding to bone marrow stromal cells, MM cells stimulate production of osteoclastogenic cytokines such as RANKL, M-CSF, and IL-6 by the stromal cells and production of osteoclastogenic factors IL-3 and macrophage inflammatory protein 1a (MIP-1a) by the MM cells [117–119]. The RANKL:OPG axis is altered in MM, with an increase in the ratio observed favoring production and survival of osteoclasts [120]. In addition to the osteolytic process, both MIP-1a as well as other growth factors released from bone matrix during the osteolytic process can serve to promote proliferation of MM cells, thereby creating a symbiotic relationship that amplifies both bone destruction and the tumor mass [121].

Osteoblasts are involved in MM-relate2d bone disease with normal or low levels of bone formation markers seen despite increased resorption, as well as decreased osteoid formation and osteoblastic activity observed histologically [122]. Recent work has focused on over-expression of DKK-1, a Wnt signaling inhibitor, by plasma cells in MM patients with bone lesions, as well as increased levels of DKK-1 in MM cells and circulating in the plasma [123]. Consistent with this finding, anti DKK-1 treatment in a murine model of MM resulted in prevention of the suppression of osteoblast number and surface seen in MM, and an increase in the bone formation rate [124].

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell disorder with a prevalence of nearly 7% in the population age 80 or older [125]. MGUS is a premalignant condition, with roughly a 1% risk per year of progression to MM. Despite the lack of osteolytic lesions seen in MGUS, there is an increased risk of fracture particularly at axial sites, and the level of the paraprotein in the blood does not seem to correlate with this increased risk [126]. RANKL levels are elevated in MGUS, and recent studies suggest that there could be bone architectural changes in MGUS, as well as a rise in serum DKK-1 and MIP-1a before progression to MM [127,128]. Measurement of serum protein electrophoresis and immunofoxation are important in the evaluation of elderly patients with osteoporosis, particularly those with unexplained fragility fractures, as that may be the first clue to an underlying plasma cell disorder that requires monitoring and potential treatment.

**Thalassemia major**

Metabolic bone disease is a known complication of thalassemia major (TM), with the incidence of osteoporosis reported as high as 50%, and an additional 45% of patients have osteopenia [129]. The precise pathogenesis of bone disease in TM is incompletely understood. Contributing factors include delay in sexual maturation, hypogonadism, decreased growth hormone and IGF-1 levels, diabetes, hypothyroidism, and vitamin D deficiency [129]. There is a decrease in the activity of osteoblasts and an increase in bone resorption, leading to a decrease in BMD [130]. Bone histomorphometry studies in adolescents with TM showed increased osteoid thickness, osteoid maturation time, and mineralization lag time, all of which indicate impaired bone maturation and mineralization [131]. Voskaridou et al. showed elevated serum levels of Dkk-1 and sclerostin in thalassemic patients compared with healthy controls, as well as increased bone turnover markers, all of which correlated with low BMD [132]. This may give clues to the pathogenesis of thalassemic bone disease, and sclerostin may make a reasonable therapeutic target. In terms of osteoclastic activity in TM, recent studies have shown elevated circulating levels of RANKL, a relatively preserved levels of OPG, yielding a shift in the RANKL:OPG ratio favoring bone resorption [133]. Bone marrow expansion, another feature of TM, can have effects on cortical thickness of bone and increased fragility [130]. Delays in recognition of TM-associated bone disease can lead to serious consequences of fractures and skeletal deformities, making screening BMD and controlling associated risk factors very important early in the disease.
Systemic mastocytosis

In systemic mastocytosis, there is diffuse infiltration of mast cells and their products such as histamine, prostaglandins, leukotrienes, and cytokines (IL-1, IL-3, IL-6) into various tissues of the body. Diagnosis is based on mast cells infiltration on a bone marrow biopsy as well as the finding of a c-kit point mutation or elevated serum tryptase levels. Osteoporosis at the spine, as well as vertebral compression fractures, is a common finding in both men and women with mastocytosis [134]. Given the often mild or nonspecific symptoms in indolent mastocytosis, the true incidence of this disease and the magnitude of its contribution to idiopathic osteoporosis is unknown. One series of asymptomatic men with idiopathic osteoporosis showed bone marrow infiltration with mast cells in 9% of cases [135]. The role of mast cells in bone turnover is still being elucidated, but a deficiency appears to induce a low remodeling state, whereas an abundance is associated with accelerated bone loss [136]. Serum IL-6 levels are elevated in patients with aggressive mastocytosis, as well as in those with bone pain and osteoporosis, implicating a role for this osteoclastogenic cytokine in the pathogenesis of the bone loss [137]. All patients with systemic mastocytosis warrant BMD testing and evaluation for vertebral fractures, and clinicians need to consider this disease in working up patients with idiopathic osteoporosis.

Infectious disease

Human immunodeficiency virus (HIV)

Osteoporosis is common in HIV infection, and has become a more important issue as treatment advances have allowed the HIV-infected population to enjoy longer life expectancy. Up to 70% of patients with HIV have evidence of low bone density, and the risk appears to increase with exposure to antiretroviral therapy [138]. Multiple factors contribute to the pathogenesis of bone loss in HIV infection, including smoking and alcohol use, low BMI, chronic inflammatory response, hypogonadism, decreased physical activity, and growth hormone deficiency. There is a significantly increased risk of fracture, with a more than fivefold higher risk of hip fracture compared with a healthy population [139]. While bone loss is described independent of medications, use of highly active antiretroviral therapy (HAART) has been associated with higher incidence of osteopenia possibly driven by increased osteoclastic activity and bone resorption [140]. Within as little as two years after initiating HAART, a 2–6% loss in BMD is seen, as well as an increased risk of fracture, and this effect may stabilize over time [141].

Recent attention has focused on the effect of the viral infection itself on pathogenesis of bone loss. Analysis of expression levels of miRNA’s in HIV patients showed changes in genes involved in the TGFb and Wnt signaling pathways, implicating potentially altered osteoblastogenesis and osteoclastogenesis, which requires further study [142]. With regards to the effect of the infection, HIV viral protein R and HIV glycoprotein, gp120 can both upregulate RANKL [143,144]. The proinflammatory cytokines induced by HIV infection include TNFa, and OPG, both of which can affect osteoclast development and function [145]. The infection itself can also increase TNF-related apoptosis-inducing ligand (TRAIL) which binds OPG, limiting the capacity of OPG to regulate RANKL-associated osteoclastogenesis [146]. Taken all together, the effects of HIV, both directly and indirectly, can alter the RANKL:OPG axis in favor of bone resorption. Combining this with experience of decreased BMD and increased fracture incidence, attention to bone health is of paramount importance in those infected with HIV.

Nephrology

Idiopathic hypercalciuria

Idiopathic hypercalciuria (IH) is defined as urinary excretion of calcium >4 mg/kg/d in women and >4.5 mg/kg/d in men without any underlying metabolic cause. There is an association between hypercalciuria and low BMD, and the prevalence is increased among Ca-containing stone-formers [147,148]. This is consistent with studies that report a fourfold increased risk of vertebral fracture observed among urolithiasis patients compared with healthy controls [149]. The deleterious skeletal
effects of hypercalciuria in the absence of stone formation is not as well established as in stone formers, and consideration should be given to a radiographic evaluation for asymptomatic stones in osteopenic patients, as this could alter management decisions [150]. Clearly bone loss needs to be aggressively addressed in stone forming IH, and the significance of increased urinary Ca in the absence of stone formation needs to be determined by the clinician on a case-by-case basis. Thiazide diuretics, which decrease urinary Ca excretion, may be associated with a decreased risk of hip fracture [151].

The precise mechanism of bone loss in IH remains incompletely understood despite recent advances. Bone histomorphometry studies have consistently documented decreased osteoblastic activity, mineralization rates, and osteoid surfaces [147,152]. IH is characterized by increased intestinal calcium absorption, increased bone resorption, and decreased renal tubular calcium reabsorption [153,154]. In 40–60% of hypercalciuric stone formers elevated circulating 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) levels are found, as well as increased monocyte expression of vitamin D receptor (VDR) [155,156]. In genetic hypercalciuric stone-forming (GHS) rat studies, administration of 1,25(OH)2D3 augments the urinary Ca concentration even in the setting of dietary Ca restriction, implying bone resorption as the source for excess Ca [157]. This is confirmed by the fact that administration of 1,25(OH)2D3 to these rats has also resulted in decreased BMD and bone formation rate [158]. The VDR protein levels are elevated in the intestinal, kidney, and bone cells of the GHS rats and are thought to mediate the altered Ca handling [159]. The significance of these findings needs to be determined in humans, but they begin to provide insights into potential pathogenic mechanisms of IH-related bone disease.

Psychiatry

Anorexia nervosa

Anorexia nervosa (AN) is an eating disorder characterized by an obsessive fear of gaining weight and refusal to maintain an adequate body weight, ten-times more common in females than in males. Significant caloric restriction and periods of amenorrhea are the norm. Low BMD is a near universal finding in AN, often occurring in young adolescent females during a time of critical bone mass accrual, with as many as 50% of young females with a z-score of less than −1 [160]. Studies have documented the detrimental effects of interruption of normal menstruation during adolescence on adult BMD [161]. Impaired cortical and trabecular microarchitecture are seen on bone histomorphometric studies in young AN females [162]. The risk of fracture during childhood and early adult years is nearly 60% higher for AN females compared with healthy-weight controls [163]. Contributors to osteoporosis in this population include the low peak bone mass accrual, decreased muscle mass, hypogonadism, decreased IGF-1 levels, and increased cortisol [164]. Increased bone marrow adiposity is seen in AN, despite decreased visceral adiposity, and this correlates inversely with BMD as it does in other disease states [165]. Even in successfully treated AN, adults will have an increased risk of fracture due to the low peak bone mass achieved, and screening for osteoporosis should be considered at a younger age.

Gastrointestinal

Celiac disease

Celiac disease affects around 1% of the world's population, and is characterized by inflammatory changes in the duodenum with loss of normal small intestinal villi affecting dietary absorption. While classically thought to begin in childhood, it is now more common to be diagnosed as an adult. The effect of celiac disease on bones has been established for a long time, with osteomalacia historically complicating childhood disease, and low BMD affecting all ages. There is as much as a 17-fold higher prevalence of celiac disease among patients with osteoporosis as compared to controls, suggesting the need for more intensive screening in this population [166]. Serologic testing for celiac is accomplished by measuring tissue transglutaminase (TT-IgA) and anti-endomesial antibody, but the gold standard remains a small bowel biopsy.

It is estimated that 40% of adults diagnosed with celiac disease will have osteoporosis, affecting both women and men [167]. Low bone mass complicates all ends of the celiac spectrum, from severe to
asymptomatic disease [168]. Observational studies of fractures in celiac disease have yielded varying results, though most agree that there is a higher risk of fracture compared to a control population [169–171].

The pathophysiology of bone loss in celiac disease is multifactorial, centered around inflammation, malabsorption, and decreased intestinal absorption. Decreased absorption of calcium and vitamin D, as well as frequent avoidance of dietary calcium, contribute to a net negative calcium balance and compensatory elevation in PTH [172,173]. The secondary hyperparathyroidism has been correlated with increased bone turnover and decreased BMD [174]. There has been a lot of attention recently on intestinal and systemic inflammation in celiac disease, with elevated levels of inflammatory cytokines detected and correlate with bone loss [175]. The RANKL:OPG axis has been extensively studied in celiac, and an increased ratio is seen favoring bone resorption [176,177]. In addition to the above factors, low BMI, hypogonadism, decreased physical activity often contribute to the bone loss associated with celiac disease. Gluten free diet can improve the status of the bone disease, though the magnitude of the improvement is less in adult patients than in children.

**Inflammatory bowel disease**

Crohn’s disease and ulcerative colitis are two forms of chronic inflammatory bowel disease (IBD) and are associated with bone loss, with as many as 40% having evidence of osteopenia [178]. Risk of fracture appears to be elevated, though the magnitude varies in different epidemiological studies [179–181]. The pathophysiology is multifactorial, including the effect of osteoclastogenic inflammatory cytokines, intestinal malabsorption, low BMI, malnutrition, decreased physical activity, and use of glucocorticoids [182]. While glucocorticoids have known deleterious effects on the skeleton, their overall contribution in IBD is debated, and low bone mass has been described in new-onset disease prior to any steroid therapy [183]. Calcium intake and absorption is often poor in this population, and as many as 50% of patients with IBD are vitamin D deficient [184,185]. In Crohn’s disease, the primary tissue involved is at the terminal ileum, where the majority of absorption of fat-soluble vitamins occurs, and resection of the terminal ileum has been described as one of the most important determinants of developing osteoporosis [186]. The RANKL/OPG system has been implicated in the metabolic bone effects of IBD, as elevated plasma levels of OPG are seen, as well as increased release of OPG from inflamed colonic mucosa [187]. The elevated OPG levels correlate with lower BMD, and are felt to be a response to osteopenia and RANKL driven osteoclastogenesis. There is little debate about the development of bone loss in IBD, though the magnitude of the effect is still in question. Routine BMD testing, dietary questioning on calcium intake, and measuring of 25-OH vitamin D levels are recommended for all patients at the onset of disease.

**Bariatric surgery**

Obesity now affects nearly 30% of the US population, and using bariatric surgery to treat morbid obesity has become increasingly popular [188,189]. While malabsorptive and restrictive bariatric procedures are associated with successful weight loss and improvement in conditions such as diabetes and hypertension, there has been growing recognition of the negative skeletal effects that occur following the surgeries. Decrease in BMD has been consistently demonstrated in the one year following bariatric surgery, as high as a 10% loss at the femoral neck and 3% loss at the lumbar spine [190]. The decrease in BMD is similar following Roux-en-Y gastric bypass and sleeve gastrectomy procedures [191]. Decreased calcium intake and absorption, low vitamin D, elevated PTH levels are common, though advanced age, menopausal status, and greater lean mass loss seem to correlate more with degree of bone loss. Most studies to date use areal BMD (aBMD) measurements to quantify bone density following surgery, a technique susceptible to artifactual changes in the setting of obesity and profound weight loss. A recent report using volumetric BMD (vBMD) with QCT showed no decline at the proximal femur following bariatric surgery, a finding discordant with aBMD, possibly related to decreased artifact with the QCT determination [192].

Bone turnover markers (urinary N-telopeptide, bone specific alkaline phosphatase, osteocalcin) are elevated as quickly as 3 months following bariatric surgery and persist through an 18 month follow up
study [193]. This indicates a high turnover state consistent with the effect of elevated PTH. The same study also showed that, even after a transient improvement in vitamin D and PTH levels following surgery (likely from aggressive repletion), they both return to preoperative levels by one year. Another intriguing observation is that following gastric bypass surgery plasma ghrelin levels fall, and the degree of this fall correlate with the degree of bone loss over one year [194]. Ghrelin is a gut derived peptide involved in energy homeostasis and growth hormone secretion, as well as a direct mitogenic and anti-apoptotic effect on osteoblasts [195]. At this point, there are no consistent long term data on fracture risk following bariatric surgery. In addition to maintaining adequate calcium and vitamin D intake, all patients should have screening BMD done at or before surgery, and have it closely monitored along with markers of bone turnover.

**Pulmonary**

*Chronic obstructive lung disease (COPD)*

COPD and osteoporosis share many common risk factors such as smoking use, advanced age, and reduced physical activity [196]. The addition of chronic steroid use, systemic inflammation, reduced muscle mass, hypogonadism, and vitamin D deficiency augment the risk of bone loss in COPD patients. In a large study of 2699 newly diagnosed COPD patients, the prevalence of osteoporosis was elevated compared to a non-COPD population (RR 3.1) [197]. Radiographic emphysema, regardless of other factors or airway obstruction, is a risk factor for bone loss, indicating a possible common pathway between lung parenchymal damage and bone loss [198]. There is significant body composition change in COPD patients, and the loss of fat-free mass is associated with osteopenia [199]. The increased risk of osteoporosis seems to be present in both steroid-users and non-users, though the rate of fractures is likely higher among those that frequently use oral or inhaled corticosteroids [200,201]. The risk of fracture is higher in those with more severe COPD, even after controlling for steroid use. Systemic inflammation in a feature COPD, including elevated levels of osteoclastogenic cytokines such as TNFα and IL-6 [202]. Vitamin D deficiency is reported in nearly half of patients with COPD, and the level is associated with both BMD and severity of the lung disease [203]. Adding to the importance of addressing bone health in COPD patients, is the fact that vertebral fractures negatively affect pulmonary function in general, thereby increasing the morbidity of both disease processes [204].

**Transplantation medicine**

*Transplantation osteoporosis*

Transplantation is an increasingly viable option for the treatment of end-stage diseases of the kidney, heart, endocrine pancreas, liver, and lung as well as for many hematological disorders. Immunosuppressive medications have improved patient and graft survival, while at the same time allowing for better recognition of long-term complications of transplantation, including osteoporosis and fractures [205]. Post-transplant bone loss is multifactorial. The primary contributors are the immunosuppressive medications, namely glucocorticoids and calcineurin inhibitors (CIs), though factors such as decreased mobility, poor nutrition, hypogonadism, and the underlying disease all play a role [206]. High doses of glucocorticoids are often used, especially in the immediate post-transplant time period, causing significant deleterious effects to bone by mechanisms reviewed above. Cyclosporine (CsA) and tacrolimus (FK506) are the principle CIs used following a transplant, and both have been shown to cause acute, rapid, and severe bone loss [207,208]. In a rat model, CsA administration resulted in increased osteocalcin and 1,25-dihydroxyvitamin D synthesis, with normal serum PTH and calcium. Histomorphometrically, a high-turnover state of bone remodeling was seen, with the resorption far exceeding the bone formation [209]. In *vitro* studies of CIs have demonstrated an inhibition of bone resorption by osteoclasts, contrary to their effect *in vivo*, and the bone loss is dependent upon the presence of T lymphocytes [210,211]. The explanation for the differing effects on bone resorption may be that while CIs can inhibit osteoclastic function themselves, their promotion of T
lymphocyte-dependent production of osteoclast-stimulatory cytokines could overwhelm the effects of CIs on calcineurin in bone [206].

Clinically, the bulk of the bone loss is in the first 6–12 months following transplantation, a time when close monitoring of BMD and other risk factors is of utmost importance. BMD at the spine tends to improve especially at 1 year but cortical bone loss at the femur continues to decline. Fragility fracture rates are generally elevated, and vary depending upon the organ transplanted, underlying condition, dosage and duration of immunosuppression, and pre-existing bone disease. Fractures add significantly to the morbidity associated with transplantation, and every effort should be made to address bone loss in a timely manner in this population.

**Cardiovascular**

**Congestive heart failure**

Congestive heart failure (CHF) affects a predominantly older population with multiple comorbidities, including things such as DM and renal insufficiency, making the interpretation of osteoporotic endpoints very nuanced. A particular metabolic bone disease has not been described formally in patients with CHF. In a population with severe CHF referred for cardiac transplantation, osteopenia was found in 43% and osteoporosis was found in 7%, indicating an increased incidence of low bone mass [212]. Among these patients, vitamin D deficiency and elevations in PTH were also more common. A population based cohort study identified a 30% increase in major fractures in those with CHF independent of other traditional risk factors and BMD [213]. Physical inactivity, polypharmacy with increased use of loop diuretics, and comorbidities all serve to complicate the picture, but an increased incidence of low bone mass and fracture risk are seen in this population, and attention to screening for osteoporosis needs to be prioritized to limit the morbidity and mortality associated with fractures.

**Drugs associated with bone loss**

**Depot medroxyprogesterone acetate (DMPA)**

The injectable contraceptive DMPA (Depo-Provera) has been associated with decreased BMD which has received tremendous attention because of its popularity as an effective form of contraception. In 2004, the US Food and Drug Administration attached a black-box warning to its label, suggesting it should only be used as a long term form of contraception only if other methods are inadequate [214]. This has been met with controversy as there is a lack of data implicating DMPA with long term serious skeletal events or increased fracture risk. As a progestin-only contraceptive, it induces a state of estrogen deficiency, which is the primary mechanism of its effect on bones [215]. A decrease in BMD is often seen in the first two years of therapy, though the loss has been shown to be mild [216,217]. A systematic review of ten trials concluded that the bone loss associated with DMPA use is reversible, often in as little as 24 weeks after discontinuation [218]. While anything that can negatively affect bone mass, particularly during development and adolescence warrants caution and discussion with patients, the use of DMPA as an effective form of contraception should not be avoided solely on the basis of its mild skeletal effects.

**Aromatase inhibitors**

Adjuvant treatment of hormone receptor positive breast cancer with an aromatase inhibitor (AI) is highly effective at decreasing the reoccurrence of the disease in postmenopausal women. By blocking the peripheral conversion of androgens to estrogen, they reduce endogenous production of estrogen by nearly 90%. This reduction in circulating estrogen has a deleterious effect on the skeleton, and induces a state of increased bone turnover [219]. For example, after 5 years of therapy in the Arimidex, Tamoxifen, Alone, or in Combination (ATAC), anastrazole was associated with a decline in BMD at the spine and total hip of 6.08% and 7.24%, respectively [220]. There is an increase in the fracture occurrence during AI therapy, that seems to decrease upon cessation of therapy [221]. The presence of low
BMD prior to treatment seems to affect the fracture incidence, as 9.8% of women with baseline osteoporosis had a fracture during three years of AI therapy, compared with 5.6% of those without baseline osteoporosis [222]. Given the demographic of women considered for treatment with an AI, bone health is often an issue even prior to treatment, with some series documenting that 80% of women have evidence of low bone mass at baseline [223].

**Thiazolidinediones**

Thiazolidinediones (TZDs) are ligands for PPARg, and are commonly used in DM2 for improved glycemic control and insulin sensitization. Evidence for the effects of TZDs on bone come from several mouse models, where PPARg deficiency is associated with increased bone mass, and activation of PPARg with rosiglitazone resulted in increased marrow adipocytes, reduced bone formation, and decreased expression of osteoblastogenic transcription factors Runx2 and osterix [224]. In the bone environment, PPARg controls differentiation of cells of mesenchymal and hematopoietic lineages, and its activation can shift away from bone formation and osteoblastogenesis and increase adipogenesis [225]. The increase in bone marrow fat is similar to that which is seen with the aging process. Additionally, PPARg activation can inhibit the Wnt/B-catenin pathway and decrease IGF-1 production, both of which have negative effects on bone formation [226,227].

There is accumulating evidence that TZD use is associated with bone loss in humans, particularly in women. In the ADOPT study (A Diabetes Outcome Progression Trial), a randomized controlled trial of 4360 patients with DM2 comparing treatment with rosiglitazone, metformin, and glibenclamide, there was an increased incidence of fractures among women taking rosiglitazone (9.3%) compared with metformin and glibenclamide (5.1% and 3.5%, respectively) [228]. In a subset of this study, a significant increase in a serum marker of bone resorption (C-telopeptide) was seen in women taking rosiglitazone, not with the other agents; there was no increase in markers of bone formation [229]. A meta-analysis confirmed the increased risk of fracture among female long-term users of TZDs, along with decline of BMD at the total hip and spine of 1–2% [230]. Taken together, while TZDs have significant benefits in terms of diabetes control and its associated complications, it may have a direct negative effect on bone metabolism and risk of fracture, particularly in women. Caution should be used when considering this medication in those at a relatively high risk of sustaining a fracture.

**Acid-suppressive medications**

Acid-suppressive medications, proton-pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs), are some of the most commonly prescribed medications worldwide. Studies have recently been reporting increased adverse consequences of chronic acid suppression, one of which has been an increased risk of fracture. In a 1997 study of male hip fractures, Grisso et al. found an increased risk in those that used cimetidine, an H2RA [231]. Several case-control studies have been done since that time and have shown an increased risk of osteoporotic fractures among PPI users [232–234]. The fracture data on H2RAs have been a bit more inconsistent, with some showing a slight increased risk, and others actually showing a slightly decreased risk. The length of time and dose used appear to increase the adverse skeletal events [231]. The effect of chronic acid suppression on BMD is unknown, with stable or mild decreases seen over short-term follow up [234,235]. In that study, females had a higher risk of non-spine fractures, and the increased risk in men was only seen in those with poor calcium intake.

The leading hypothesis for the mechanism of adverse skeletal events in the setting of acid suppression was that it induces a state of hypochlorhydria and affects calcium absorption leading to a negative calcium balance [236]. Recent studies have refuted that finding that calcium absorption is the cause [237]. The difficulty in controlling for multiple confounding factors has limited our understanding of the full scope of the effect of acid suppressive medications on bone health, and while the overall fracture risk may be small, the large number of people potentially affected make this a serious issue. At this point, it is advisable to recommend optimal calcium intake in people that need PPIs, address other contributors to fracture risk, and limit the use to the lowest dose and shortest time possible. The calcium supplement which may be the most suitable is calcium citrate because of its better absorption profile [238].
Antiepileptic drugs

The association between antiepileptic drugs (AEDs) and metabolic bone abnormalities has been observed since the 1960’s, when anti-convulsants and osteomalacia were linked together. Since that time there have been several cohort and prospective studies that have shown an association of AEDs with low BMD and increased fracture risk [239–241]. The pathophysiology was felt to be primarily through induction of the cytochrome P450 enzyme system in the liver, which would convert 25(OH)D to an inactive metabolite, leading to less active vitamin D, less calcium absorption, and increase in PTH levels [242]. In fact, in a randomized trial, Mikati et al. showed that using high dose vitamin D supplementation in patients on AEDs could help stabilize the BMD at the spine and total hip compared with low dose vitamin D supplementation [243]. Some studies have found an association of lower BMD even with AEDs that don’t induce the cytochrome P450 system, suggesting an alternative mechanism. A recent retrospective study of some of the newer anticonvulsants (gabapentin, topiramate, levetiracetam) did not show any adverse effects on BMD [244]. Clearly more studies need to be done to definitively link AEDs with bone loss and fractures, and it is recommended to screen for vitamin D deficiency, particularly in those on enzyme-inducing AEDs, and address other aspects of bone health on an individual basis.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed antidepressant medications that have recently received a lot of attention for negative effects on bone and fracture risk. They act by potently blocking the serotonin transporters (5-HTT) which are located in the CNS as well as in the periphery, such as bone [245]. While depression itself has been linked with bone loss, cross-sectional studies have supported an association between decreased BMD and SSRI use in both men and women [246–248]. Longitudinal studies have documented a 1.6-fold greater decline in BMD in those using SSRIs compared with non-users [249]. These studies, however, have been contrasted by investigations of several large databases (The National Health and Nutrition Examination Survey III, Womens Health Initiative, and Study of Women’s Health Across the Nation) that did not reveal an association of BMD decrease with SSRI use [250,251]. Even though there is discrepancy on the effect of SSRI on BMD, most agree that there is an increased risk of fragility fractures among depressed individuals on SSRIs [248,250,252].

The exact mechanism of bone loss among users of SSRI is unknown, and recent focus has been on the effect of serotonin on osteoblasts. Circulating serotonin, of gut origin, was shown to reduce osteoblast proliferation by Yadav et al., an effect modulated by LDL-receptor related protein 5 (LRP5) [253]. The pathways of how serotonin and LRP5 may affect bone mass is an active area of intense research and will likely guide our understanding and recommendations around SSRI use and osteoporosis.

Heparin

The long-term use of unfractionated heparin has been associated with reduced BMD, increased rates of bone loss, and an increased risk of fracture [254,255]. Using rat histomorphometry and bone turnover markers, it has been shown that extended use of heparin reduces bone formation and increases bone resorption; low molecular weight heparin (LMWH) only seems to reduce bone formation markers, possibly contributing to its lessened effects on bone [256]. Recently, long-term use of heparin is mostly limited to treatment of thromboembolism during pregnancy, and as such should be a consideration of bone loss in these women.

Antihypertensives

There are many classes of antihypertensive medications, and the choice of which drug to use is tailored to the individual patient’s indication and comorbidities. The frequency of use of antihypertensives increases with advanced age, as does the incidence of falling, which has led to numerous studies of the effects of these medications on BMD and fracture risk [257]. There is an increased risk of
falls when initiating any antihypertensive medication in an elderly patient, particularly within the first few weeks, which has obvious implications on fracture risk [258]. Diuretics appear to have differential effects on bone based on their mechanism of action, as loop diuretics increase urinary calcium excretion and are associated with elevated markers of bone turnover and lower BMD, while thiazide diuretics decrease urinary loss of calcium and may have protective effects on bone and the risk of fracture [257,259]. Baseline osteoporosis status and fracture risk should be considered when placing a patient on an antihypertensive medication, especially with the elderly.

Summary

As outlined in this brief review, the metabolic activity and strength of bone is affected by a wide array of diseases and medications. An understanding of the degree to which bone is affected is of utmost importance because these conditions will not only decrease the quality of bone, but can significantly increase the risk of fragility fractures as discussed. The burden of fractures can add incredible morbidity to disease processes already affecting the overall health of the patient in so many ways.

Several causes of secondary osteoporosis have been studied extensively, such as the effect that excess glucocorticoids, hypogonadism, inflammatory cytokines, and hypercalciuria can have on bone quality. Active areas of research are now focusing on the role of these diseases and medications in altering bone biology via cellular pathways affecting the RANKL/OPG axis as well as regulators of the Wnt signaling pathway. This work will not only augment our understanding of the pathophysiology, but also guide the direction of future therapeutic options. The appreciation of other causes, such as the bone effects of HIV infection, diabetes, myeloma cells, TZD medications, and SSRI’s is going through rapid expansion in recent years.

A common theme is the need of the general clinicians to understand that many common conditions and medications can adversely affect bone, and there are many patients in addition to postmenopausal females and the elderly that are candidates for screening and treatment of osteoporosis. In so doing many painful fractures can surely be avoided.

Practice Points

<table>
<thead>
<tr>
<th>Glucocorticoid excess</th>
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<tbody>
<tr>
<td>● Up to 50% of patients on chronic GC therapy will experience a fracture</td>
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<td>● Bone loss occurs within the first few months of therapy with GC</td>
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<th>Hyperparathyroidism</th>
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<tr>
<td>● PHPT causes high bone turnover and decreased BMD at areas rich in cortical bone</td>
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<th>Hyperthyroidism</th>
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<tr>
<td>● Severe thyrotoxicosis is associated with an increased risk of fracture despite the underlying cause</td>
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<th>Male hypogonadism</th>
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<tr>
<td>● Testosterone and estrogen play important roles in regulating male skeletal health, and both levels can decline with aging</td>
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<tr>
<td>● Low bioavailable estradiol levels and high SHBG levels are associated with an increased risk of fracture</td>
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<th>Diabetes</th>
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<tr>
<td>● Both type 1 and 2 DM are associated with increased fracture risk</td>
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<td>● The BMD in T2DM is often normal, though the quality of bone is compromised</td>
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<th>Vitamin D deficiency</th>
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<tr>
<td>● Vitamin D, via VDR in the intestine, is crucial for calcium absorption</td>
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<th>Immobilization</th>
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<td>● Bone loss occurs quickly following a spinal cord injury or immobilization</td>
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<th>MGUS</th>
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<tr>
<td>● Bone loss in MM is associated with increased osteoclastic activity and decreased rate of bone formation, leading to osteolysis</td>
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</table>
- Factors released from bone matrix at lytic areas can serve to promote survival of MM cells
- MGUS, though not associated with lytic lesions, is associated with an increased risk of axial fractures.

HIV
- Significant bone loss is seen within two years of starting HAART

Hypercalciuria
- Low BMD and increased fracture risk is seen in hypercalciuric stone-forming patients.

Celiac
- Screening for vitamin D deficiency is imperative in celiac disease
- Decreased absorption as well as systemic inflammation play a role in the development of bone loss in celiac disease

Bariatric surgery
- Maintaining adequate calcium and vitamin D intake is often difficult in bariatric surgery patients, and contributes to the increased risk of bone loss

COPD
- Osteoporosis is common in COPD patients, even in the absence of steroid use
- There is an increased risk of fracture in COPD patients, that is higher in those that use steroids

Transplantation
- Immunosuppressive medications, such as steroids and calcineurin inhibitors, are associated with promoting bone loss in the early post-transplantation period

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<th>Research agenda</th>
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<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>- Understanding the main effects of PHPT on regulators of Wnt signaling will aid our understanding of the pathophysiology of bone loss and directions for treatment</td>
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Hyperthyroidism
- Further research into the role of TSH as a regulator of bone turnover will influence the risk to those with subclinical disease or on thyroid replacement.

Diabetes
- The extent of the fracture risk with TZD medications will be important to quantify as these medications are widely used in T2DM

Vitamin D deficiency
- Isolating the effects of vitamin D deficiency in a heterogeneous osteoporosis population is difficult, but would allow for more solid guidelines on adequate levels for patients.

MGUS
- MGUS, though not associated with lytic lesions, is associated with an increased risk of axial fractures.

HIV
- Further exploration of the role of HIV proteins in altering the regulation of RANKL may help explain the bone loss seen in HIV independent of therapy and comorbidities, and guide future treatments

Hypercalciuria
- The utility of detecting stones in asymptomatic hypercalciuric patients with osteoporosis is yet to be determined, though could affect decision to treat the hypercalciuria

Celiac
- More studies are needed to quantify any increased fracture risk in celiac

Bariatric surgery
- Further studies to define the incidence of fragility fractures in the long term following surgery are needed
References


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