

SECONDARY OSTEOPOROSIS: A REVIEW OF THE RECENT EVIDENCE

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ABSTRACT

Objective: To review several causes of secondary osteoporosis as well as screening recommendations for underlying disorders.

Methods: We conducted a review of the literature on many of the causes of osteoporosis that have been published during the past 15 years, focusing on those sources available from 2000 through the present. Indeed, more than two-thirds of the articles that we reviewed were printed during the past 6 years. These reports examined secondary osteoporosis in general, as well as many of the specific causes.

Results: Secondary osteoporosis occurs in almost two-thirds of men, more than half of premenopausal and perimenopausal women, and about one-fifth of postmenopausal women. Its causes are vast, and they include hypogonadism, medications, hyperthyroidism, vitamin D deficiency, primary hyperparathyroidism, solid organ transplantation, gastrointestinal diseases, hematologic diseases, Cushing's syndrome, and idiopathic hypercalciuria. These causes have their own pathogenesis, epidemiologic features, and effect on the skeleton.

Conclusion: The causes of secondary osteoporosis are numerous, and an understanding of their characteristics with respect to bone density and potential fracture risk is essential in the management of osteoporosis. A heightened awareness of the possibility of their existence is necessary to provide optimal care. (*Endocr Pract.* 2006; 12:436-445)

Abbreviations:

ADT = androgen deprivation therapy; BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry; GnRH = gonadotropin-releasing hormone; IGF-I = insulin-like growth factor-I; IH = idiopathic hypercalciuria; MGUS = monoclonal gammopathy of undetermined significance; OCs = oral contraceptives; 25-OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone; UC = ulcerative colitis

INTRODUCTION

Osteoporosis is a common disease, affecting about 4 to 6 million women and 1 to 2 million men in the United States (1). It increases a person's risk for fractures and, thus, is associated with considerable morbidity and mortality. Although this disease most frequently affects postmenopausal women, it does not spare men or premenopausal women. Current therapies for osteoporosis can increase bone mineral density (BMD) and reduce fractures substantially. Nevertheless, correctable factors that contribute to low BMD do exist, and failure to identify and treat these causes can hinder improvement in osteoporosis. Such secondary causes have been reported in many patients with osteoporosis—specifically, up to 64% of men (2,3), more than 50% of premenopausal and perimenopausal women (2,4), and about 20% to 30% of postmenopausal women (3,5). In light of the prevalence of these factors and the benefits of their correction, recognition and treatment of these causes can be important in the management of osteoporosis.

The vast array of secondary causes of osteoporosis has been reported in many articles. Some of the most common causes include hypogonadism, medications, hyperthyroidism, vitamin D deficiency, primary hyperparathyroidism, solid organ transplantation, and idiopathic hypercalciuria. In men, the 3 most common causes are hypogonadism, treatment with corticosteroids, and alcoholism (1,2). In premenopausal women, the most common causes are likely hypoestrogenemia and use of corticosteroids (4). These 2 causes are also often seen in perimenopausal women, as are anticonvulsant therapy and

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hyperthyroidism (2). Recent data have been published on many of these causes. In this article, we will review much of this information.

HYPOGONADISM

As previously noted, hypogonadism is one of the most common causes of osteoporosis in male patients. Testosterone and estrogen have roles in the maintenance of bone density. These hormones aid in bone formation and help prevent bone resorption (2,6-8); interestingly, estrogen may have more of a role in halting bone resorption than does testosterone (7). Indeed, 70% of the gonadal effect on BMD in male subjects may be due to estrogen (7). This contribution of estrogen is being increasingly more frequently recognized. Barrett-Connor et al (9) found that older men with a vertebral fracture had lower estradiol levels without reduced testosterone levels. In a 4-year follow-up of 200 men, Gennari et al (10) noted that testosterone and bioavailable estradiol levels declined with advancing age. The estradiol levels showed an inverse correlation with changes in BMD and with bone turnover markers, which was not seen with testosterone levels. Therefore, although testosterone does have a role in achieving and sustaining BMD, estrogen is emerging as one of the dominant factors in this capacity.

Besides aging, other conditions can produce a hypogonadal state. One such situation is androgen deprivation therapy (ADT) for prostate carcinoma. Several published studies have examined the relationship between this therapy and BMD decline. A small study by Mittan et al (11) demonstrated that, after 12 months of gonadotropin-releasing hormone (GnRH) therapy, a significant decrease in BMD at the hip and the ultradistal radius occurred in comparison with the control group. N-telopeptide was increased at 6 and 12 months. Two other studies (12,13) compared patients receiving GnRH agonist therapy with healthy patients and with patients who had prostate cancer but were not receiving ADT. Both studies showed that BMD decreased significantly in those patients receiving therapy. N-telopeptide was again elevated, and serum alkaline phosphatase was increased in the study by Stoch et al (12). Basaria et al (13) also found a correlation between the duration of therapy and the decrease in BMD. ADT not only decreases BMD but also increases fracture risk.

Investigators have examined the risk of fractures in patients receiving ADT. Shahinian et al (14) assessed more than 50,000 men with prostate cancer and compared those patients who had received ADT within the first 6 months after diagnosis and those who had not received such therapy. During the first 5 years after diagnosis, those in the treatment group sustained significantly more fractures than those who had not received ADT—19.4% versus 12.6%, respectively. A positive correlation was found between fracture risk and number of doses of GnRH agonist. Of note, those patients who had undergone orchiecto-

my had the highest risk among the treatment subgroups, with a relative risk for fracture of 1.54. In this study, the number needed to harm by ADT was 28 for any dose of a GnRH agonist and 16 for orchiectomy. Lopez et al (15) compared male patients who received luteinizing hormone-releasing hormone agonists, with or without peripheral androgen receptor blockers, and control subjects for a period of 4 to 5 years. They found that, during that time, 11% of the treatment group and 4% of the control group sustained fractures. In comparison with the control subjects, the members of the treatment group were often older, more of them drank alcohol, and more had already sustained a fracture.

Hypogonadism, particularly hypoestrogenism, can be diagnosed throughout the life cycle of women. In young women, diseases that cause low estrogen states result in decreased peak bone mass (3,5). Two common examples are amenorrhea and anorexia nervosa.

Amenorrhea can lead to osteoporosis, even in young women. If a female subject misses half of her menstrual periods by age 20 years, she can experience a decrease in BMD (5). In addition to the severity of the disturbance in the menstrual cycle, the duration of this alteration may also affect bone density (16). In a study of amenorrheic and normal dancers and nondancers, the subjects with amenorrhea had lower baseline BMD—up to 8% less than the control subjects (17). Also, their BMDs remained lower during the 2 years of follow-up. The subjects with amenorrhea whose menses resumed during the study had an increase in BMD, but the bone density did not reach that of the control subjects. In addition, decreased spine BMD correlated with the development of stress fractures.

Anorexia is another common cause of amenorrhea in young women, and the resulting hormonal and nutritional deficiencies contribute to the decreased BMD in this situation (3,5). Grinspoon et al (16) showed that the majority of 130 women with anorexia in their study had decreased BMD on dual-energy x-ray absorptiometry (DEXA) scan, with more than 90% having *T*-scores of -1 or less and almost 40% with *T*-scores of -2.5 or less. Weight, the age at first menses, and the duration of amenorrhea were factors that increased the risk for decreased BMD. In addition to the effects of hypoestrogenemia, these women can also have secondary hyperparathyroidism, hypercortisolemia, and malnourishment (3,5). Insulin-like growth factor-I (IGF-I) may also have a role.

The effect of decreased IGF-I concentrations in women with anorexia has been explored by some investigators. Soyka et al (18) found significantly decreased IGF-I levels in those female adolescents with anorexia nervosa in comparison with the control subjects, as well as a correlation between IGF-I levels and such reflections of nutritional status as body mass index, percent body fat, lean body mass, and leptin but not hypogonadism.

Treatment of decreased BMD in patients with anorexia is a topic of debate. Whether successful therapy for anorexia improves BMD is controversial (5). A recent

study did not demonstrate a significant increase in BMD during a 1-year period in adolescent girls with anorexia who gained weight (19). The benefit of oral contraceptives (OCs) in this setting is also controversial. A trial with supportive evidence for OCs compared 65 women with anorexia and 52 healthy control subjects (20). Of those study subjects with anorexia, 16 had taken OCs. In comparison with those patients who had anorexia and had not taken OCs, their BMD at the lumbar spine was significantly higher, although it was still lower than the BMD in the control group. Subsequent longitudinal trials, however, did not show an increase in BMD with OCs or hormone replacement therapy alone (21,22).

One must remember that not all patients with anorexia are female. From 5% to 10% of such patients are male (3). Although osteoporosis has been reported in male patients with anorexia, limited data are available regarding its prevalence and the effects of treatment. Further studies need to be conducted regarding this issue.

MEDICATIONS

Numerous medications have been implicated in causing loss of BMD. Some of the most common offenders are immunosuppressants, heparin, and anticonvulsants. Most often, corticosteroids have been identified as a cause of osteoporosis (2,23). These drugs are used frequently—in 0.5% of one population examined (24). Even a relatively small dose can cause detrimental effects on BMD. One trial found that less than 2.5 mg of prednisolone per day was associated with an increased risk of fractures (25). BMD loss begins during the first weeks to months of therapy (26,27), and the decline of bone density is most rapid during this time (26). A loss of up to approximately a quarter of the BMD during the first 6 to 12 months of therapy has been reported (23). The extent of this effect is broad, inasmuch as up to a half of the patients receiving long-term glucocorticoid therapy will lose bone density and sustain fractures (26). A small study of men receiving 50 mg of prednisolone daily for 1 to 6 months revealed a decrease in BMD by a mean of up to 4.8% (27). Another study showed that the patients taking corticosteroids for management of rheumatoid arthritis doubled their risk of hip fracture with respect to control subjects (28). Investigators have not yet decided whether the cumulative glucocorticoid dose or the peak dose is more important. Many studies favor the cumulative dose (23); the aforementioned small study in men revealed an inverse correlation between lumbar spine BMD and cumulative corticosteroid dose (27). The United Kingdom General Practice Research Database Study (29), however, demonstrated increased fracture risk with peak dose over cumulative dose.

Inhaled glucocorticoids have also been linked to decreases in BMD with long-term use. Israel et al (30) studied 109 premenopausal women with asthma treated with triamcinolone. They found that the bone density at

the hip and the trochanter decreased by 0.00044 g/cm² for every inhaled puff of triamcinolone taken per year on the treatment. The association was maintained after accounting for all other corticosteroids, age, and use of OCs. Wong et al (31) showed a decrease in BMD with increased cumulative inhaled corticosteroid dose, which persisted after accounting for other corticosteroids.

Glucocorticoids lower bone density by a variety of mechanisms. The main effect of glucocorticoids is on the osteoblast, causing a decrease in bone formation (23). These bone-forming cells also have reduced function and life span (23,26,32). Another effect of glucocorticoids on loss of BMD is increased bone resorption (23), possibly attributable, in part, to secondary hyperparathyroidism (26). Other pathways by which corticosteroids decrease BMD include decreased absorption of calcium, increased calcium excretion, and decreased synthesis of sex hormones (23,26). A decrease in the glucocorticoid dose or discontinuation of the glucocorticoid therapy altogether can help halt this process. For example, in the United Kingdom General Practice Research Database study (29), those patients who stopped taking glucocorticoids had a decreased risk of nonvertebral fractures.

In rat models, heparin has been noted to decrease bone formation and increase bone resorption (33). Many of the studies evaluating the effects of heparin on BMD and fracture risk have investigated female patients receiving heparin during pregnancy. One such study of 184 women, who received 15,000 to 30,000 IU of heparin per day for 7 to 27 weeks, revealed symptomatic vertebral fractures in approximately 2% of the study participants (34). Decline in BMD seems to begin with a heparin dosage of at least 15,000 IU daily for more than 3 months (35). The effects of low-molecular-weight heparin on the skeleton have not been found to be as significant (35,36).

Anticonvulsants have also been linked to diminished BMD. One of the primary mechanisms by which they induce this damage may be by decreasing vitamin D activity and, thus, calcium absorption (35). Some of the more common culprit antiepileptic medications include phenytoin, phenobarbital, primidone, and carbamazepine (35,37). The degree of BMD loss has been related to the frequency and the duration of use of these agents. One study (38) reported a hip BMD loss of 1.16% per year in patients receiving such medications continuously for several years, and a 1.7-fold increased rate of BMD decline at the hip over those not taking such medications. With respect to fracture risk, a study by Vestergaard et al (39) found a small but significant increase in the risk of occurrence of fractures with use of some anticonvulsants, including carbamazepine and phenobarbital.

Immunosuppressants, such as cyclosporine and tacrolimus, have been shown to exert negative effects on bone density in animal models (40,41), but these effects in clinical trials have been less clear. Although decreased BMD has been noted in patients receiving these medications, a possible confounder may be the concomitant use

of glucocorticoids in these cases (42). Their effect on fracture risk is also uncertain; for example, one trial did not find these medications to be significantly correlated with the risk of occurrence of a fracture (43).

HYPERTHYROIDISM

Hyperthyroidism can cause osteoporosis as well, decreasing BMD by 10% to 30% in women (5). The cause of the hyperthyroidism does not seem to affect the degree of bone loss. Jodar et al (44), who compared the BMDs of patients with overt hyperthyroidism or controlled hyperthyroidism and healthy patients, found a decrease in BMD in those with overt hyperthyroidism or controlled hyperthyroidism in comparison with that in the healthy patients. In addition, the patients with overt hyperthyroidism had more bone loss than did those with controlled hyperthyroidism. Of note, these investigators did not find a significant difference in BMD between the patients with Graves' disease and those with toxic multinodular goiter. Both osteoclasts and osteoblasts are increased in hyperthyroidism; however, osteoclasts are amplified more (5). Hyperthyroidism may also decrease intestinal calcium absorption (3).

Attaining a euthyroid state is important for increasing BMD. Kumeda et al (45) demonstrated that patients with hyperthyroidism receiving drug therapy, who still had a low serum thyrotropin concentration despite normal thyroid hormone levels, had persistent increases in bone turnover markers. With resolution of thyroid disease, BMD increases but it may not normalize (5). Some available data, however, support normalization of bone density to that expected for the age of the patient. For instance, Karga et al (46) compared both untreated and treated patients with hyperthyroidism with age-matched women who had not had prior hyperthyroidism. They found that, although BMD was decreased with respect to that in control subjects in untreated hyperthyroidism or up to 3 years after initiation of treatment, BMD was not significantly different from that in control subjects when patients with prior hyperthyroidism were assessed at least 3 years after therapy had been instituted.

VITAMIN D DEFICIENCY

Decreased vitamin D concentrations can have deleterious effects on bone metabolism. Two important metabolic bone derangements that can result from this situation are secondary hyperparathyroidism and osteomalacia. Secondary hyperparathyroidism develops when the vitamin D concentration decreases to an insufficient level (47). Consequently, evidence of increased bone turnover (47,48) and decreased BMD (48-50) can be found. Lips (47) suggested that vitamin D insufficiency ranges from 10 to 20 ng/mL (25 to 50 nmol/L). Variations do exist; Chapuy et al (51) found that parathyroid hormone (PTH) levels increased with slightly higher 25-hydroxyvitamin D

(25-OHD) concentrations—up to 31 ng/mL (78 nmol/L). Osteomalacia may develop after prolonged vitamin D deficiency (47,49). According to Lips (47), this can be found at 25-OHD levels of <5 ng/mL (<12.5 nmol/L). Various trials have further substantiated these theories, confirming an inverse correlation with PTH and 25-OHD (48,52). In addition, the presence of increased bone turnover can be inferred by the inverse relationship between bone turnover markers and vitamin D levels (48,52). The “gold standard” for diagnosing osteomalacia is bone biopsy; however, this technique is not always readily available. Frequently, the diagnosis can be inferred from the presence of a high total or bone-specific alkaline phosphatase value, in conjunction with a low vitamin D level, hypocalciuria, and secondary hyperparathyroidism. Affected patients complain of bone pain (deep aching hip or pelvic pain), motor weakness, and recurrent fractures.

The loss of bone density has been demonstrated in various trials. For example, Mezquita-Raya et al (50) showed a positive correlation between 25-OHD concentrations and BMD. Elsewhere, a 4% lower trochanter BMD has been demonstrated with 25-OHD levels of <10 ng/mL (<25 nmol/L) (48). Moreover, Sahota et al (52) reported a significant decrease in BMD at the hip with 25-OHD concentrations between 6.1 and 12 ng/mL (15.25 and 30 nmol/L). One might further reason that decreased vitamin D is linked to an increase in risk of fracture. These data are not as firm, but reports of an association have been published (47,53).

The effect of vitamin D deficiency on bone density can also be illustrated by changes that occur after vitamin D supplementation. With such replacement, the serum PTH concentration decreases, bone turnover calms, and BMD increases (47,54). In addition, the incidence of fractures decreases. For instance, Adams et al (54) showed a 4% to 5% increase in BMD at the lumbar spine and the femoral neck per year with vitamin D repletion. Furthermore, Dawson-Hughes et al (55) demonstrated a significant increase in BMD and a significant decrease in nonvertebral fractures after calcium and vitamin D supplementation for 3 years.

Vitamin D deficiency is increasingly being recognized as a cause of decreased BMD. In fact, Favus (56) has postulated that it is possibly the most common etiologic factor. Numerous studies assessing its prevalence have been performed. The Multiple Outcomes of Raloxifene Evaluation clinical trial (48) found that 4% of their study subjects had a 25-OHD level of <10 ng/mL (<25 nmol/L) and almost a quarter had a level of 10 to 20 ng/mL (25 to 50 nmol/L). In an assessment of postmenopausal women in North America receiving osteoporosis treatment, Holick et al (57) found that half of them had a 25-OHD level of <30 ng/mL (<75 nmol/L). Chapuy et al (51) reported a 25-OHD concentration of 12 ng/mL (30 nmol/L) or less in 14% of the French women in their study. In addition, 75% of their subjects had a 25-OHD level of <31 ng/mL (<78 nmol/L). In a study of 104 patients at least 98 years old, 99

had an undetectable concentration of 25-OHD (58). Although this deficiency was found in subjects who lived independently, it is more common in hospitalized patients, those living in nursing homes, and patients who have sustained hip fractures (47,53). For example, a study of hospitalized general medicine patients (59) revealed that 57% had a 25-OHD level of <15 ng/mL (<37.5 nmol/L). Seventy-seven of the patients in this study were younger than 65 years and were without known risks for deficiency of vitamin D; 42% of this subgroup had vitamin D deficiency. Although not as common, decreased concentrations of vitamin D have also been detected in the younger population. For example, Tangpricha et al (60) found that 36% of the patients who were 18 to 29 years of age in their study had 25-OHD levels of <20 ng/mL (<50 nmol/L) at the end of winter; this decreased to less than 10% at summer's end.

Several reasons exist for the increased prevalence of vitamin D deficiency in the aged population, including less exposure to sunlight (47,53,56,61) and decreased ability to synthesize vitamin D₃ (47,56,61). Moreover, not enough vitamin D is supplemented orally (47,51,56,61). In addition, dysfunction of the liver or the kidneys can contribute to this deficiency (53,56), as can the ingestion of medications that increase vitamin D clearance (56).

Because much of one's vitamin D supply is derived from exposure to sunlight, it seems logical that concentrations may fluctuate with the seasons and with location. Multiple studies have confirmed such a seasonal variation, with lower levels in the winter than in the summer (48,60,62). This has also been shown with respect to the inverse relationships of 25-OHD with PTH (47,53,60) and with bone turnover markers (47). In addition, Chapuy et al (51) found a difference in 25-OHD concentrations based on geographic location, with a significant decrease in the north in comparison with the south of France.

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism can cause decreased BMD, and it may increase the risk of fractures. This outcome is mainly attributable to an increase in bone resorption (49). PTH is likely catabolic in cortical bone, such as in the distal radius, and anabolic in cancellous bone, such as in the lumbar spine (63-65). Thus, usually more cortical bone is lost than cancellous bone (49,63), although decreased density of cancellous bone has also been seen (63-65). The correlation between PTH and BMD has been shown in such studies as that by Sitges-Serra et al (66), who found a significantly increased PTH concentration in patients with osteoporosis. Although it seems that this decreased bone density would correlate with an increase in fractures, results for this relationship are not completely clear. Some trials have shown an increased fracture risk, such as the study by Khosla et al (67). In comparing the fracture risk in more than 400 patients who had mild primary hyperparathyroidism with that in the general popula-

tion, they found a significantly increased risk of vertebral and pelvic fractures particularly. Other trials, however, have not found an increased risk of fractures (63,64).

Effects of primary hyperparathyroidism can also be seen by assessing bone density and fractures after parathyroidectomy. Several studies have investigated these changes, and they have demonstrated an increased BMD and a decreased fracture risk postoperatively. In a study by Silverberg et al (68), 121 patients with primary hyperparathyroidism participated in follow-up for 10 years. They noted that the patients who underwent parathyroidectomy had an increase in BMD—8% at the lumbar spine and 6% at the femoral neck after the first year and then 12% at the lumbar spine and 14% at the femoral neck after 10 years. Sitges-Serra et al (66) compared the DEXA scans of 28 patients with hyperparathyroidism obtained before and 1 year after parathyroidectomy. They demonstrated a significant increase in BMD at the femoral neck and the proximal femur, especially in the patients with osteoporosis. In a study of 53 patients with mild primary hyperparathyroidism, Rao et al (69) randomized these subjects to surgical treatment or no surgical treatment. Small but significant yearly increases in BMD were seen at the femoral neck and at the total hip after parathyroidectomy. Finally, Vestergaard and Mosekilde (70) showed a 31% decreased risk of fracture after parathyroidectomy.

TRANSPLANTATION

Multiple factors contribute to the decline in BMD in patients with solid organ failure, as well as those who have received transplants. The disease itself, risk factors that develop because of the disease, and related medications, including loop diuretics and glucocorticoids, all contribute to the decreased BMD in such patients. Commonly, patients with end-organ failure are older, immobile, malnourished white subjects who have vitamin D deficiency or hypogonadism and who use tobacco or consume alcohol (5,41,71). After transplantation, many of these risks still exist. In addition, of prime importance are the immunosuppressants used after transplantation (5,41).

Osteoporosis has been documented in patients before and after transplantation. In the pretransplantation setting, it has been reported in up to 19% of patients with heart failure (71), 29% to 61% with lung disease (41,72,73), and 26% to 52% with liver failure (41,74). Fractures have also been reported in these patients; for example, 25% to 29% of patients with end-stage lung disease were found to have sustained a vertebral fracture in one study (72). After transplantation, much of the loss of BMD occurs during the first several months (5,41). Shane et al (75) showed that patients who underwent cardiac transplantation lost a mean of 7% to 11% of the density in their lumbar spine and femoral necks during the first year postoperatively; most of this loss occurred during the first 6 months in the lumbar spine. This finding is similar to other reported data (41). After liver transplantation, patients may lose up to a

quarter of their BMD at the spine during the first year, although this outcome is controversial (41). Bone density in liver transplant patients may improve as early as 6 months after transplantation, at times increasing to pre-transplantation density (5,41,76,77). After lung transplantation, 2% to 5% of bone density is lost during the first year (41). An increased risk of fracture after transplantation has also been reported. During the first year postoperatively, up to two-thirds of patients can sustain a fracture (78). Leidig-Bruckner et al (79) found that, after 2 years, about 25% of the heart transplant patients and about 20% of the liver transplant patients had a vertebral fracture.

GASTROINTESTINAL DISEASES

Various gastrointestinal diseases have been linked to osteoporosis, particularly inflammatory bowel disease and celiac sprue. Up to three-quarters of patients with inflammatory bowel disease may have decreased BMD (80). One study assessing 51 patients with Crohn's disease and 40 patients with ulcerative colitis (UC) found that 55% of the patients with Crohn's disease and 67% of those with UC had osteopenia, and 37% of the former group and 18% of the latter group had osteoporosis (81). Although that study did not have such findings, many other studies have found that the decline in BMD is more pronounced with Crohn's disease than with UC (80). With this BMD decline, an increase in fracture risk over that in the general population has been seen, but the actual risk is likely still small (80,82,83). Aspects of gastrointestinal disease and its treatment contribute to the loss of BMD, particularly glucocorticoid use, malabsorption, vitamin D deficiency, undernutrition, and cytokines (80,83).

Celiac sprue has also emerged as a disease associated with loss of bone density. The primary pathogenesis is malabsorption and subsequently decreased calcium and vitamin D (84). Secondary hyperparathyroidism also has a role (85). BMD with *T*-scores in the osteoporotic range has been noted in one-quarter to one-third of the patients with celiac disease (86). Stenson et al (87) found sprue to be more common in patients with osteoporosis than in those without osteoporosis. In their study, they diagnosed celiac sprue in 3.4% of the 266 patients with osteoporosis in comparison with 0.2% of the 574 study subjects without osteoporosis. With respect to fracture risk, the findings have been inconsistent. For instance, one study found the risk to be 3½ times higher in patients with celiac disease (84), whereas another study did not find an increased risk of fracture in such patients (88). Part of the explanation for these disparate findings may be the usual young age of these patients.

Of note, the diagnosis of celiac sprue is suggested by positive antigliadin, antiendomysial, or transglutaminase antibodies. These antibodies can be low when patients are consuming a gluten-free diet. The optimal diagnostic approach is demonstration of atrophic villi on an upper gastrointestinal biopsy specimen.

HEMATOLOGIC DISEASES

Several hematologic diseases, such as multiple myeloma, systemic mastocytosis, leukemia, and lymphoma, have been associated with decreased BMD (3). Of these, one of the most studied disorders is multiple myeloma. The main mechanism for the BMD loss in multiple myeloma is the synthesis of cytokines that activate osteoclasts by the plasma cells involved in this disease. Up to one-quarter of the patients with multiple myeloma can have low bone mass (3). Abrahamsen et al (89) found an increased prevalence of multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS) in patients with osteoporosis in comparison with patients without osteoporosis. Either multiple myeloma or MGUS existed in about 5% of those patients who had osteoporosis. In contradistinction, no patients without osteoporosis had multiple myeloma and only 2% had MGUS. A study done at the Mayo Clinic revealed an increased risk of fracture in patients with multiple myeloma of about twice that found in the general population (90).

CUSHING'S SYNDROME

Elevated cortisol concentrations resulting from exogenous sources and endogenous production can adversely affect BMD (3). Numerous studies have evaluated the effect of endogenous hypercortisolism on the human skeleton. Normal subjects have exhibited a positive correlation between plasma cortisol concentrations and the rate of bone loss (91,92). Decreased BMD has been found in those patients with subclinical hypercortisolism (93). In patients with Cushing's syndrome, a negative association between cortisol concentrations and BMD has also been shown. Decreases of BMD of approximately 21% at the lumbar spine and 18% at the femoral neck in patients with Cushing's syndrome have been reported (94). Of note, the degree of loss of BMD may be more severe in patients with Cushing's syndrome of adrenal origin than those with Cushing's disease (95).

IDIOPATHIC HYPERCALCIURIA

Idiopathic hypercalciuria (IH) is found in more than half of the patients with recurrent renal stones (96). In addition to causing nephrolithiasis, IH is also associated with decreased BMD (97-99). Studies have reported a decrease in BMD of up to 20% (98-99). IH causes bone loss by many mechanisms. First, patients have increased bone resorption, likely stimulated by cytokines. Misael da Silva et al (99) studied 40 patients with recurrent renal stones, subclassified into hypercalciuric and normocalciuric groups, as well as 10 patients without nephrolithiasis. They found that the patients with hypercalciuria had more bone erosion and osteoclasts; these findings were even more pronounced in the patients with hypercalciuria who had osteopenia. In addition, interleukin-6 and tumor

necrosis factor were elevated in the osteopenic hypercalciuric group in comparison with the normocalciuric group. Second, another process by which bone density may be lost in patients with IH is through increased synthesis of prostaglandin E₂ (97). Finally, reabsorption of less calcium by the kidneys can cause a relative hypocalcemic state (97).

The foregoing changes result in decreased BMD. One study demonstrating this was conducted by Garcia-Nieto et al (97), who assessed 80 patients with IH. In addition to T-scores of less than -1 in more than 60% of the adult female patients, a Z-score of less than -1 at the lumbar spine or the femoral neck (or both) was found in about 48% of them. The Z-score was significantly lower at the lumbar spine relative to that in control subjects (97).

SCREENING

Various recommendations exist regarding when to search for secondary causes of osteoporosis. According to Stein and Shane (5), all women who have not entered menopause and all men who experience fragility fractures or have a Z-score of less than -1 should undergo further evaluation. Several approaches to this investigation have been proposed. For example, the aforementioned investigators have suggested that, in all patients with osteoporosis, a complete blood cell count, complete metabolic panel, erythrocyte sedimentation rate or C-reactive protein, thyroid function tests, and a 24-hour urine specimen for assessment of calcium and creatinine should be performed; in addition, men should have testosterone, luteinizing hormone, and follicle-stimulating hormone levels determined. Favus (56) suggested a fasting calcium, creatinine, 25-OHD, creatinine clearance, and 24-hour urine collection for calcium; the PTH value should then be determined if the calcium level is abnormal or the creatinine clearance is decreased. One study analyzed the necessity of searching for secondary causes of osteoporosis in otherwise healthy postmenopausal women with this disease (100). That investigation found that determining the serum calcium and PTH levels and assessing a 24-hour urine collection for calcium, as well as measuring the thyrotropin level if the patient is receiving thyroid therapy, diagnosed secondary causes in 47 of 55 patients with such disorders and cost \$75 per patient. The presence of a secondary cause in a patient should at least prompt performance of a DEXA scan. Further studies need to be done to guide clinicians in determining the extent of work-up for secondary causes of osteoporosis and the threshold at which such an investigation should be undertaken, perhaps based on DEXA Z-scores and other variables.

CONCLUSION

Secondary osteoporosis is a common disease that affects patients who have not typically been considered at high risk for decreased BMD—namely, men and pre-

menopausal women. It also contributes to low BMD in postmenopausal women, in whom, historically, classic primary osteoporosis is prominent. The causes of this disease are broad. We reviewed some of the more common etiologic factors that have been discussed recently in the medical literature. Heightened awareness of the potential presence of secondary osteoporosis and increased vigilance for its detection are essential in improving bone health in these patients.

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