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Secondary Osteoporosis

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Osteoporosis is defined as a skeletal disorder characterized by a decline in bone strength leading to enhanced risk of fracture. The decline in bone strength or integrity is a result of both low bone mineral density (BMD) and the deterioration of microarchitecture. Assessment of microarchitecture requires a bone biopsy, which rarely is performed in a clinical setting. Since a close relationship has been noted between BMD and the risk of fractures, BMD is used as a noninvasive convenient technology for the assessment of osteoporosis. Diagnosis of osteoporosis frequently is made by a documentation of low BMD, i.e., T score less than 2.5 as defined by the National Osteoporosis Foundation (NOF) or the World Health Organization (WHO). (*See Table 1.*) The T score is calculated by comparing the BMD of an individual person to that of a 27-year-old healthy young woman. Unfortunately, the T score for BMD in men also is established by comparing the patient's BMD to that of a 27-year-old woman. Thus, it is difficult to establish the diagnosis of osteoporosis in population of younger than 27 years. In this population as well as the others, the Z score is determined. The Z score denotes the comparative score of BMD for an individual with the average BMD of individuals of the same age.

More frequently than not, low BMD is expressed as "osteoporosis" in clinical practice. It must be realized that low BMD alone does not always indicate the presence of osteoporosis, since the actual measurement of BMD determines the quantity of the calcium in the bone, e.g., mineral content per cm^2 of bone surface area. A decrease in mineral content of the bone is an expression of a lytic state present in several metabolic bone disorders including osteoporosis, osteomalacia, multiple myeloma, Paget's disease of bone, etc. The distinction between the other lytic disorders and osteoporosis easily is established by a simple laboratory testing with the determination of serum calcium and albumin or ionic calcium as well as phospho-

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rus and alkaline phosphatase. Osteoporosis is characterized by normal concentrations of these, whereas almost all other bone disorders with low BMD the levels of calcium, phosphorus, and alkaline phosphatase are either individually or collectively altered. Low BMD secondary to many disorders frequently has a multifactorial origin and involves multiple pathophysiologic mechanisms.

In reality, osteoporosis almost always is secondary in origin, including the post-menopausal variety since a lack of estrogen is the cause. With increasing knowledge of the disorder over the last several decades, idiopathic or primary osteoporosis without a definite causality has become a rare entity. Post-menopausal osteoporosis, however, frequently is referred to as a "primary type." This report discusses osteoporosis other than the post-menopausal type. Secondary osteoporosis thus arises from many diseases of different origins. (*See Table 2.*) A number of different mechanisms co-exist in the same disorder, and frequently more than one cause of bone loss is present. Although the management of secondary osteoporosis bears similarity to the treatment of the post-menopausal type, the successful outcome almost always requires treatment of the underlying illness and pathophysiology. Whatever the underlying cause, the benefits of treatment to halt or reverse a decrease in bone density and to promote healthy bone are multiple and must be aggressively pursued to prevent fractures with their subsequent morbidity and mortality, including lifelong debilitation. The common causes of osteoporosis in men and premenopausal women contribute to increasing prevalence of fracture in these groups. This report attempts to describe various disorders associated with osteoporosis, but a detailed description of every probable cause of osteoporosis is beyond the scope of this article.

Chronic Disorders

Gastrointestinal Disorders. *Cystic Fibrosis.* Cystic fibrosis is an autosomal recessive multisystem disorder that mainly affects the pulmonary and gastrointestinal systems. Due to therapeutic advances, patients with cystic fibrosis now live longer than they did a few years ago, with the median age of survival increasing from 14 years in 1969 to 40 years in 2005.[1-6] Low BMD culminating in an increased fracture risk now is seen more frequently. It is estimated that two out of three adult cystic fibrosis patients have a decline in the bone density and one-quarter of them have osteoporosis at one or more sites.[5-7] In addition, bone density is likely to be compromised further following lung transplantation due to long-lasting immunosuppressive regimens, especially glucocorticoid administration, required to prevent rejection.[7] In cystic fibrosis, overall bone density is impacted by inadequate bone formation as well as excessive bone resorption. Thus, peak bone mass often is not reached in children with the disease. Instead of maintaining bone mass, children with cystic fibrosis lose bone mass at a rate of one standard deviation per 6-8 years.[1,4,6,7] Their adult counterparts have been shown to lose bone density at the femoral neck at a rate nearly 2% per year in one study, with the degree of reduction correlating with declining forced expiratory volume in one second (FEV1) in many studies.[5] Along with low body weight and delayed puberty (which also are risk factors for low bone density), low FEV1 is an indicator of the degree of progression of cystic fibrosis, thus confirming the role of disease severity as "the best obvious predictor of low BMD."[1,4] Other risk factors for osteoporosis include testosterone deficiency in men and estradiol deficiency in both genders, physical inactivity, and inflammation.[3] Inflammation (both acute and chronic in nature), as well as the caehexia and weight loss noted in these ill patients, is accompanied by an increase in circulating inflammatory cytokines such as IL-1, IL-6 and TNF-alpha with TNF-alpha in particular being shown to be a potent inhibitor of bone collagen synthesis, a major part of the matrix.[7] These cytokines promote bone resorption by osteoclasts, with the net effect being further decrease in bone density.[7] Finally, GI malabsorption along with chronic glucocorticoid use induce overall vitamin D deficiency as well as inactivation of absorbed vitamin D in the liver, respectively.[3,6,7]

The site of bone density loss also is an important factor in this disorder. A recent study showed greater osteoporosis in the lumbar spine in comparison to the hips.[4] It is also apparent that loss of vertebral bone mass is particularly detrimental because the resulting spinal deformities such as kyphosis precipitate a further decline in respiratory function and abdominal symptoms.[4] Thus, declining bone density in this disorder is attributed to both osteoporosis and osteomalacia and, therefore, the treatment is complex. Bisphosphonates, approved for postmenopausal osteoporosis as well as glucocorticoid-induced osteoporosis, increase BMD and reduce fracture rates.[6] Two studies reported the efficacy of intravenous pamidronate in improving bone density in

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Table 1. Diagnostic Criteria for Osteoporosis

DIAGOSTIC CRITERIA *	CLASSIFICATION
T is above or equal to -1	Normal
T is between -1 and -2.5	Osteopenia (low bone mass)
T is -2.5 or lower	Osteoporosis
T is -2.5 or lower + fragility fracture(s)	Severe or established osteoporosis

* Measured in T scores. The T score indicates the number of standard deviations below or above the average peak bone mass in young adults.

Table 2. Causes of Osteoporosis

Chronic Disorders

Inflammatory Disorders

- Examples are rheumatoid arthritis, asthma, and lupus that are treated with steroid medications (glucocorticoid-induced osteoporosis)

Endocrine Disorders

- Growth hormone deficiency
- Low sex hormone levels—hypogonadism
- Cushing syndrome or disease (endogenous hypercortisolemia)
- Hyperthyroidism (excessive thyroid hormone)
- Hyperparathyroidism

Toxins

Drugs

Organ Transplantation

Immobilization

Eating Disorders

Miscellaneous

- Multiple myeloma and related disorders, lytic metastatic bone involvement, osteogenesis imperfecta, hypophosphatasia

patients with cystic fibrosis.[7,8] Furthermore, oral bisphosphonates have been used successfully despite patients having to follow precautions to reduce GI side effects and improve absorption. A retrospective study demonstrated that 36 of 83 patients receiving bisphosphonates (alendronate or risedronate) maintained better bone densities.[5] Use of bisphosphonates resulted in a significant rise in bone density at the lumbar spine and prevented bone loss at the femoral site over 19 months. Alternatively, a prospective, randomized, double-blind, placebo-controlled trial demonstrated a 4.9% increase in bone density in the spine and a 2.8% increase at the femur over one year using the oral bisphosphonate alendronate in comparison to placebo, while yet another prospective but unrandomized study found a similar increase over a 32-month period.[8] In this study, both adults and adolescents were included, denoting the efficacy of oral bisphosphonate irrespective of the age and severity of the disorder.[6] Finally, bisphosphonates also have been shown to be effective in post-lung transplant patients with CF.[8] However, calcium absorption is poor in many of these patients probably because of low plasma 25 hydroxyvitamin D due to maldigestion and malabsorption due to chronic lack of pancreatic lipase.[3] Therefore, supplementation of pancreatic enzymes with adequate vitamin D and calcium intake are crucial in improving osteomalacia contributing to low BMD.

Celiac Disease. Celiac disease is associated with reduced bone mineral density and bone deformities. Since the 1920s, this association has been reported in medical literature as causing marked bone deformities in some patients.[9] The advent of bone densitometry made it possible to recognize bone disease in subtle forms. Presently, it is apparent that the majority of celiac disease patients manifest some degree of bone loss. Bone biopsies indicate that bone loss is multifactorial and is attributed both to osteoporosis and osteomalacia. The fractures occur mostly in patients symptomatic with the disorder.[10] Contrary to GI malabsorption as the major cause of decreased bone density where the diagnosis is made early in life as in cystic fibrosis, celiac disease is diagnosed most often in the third or fourth decade of life. However, the diagnosis in adulthood and subsequent management of the disease with a gluten-free diet does not afford the same success in increasing bone mass as it would if the diagnosis is made earlier in life.[9,11-13] Initially, the bone loss was attributed to osteomalacia caused by both the restrictive dietary vitamin D and calcium intake as well as poor absorption secondary to the disease itself. Moreover, decreasing vitamin D levels induce PTH secretion in an attempt to facilitate intestinal transport of calcium. However, the immature enterocytes contain smaller than normal amounts of vitamin D-dependent calcium binding protein (calbindin), rendering the process less than effective.[14,15] Moreover, the higher levels of PTH itself induces bone resorption[16] leading to osteoporosis.[16] Recent studies, though, have revealed a more complex physiology. Elevated cytokines found in the serum of patients with celiac disease increase osteoclastogenesis and impair the function of osteoblasts promoting osteoporosis.[17,18] Moreover, the results of these experiments paved the way for further studies in patients with celiac disease. In one report, the proinflammatory cytokine interleukin-6 level was inversely correlated with lumbar bone density values, whereas bone-specific antibodies also have been detected recently in several patients with celiac disease.[9,19] Although bone loss is greater in patients with malabsorption at diagnosis, approximately 50% of patients with celiac disease without documented malabsorption also manifest bone loss, thus indicating that mechanisms other than malabsorption must play a role.[9] Bone density also may be reduced by the frequent accompaniment of hypogonadism in these patients, both men and women.[20] The effects of GI malabsorption and excessive circulating cytokines on bone are reflected in elevated bone resorptive markers indicating that new bone formation is outweighed by bone resorption, resulting in a net decrement in bone mass labeled "high turnover osteoporosis."[9] In the final analysis, noncompliance with a gluten-free diet, use of steroids, untreated hypogonadism, weight loss resulting in low body mass index, as well as a previous fracture contribute to a higher fracture risk in these patients when compared with the normal age-matched population.[21]

A gluten-free diet has been successful in retarding bone loss, but the mechanism by which this occurs is yet to be elucidated. It has been postulated that the increase in bone density after gluten withdrawal may be due to a reversal of malabsorption of vitamin D and calcium with consequential improvement in secondary hyperparathyroidism.[22] This effect is most optimal in children, although bone density in adults improves as well, without a return to normal.[23-25] Finally, the effects of a gluten-free diet are prompt, as noted in the first year of therapy, and persistent, providing a long-term benefit.[9] Therefore, current guidelines[9] suggest evaluation of bone density at diagnosis and annually thereafter following initiation of a gluten-free diet in all adults with the disorder including premenopausal women.[9,26-28] In addition to a gluten-free diet, patients with celiac disease also are advised to ingest at least 1200 mg of elemental calcium and 800 units of vitamin D per day and to maintain physical activity. Initiation of therapy with antiresorptive drugs is recommended for those in whom BMD declines or the rise is less than 3% per year, a change considered to be significant by NOF and WHO.

Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis. Osteomalacia and osteoporosis are serious and common sequelae of inflammatory bowel disease, with estimates of osteopenia ranging from 39-51% and osteoporosis from 5-41%.[29-50] Crohn's disease is associated with an increased incidence of osteopenia and osteoporosis, 23% and 36% respectively.[48] Despite possible discrepancies as to whether osteopenia/osteoporosis is as or less common in patients with ulcerative colitis as it is in Crohn's disease, contributing risk factors remain similar in both disorders.[44] Moreover, patients undergoing surgical procedures (e.g., proctocolectomy and ileal pouch-anal anastomosis) are at a higher risk for a further decrease in BMD because of villous atrophy and ileal dysfunction caused by inflammation ("pouchitis").[35]

The risk is greatly increased with treatment by disease-modifying agents, such as glucocorticoids, azathioprine, 6-mercaptopurine, and cyclosporine, since they adversely affect bone density. In both diseases, low bone density frequently is present at diagnosis, suggesting that factors other than medications are responsible, including a protein catabolic state induced by protein malabsorption resulting in collagen breakdown as well as defective vitamin D and calcium absorption.[34,37,41,44] The contribution of individual factors, however, is inconsistent in various reports. According to a recent cross-sectional study, declining bone density was significantly related to disease duration in Crohn's disease, whereas glucocorticoid use was a major contributing factor in patients with ulcerative colitis.[30] In another study, low BMD was significantly related to BMI and was noted more frequently in women with both diseases, while the use of corticosteroids was the prominent factor only in patients with Crohn's disease.[48] In this study, though, patients with Crohn's disease received higher doses of steroids in comparison to those with ulcerative colitis.[48] Finally, a recent study showed that a daily dosage of more than 7.5 mg of prednisone equivalent, a cumulative duration of longer than 12 months, and a total dose of greater than 5 g were significant risk factors for osteoporosis in these patients.[48,51] Thus, most studies concur that glucocorticoids may be the most important risk factor for bone loss. However, an occasional study has reported bone density of age-matched normal controls in patients receiving minimal lifetime corticosteroid exposure.[52] In yet another study, the mechanism was reported to be slightly different with bone loss in ulcerative colitis showing a more significant increase in serum levels of osteocalcin, alkaline phosphatase, and type 1 collagen c-terminal telopeptide, suggesting a high bone turnover, whereas, in other studies, hypovitaminosis D was more frequently noted in Crohn's disease due to maldigestion and malabsorption.[30,34,37,42,44] Moreover, hypogonadism frequently present in these patients also plays a major role in lowering BMD.[48] Alternatively, inadequate hepatic conversion into 25 OH vitamin D_3 induced by glucocorticoids may further promote osteomalacia resulting in a greater reduction in bone density.[52,53] Finally, inflammatory mediators such as cytokines released from the damaged bowel as well as genetic abnormalities occurring in these disorders (e.g., polymorphisms in the interleukin-1 receptor antagonist gene, the Interleukin 6 gene, and collagen type 1alpha1 [COL1A1] gene mutations) apparently also play a role.[47,55]

Irrespective of the differences in pathophysiology, the fracture risk rises markedly in patients with both disorders and the fractures occur 10-15 years earlier in comparison to the healthy age-matched population.[32,33,49] A 40% increase in an overall fracture risk has been cited as the result of decreased bone density in these patients, with a 22.5% prevalence of vertebral fractures and a 60% risk of hip fractures.[31,36,45]

Moreover, in view of the well documented enhanced fracture risk by the vast data in patients with inflammatory bowel disease, prophylaxis must be emphasized. Supplementation with calcium (1200-1500 mg per day) and vitamin D (400-800 IU per day) appears essential. Moreover, patients should be informed about the importance of both the smoking cessation and adequate physical activity. Finally, bisphosphonate therapy (i.e., oral risedronate and parental pamidronate) is shown to improve or prevent decreasing bone density in patients with both Crohn's disease and ulcerative colitis.[39,48,52-57] Alternatively, administration of infliximab, a chimeric antibody against tumor necrosis factor alpha (TNFalpha), is shown to induce an increase in markers of bone formation and a decrease in markers of bone resorption after only 8 weeks of therapy in patients with Crohn's disease.[43] Therefore, it is apparent that appropriate intervention may be able to decrease fracture risk in these disorders.

Gastric Bypass Surgery. Due to the high prevalence of obesity, demand for gastric surgery has increased recently. The older procedure of jeuno-ileal bypass has been replaced by a restrictive operation (e.g., vertical band gastroplasty) and even more frequently by another procedure (e.g., roux-en-Y gastric bypass) because of its malabsorptive property causing metabolic bone disease in the majority of patients (73%) as well as other complications including liver dysfunction.[58] Patients undergoing the newer procedures, however, also are prone to decreased BMD, with the major cause being osteomalacia induced by malabsorption of calcium and vitamin D with further contribution by con-

Table 3. Multiple Factors Involved in Induction of Low BMD in Chronic Renal Failure

OSTEOPOROSIS

- Hypogonadism secondary to chronic illness
- Renal calcium wasting
- Secondary hyperparathyroidism
- Ch calabolic state causing excessive matrix collagen breakdown
- Lack of adequate activity

OSTEOMALACIA

- Lack of formation of 1 25 OH vitamin D_3
- Inadequate vitamin D intake or exposure to sunlight due to reduced activity

ADYNAMIC BONE DISEASE

sequential secondary hyperparathyroidism.[58-62] Osteoporosis also is a contributing factor as revealed by an increase in markers of bone resorption (serum and urine telopeptides) within the first year after the procedure. A decline in circulating concentrations of sex steroids occurring as a result of weight loss and adipose mass reduction also is implicated in induction of osteoporosis.[58,62] However, the enhanced fracture risk due to declining BMD may be reduced by appropriate intervention mentioned earlier, although the data in the literature in this regard are scanty.

Renal Disorders. Bone loss is common in a variety of renal disorders including renal insufficiency with subsequent renal transplantation, distal renal tubular acidosis, and primary hypercalciuria syndromes.

Renal Failure. Bone mineral density does not appear to decline significantly in patients with mild to moderate chronic renal insufficiency.[63] However, patients with end stage renal disease, especially those requiring hemodialysis, demonstrate reduced bone mineral density and increased fracture rates.[64-70] The duration of renal failure despite starting dialysis at an earlier age and undergoing transplantation at a younger age appears to confer a major risk of decreased BMD.[71] The decline in bone density is multifactorial in origin.[65,66,71-78] (*See Table 3.*) Although successful renal transplantation ameliorates some of these risks, others arise, such as long-term therapy with glucocorticoid and other immunosuppressive agents (e.g., tacrolimus, rapamycin, and cyclosporine), persistent secondary hyperparathyroidism, and pre-existing bone disease.[72] It is apparent that renal transplantation increases the risk of bone loss particularly in the first year with bone density decreasing 3-7%.[70] The major mechanisms for decreased bone density after transplantation occur via both osteomalacia caused by inhibition of conversion into active form of inactive vitamin D in the liver by glucocorticoid and osteoporosis induced by activation of osteoclasts as well as a reduction in the activity of osteoblasts.[73-83]

Treatment with adequate vitamin D intake, especially 1 25 OH Vit D_3, as well as calcium supplementation are recommended for these patients even prior to transplantation.[79-82] An aggressive therapy, parathyroidectomy, may be performed in patients with persistent secondary/tertiary hyperparathyroidism.[84,85] Calcitonin administration may be initiated along with treatment of accompanying hypogonadism or selective estrogen receptor modulators in women.[83-87]

Bisphosphonates currently are contraindicated in the presence of renal dysfunction[89] and, therefore, treatment with calcimimetics recently was approved for patients with chronic renal failure and secondary hyperparathyroidism.[90]

Hypercalciuria. The presence of chronic acidosis as in diseases such as distal renal tubular acidosis results in hypercalciuria leading to secondary hyperparathyroidism promoting osteoporosis.[91] However, it appears that chronic acidosis itself plays a large part in suppressing bone formation and increasing bone resorption.[91] On the other hand, patients with familial hypercalciuria due to renal leak also manifest high rates of bone loss.[92-95] However, hypercalciuria secondary to excessive calcium intake or enhanced GI absorption inhibit PTH secretion and therefore is not associated with reduced bone density.[94] Thus, hypercalciuria of renal leak above is associated with a 10-30% reduction in bone density as well as an increase in fracture rates.[92-96] Finally, lack of improvement in bone density in postmenopausal women with appropriate therapy should raise the suspicion of hypercalciuria as a contributing factor since 10-25% of post-menopausal women with osteoporosis also manifest hypercalciuria.[95] Major treatment of this syndrome is a thiazide diuretic because of its property in enhancing tubular reabsorption of calcium.[91-96]

Other Chronic Disorders Involving the Liver and Lung and Those of Inflammatory Origin. (*See Table 2.*) Osteoporosis in these disorders is attributed to multiple pathogenetic factors such as chronic disease, medications, immobilization, etc., described in detail elsewhere in this report.

Endocrine Disorders

Growth Hormone Deficiency. Growth hormone is crucial in maintaining bone mass and metabolism in both early life and in adulthood. IGF-1 mediates many of the actions of growth hormone. However, growth hormone may also have direct effects on bone. Growth hormone excess increases bone density and decreases fracture risk, as illustrated in a recent report.[96] Children with growth hormone deficiency manifest decreases both in bone mineral content and in bone mass with improvement following human growth hormone therapy.[97-99] Moreover, cessation of human growth hormone therapy on attaining adulthood in subjects with a history of childhood growth hormone deficiency also results in a decline in bone density.[99] Finally, adults with growth hormone deficiency also manifest osteopenia,[100-101] and administration of growth hormone induces an increase in bone density at both cortical and trabecular sites in these subjects.[100,101] However, many patients with acromegaly frequently manifest low BMD because of accompanying hypogonadism.[102,104]

Hypogonadism. Osteoporosis in post-menopausal women and elderly men is attributed to a decline in circulating estrogen and testosterone concentrations, respectively.[105-109] In both young men and premenopausal women, hypogonadism is one of the most common causes of osteoporosis irrespective of the

etiopathogenesis of hypogonadism.[105-109] Hypogonadism always contributes to declining bone densities in most chronic wasting disorders such as chronic renal, liver, or GI disorders. Introgenic hypogonadism induced for management of genital cancers, especially breast cancer in women and prostate cancer in men, as well as chronic treatment with steroids and other immunosupressants in patients following organ transplantation plays a major role in facilitating osteoporosis in these patients and therefore may be prevented by use of antiresorptive therapies.[108-112] Congenital or prepubertal hypogonadism (e.g., Turner's syndrome and Klinefelter syndrome) also is well documented to be associated with osteoporosis.[106,115,117]

Another common cause of hypogonadism is hyperprolactinemia. It has been described in children, adolescents, and adults.[118-124] In women with hyperprolactinemia and amenorrhea, trabecular BMD has been found to be reduced by about 20% with a lesser although significant decline (6%) in cortical density.[124] The hypoestrogenic state caused by hypoprolactinemia is thought to be the major cause of the lowered bone density since improvement in the bone density occurs with recovery from hypogonadism rather than with the normalization of prolactin levels.[118,120,124] Some authors, however, believe that high prolactin itself decreases bone density independent of hypoestrogenic state.[118,123,124] This conclusion is questionable, though, since persistent normalization of the prolactin concentration following dopamine therapy over 2 years failed to restore the bone mass in another study.[120] Patients with schizophrenia (already at increased risk for osteoporosis due to poor diet, lack of exercise, polydipsia, and cigarette smoking) may incur further risks of osteoporosis due to prolactin raising effects of antipsychotic agents.[121-128] Thus, the prolactin-raising properties of antipsychotic agents promote a decrease in sex hormones resulting in lowering of bone density. In a recent study, patients with schizophrenia receiving newer atypical antipsychotics with a distinct propensity to raise prolactin manifested significantly lower bone density in comparison to patients not being treated with prolactin raising medications. Therefore, the prolactin-raising property of an antipsychotic agent should be considered when choosing such a medication.[121,125,127-129] Specifically, the atypical antipsychotic risperidone is associated more frequently with raised prolactin levels and a decrease in bone density than others (e.g., olanzapine or clozapine).[127-129] Another recent study documented that hyperprolactinemia leads to bone loss only when associated with untreated amenorrhea secondary to estrogen deficiency in women as well as testosterone deficiency in men,[130,131] confirming the greater role of the lack of sex hormones when compared with to elevated prolactin in declining BMDs noted in these patients.

Glucocorticoid Excess. Although glucocorticoids improve outcomes in many diseases, their use is associated with serious side effects, with the common one being low BMD (i.e., glucocorticoid- induced osteoporosis [GIOP]). Bone loss secondary to long-term administration of glucocorticoids reportedly is the most prevalent form of secondary osteoporosis, with the prevalence being similar irrespective of gender, age or race, with between 30% and 50% of patients sustaining fractures.[132-138] Although the adverse effects of glucocorticoids on bone have been known for over 70 years, according to a recent update GIOP may be more prevalent than ever before because of the increasingly widespread use of glucocorticoids in many disorders. Glucocorticoids have both direct as well as indirect impact on bone matrix as well as mineralization, secondary to multiple mechanisms. The increase in osteoclast recruitment and differentiation causes enhanced bone resorption. Simultaneously, bone formation also is blunted by decreasing osteoblast proliferation and differentiation as well as by a decline in osteocalcin and osteoprotegerin as well as increased apoptosis of cells involved in repair of microdamaged bone.[139] The indirect effect of glucocorticoids on bone occur via induction of hypogonadism with reduction in circulatory sex steroids induced by chronic glucocorticoid administration.[135-139] Glucocorticoids also decrease intestinal calcium absorption and increase renal calcium clearance due to lack of conversion of active vitamin D_3 into active 25 OH Vit D_3 in the liver (i.e., Hepatic osteomalacia).[137-141] Thus, the overall consequences are both osteoporosis and osteomalacia.

Often, the use of glucocorticoids raises the osteoporosis risk for patients with several chronic diseases (e.g., cystic fibrosis, inflammatory bowel disease, chronic renal failure), which themselves are known to increase bone loss. Additional risk factors for GIOP include age over 65 years, low body mass index, vitamin D insufficiency, immobilization, smoking and excessive alcohol consumption, and postmenopausal women not receiving hormone replacement therapy.[135-139] The risk for osteoporosis and subsequent fractures appear similar in both men and women of all races and ethnic heritage. Although the incidence of vertebral and not-vertebral fractures is related to the dose and duration of glucocorticoid exposure, fractures have been reported even with daily doses as low as 2.5-7.5 mg of prednisone and equivalents.[135,136,142] Thus, with BMD declining over 3% as early as 3 months on initiation in some patients, no conclusive evidence exists for either a safe minimum daily dose or the minimum duration of glucocorticoid exposure.[143] With an increasing daily dose, the risk for fracture exacerbates. With administration of the daily dose of 10 mg of prednisone or equivalent, the risk of hip fracture increases seven-fold and the risk of vertebral fractures rises 17-fold.[143,144] The fracture risk appears to decline when glucocorticoids are discontinued.[135-139] The loss is more prominent in trabecular bone compared to cortical bone.[144] There is an ongoing debate, however, as to the role of the route of administration in the extent of osteoporosis risk. Although the association of decreased BMD and increased fracture risk with both oral and intravenous glucocorticoid use is well proven, the data regarding the risk of inhaled glucocorticoids are conflicting.[133,145] Possibly the differences in potencies and the daily dose of the inhaled preparations as well as the fact that patients with chronic lung disease have an inherent greater risk of osteoporosis in comparison to the healthy population may be responsible for the variable outcomes in terms of both the BMD and the fractures in this group.[133,145] Finally, patients losing BMD due to the use of exogenous glucocorticoids appear to be similar to patients who mani-

fest an increase in endogenous glucocorticoid production (i.e., Cushing's disease or syndrome) with similar fracture rates in both groups (30-50%). However, therapy for endogenous hypercortisolemia results in gradual improvement in bone loss with an incomplete recovery.[130,132,143]

Guidelines for preventive measures for GIO published by the American College of Rheumatologists and Royal College of Physicians of the United Kingdom advocate administration of calcium (1500 mg daily) and vitamin D 800 IU, respectively, and the use of bisphosphonate therapy, with initiation sooner rather than later.[143-147] Calcitonin does not appear to be useful.[146] Two recent studies have examined the use of parathyroid hormone (1-34 hPTH or teriparitide) with a finding of a significant increase in bone density in the spine and less at the hip.[146,147] Finally, administration 25OH vitamin D_3 or 125 OH Vit D_3 instead of inactive vitamin D may be more physiological since lack of the conversion of inactive Vit D to 25 OH vitamin D in the liver is induced by glucocorticoids, and this has been shown to provide a marked improvement in bone density.[141]

Hyperthyroidism. Thyroid hormone is widely prescribed and is thought to be associated with a decrease in bone density. Supplementing daily dose of levothyroxine in subjects with primary hypothyroidism required to maintain normal serum TSH levels rarely induces osteoporosis since excessive protein catabolism and consequential matrix turnover is avoided.[148,149] In contrast, a slight excess in concentrations of circulating thyroid hormones resulting from TSH suppressive dose of LT4 as in patients with thyroid cancer leads to increased matrix breakdown and increased osteoclast activity, resulting in declining bone density.[150-153] However, the data are controversial. These observations were confirmed in recent studies in which a number of other factors were associated with a decrease in bone density in patients receiving thyroid hormone preparations including the daily LT4, daily intake of calcium and vitamin D, physical activity, as well as the stage of life of the patient, especially in women (i.e., prior to as opposed to after menopause).[154,155]

Hyperparathyroidism. The classic manifestation of osteitis fibrosa cystica secondary to primary hyperparathyroidism has now become a rare occurrence because of the early diagnosis and prompt management.[156] However, decreased BMD is detected by DEXA in many subjects with this disorder and fracture risk rises at all sites probably with the exception of hip.[157-159] Therefore, declining BMD has been deemed to be one of the indications for surgery because improvement is reported following appropriate surgery to correct primary hyperparathyroidism.[156-159] In contrast, bone disease remains a major outcome in patients with secondary or tertiary hyperparathyroidism as described elsewhere in this report.

Toxins

Smoking. Tobacco smoking has been implicated as a risk factor for decreased BMD. In a study using clinical information from the NHANES-III (Third National Health and Nutrition Survey) from more than 14,000 subjects, cotine, a metabolite of nicotine with a longer half-life and therefore a reliable marker of tobacco exposure, was documented to be a significant risk factor for low bone density in both men and women.[160] Smoking also has been implicated in increasing incidence of fracture with one study showing a 50% increased risk of hip fracture in current as opposed to life-long non-smokers.[161] In women, the effects of smoking appear to be most detrimental after menopause and the occurrence of a hip fracture was relatively correlated especially to the duration of smoking.[161] The longer the duration of smoking, the earlier in life the hip fracture occurred. The same study also noted that the risk of lowering bone density and hip fractures gradually declined on smoking cessation and returned to that in nonsmokers at about 15 years.

The pathophysiology of decreased bone density caused by smoking remains unclear. Several mechanisms have been implicated. Declining BMD in smokers is attributed to reduced circulating estrogen levels due to increased catabolism induced by smoking.[160] Smoking also frequently is associated with low body weight, increased alcohol consumption, and low calcium intake, all of which contribute to declining bone density.[160] Alternatively, smoking also seems to blunt calcium absorption by the gut secondary to decreased vitamin D levels as well as resultant rising PTH concentration.[162] Finally, nicotine is documented to promote a direct toxic effect on cell metabolism, thus influencing both the bone formation and the bone resorption.[162] Simultaneous administration of estrogens is shown to ameliorate the effects of smoking in lowering BMD as shown in a recent study documenting reversal of declining BMD with administration of contraceptives in young Swedish female smokers over a two-year period.[160] Adequate calcium intake, with minimum of 750 mg elemental calcium per day, also was beneficial in attenuating the risk of lowering bone density.[160]

Alcohol. A number of studies have shown a better perspective of bone and lower incidence of fractures in elderly who consume moderate amounts of alcohol,[163] moderate being defined as 4-8 oz of wine or 8-12 oz of beer per day respectively.[163,164] The beneficial effect with regard to bone is attributed to enhanced aromatization of androgens to estrogen inducing inhibition of osteoclasts with decreased bone resorption, a lowering of PTH, and an increase in 1,25 dihydroxy vitamin D.[163,164] However, chronic heavy drinking compromises bone density especially if the alcohol consumption began during adolescence or young adulthood and unfortunately, the damaged bone does not repair despite maintaining a prolonged abstinence.[165] An increased risk of both hip and forearm fracture was found in a study of 85,000 women consuming more than two alcoholic drinks per day.[164] Furthermore, both men and women drinking more than 2 units of alcohol per day were found to have a significant increased risk of fracture of any bone.[162] Studies in animals also have corroborated that chronic excessive alcohol administration inhibits bone repair after injury, decreases bone growth, and may exert some of its effects via direct osteoblast inhibition, also noted in human studies.[166-168] Finally, excessive alcohol intake often leads to poor nutritional status with subsequent decrease in calcium intake along with decreased absorption caused by the alcohol-induced decrease in activated vitamin D levels and a decrease in hor-

Table 4. Organ Transplant and Osteoporosis

- Fractures 8%-65% in 1 year
- Lowest with kidney, highest with liver for biliary cirrhosis
- Loss of BMD > 3%, and fracture risk: greatest in first 6-12 months
- Worse in postmenopausal women and hypogonadal men
- Rx with antiresorptive agents, pretransplant useful in prevention and improvement

mones, e.g., steroid hormones and growth hormone, regulating bone matrix turnover as well as calcium balance, both directly and indirectly.[165,166] These abnormalities appear to improve with abstinence[165] and the effects of binge alcohol exposure on BMD may be mitigated by treatment with a bisphosphonates (e.g., risedronate) as demonstrated in an animal model.[169]

Caffeine. The data regarding intake of caffeine on bone density are sparse. However, a longitudinal study has shown detrimental effects of excessive caffeine intake on BMD in postmenopausal women.[164,170]

Medications

Anti-convulsants. Chronic administration of anti-seizure medications is known to reduce bone density and increase fracture rate and is a common cause of decreased bone mineral density induced by multiple factors: inhibition of hepatic 25 hydroxylase enzyme leading to a decrease in active 25-hyroxy vitamin D and a consequential increase in parathyroid hormone level.[171-175] Phenytoin, phenobarbital, carbamazepine, and primidone increase this hepatic metabolism of vitamin D into an inactive pathway.[172,175] Alternatively, carbamazepine and valproate also increase bone turnover.[168] The ultimate outcome is decreased bone density in several sites including the hip, the spine, and the femur.[171,172,175] Some drugs (i.e., phenytoin, carbamazepine, and valproate) also have been shown to compromise bone density when used as mood stabilizers in psychiatric patients.[171-175]

Thyroid Hormone. (*See Endocrine causes.*)

Antipsychotics. (*See Endocrine causes—hyperprolactinemia.*)

Heparin. Chronic heparin therapy when used in a daily dose of over 15,000 international units for 3 months or longer has been shown to increase the risk of osteoporosis as well as fractures during pregnancy.[176] Fortunately, recently formulated low molecular weight heparin appears to have no untoward effect in terms of bone mineral density or fractures.[176,177]

Immunosuppressive Agents. Drugs such as cyclosporine and tacrolimus are documented to lower BMD in animals and probably are responsible for lowering bone density in humans.[178,179] However, their role in lowering BMD in humans has been difficult to prove because of their use in conjunction with glucocorticoids in most patients.[180,181]

Organ Transplantation

Organ transplantation is one of the few situations markedly increasing the risk of both osteoporosis and fractures in all age groups. (*See Table 4.*) The mechanism for this enhanced risk revolves around multiple factors. All organ transplants are performed to attain and maintain remission from chronic debilitating disorders. These disorders themselves are catabolic in nature and therefore lead to bone matrix breakdown with further compromise of BMD induced by accompanying hypogonadism, maldigestion, and/or malabsorption of vitamin D and consequential hyperparathyroidism.[178-194] Finally, administration of glucocorticoids and other immunosuppressive drugs required to prevent transplant rejection also play a role in lowering BMD and raising fracture risk.[180,181,192-195] Use of antiresorptive agents with adequate calcium intake and appropriate vitamin D supplementation have been documented to prevent onset, retard, and/or improve low BMD, and in turn reduce risk for fractures.[189-194]

Immobilization

Lack of adequate physical activity promotes bone loss. Osteoporosis is further exacerbated by immobility as documented in subjects with permanent paralysis (i.e., paraplegia, quadriplegia) as well as in local areas of the body (i.e., osteoporosis in fingers, toes, etc.) in subjects with rheumatoid arthritis.[196-204] Treatment with antiresorptive agents as well as calcium and vitamin D supplementation has been documented to prevent or improve BMD and alleviate fracture risks.[205-208]

Eating Disorders

Eating disorders are yet another common cause of osteoporosis, especially in young women.[209-220] Once again, multiple factors play a role in this disorder including hypogonadism, decreased insulin growth factor 1 (IGF-1) concentrations, decreased intake as well as maldigestion and malabsorption of vitamin D and calcium with consequential secondary hyperparathyroidism, hypercortisolemia, and global malnourishment.[209-220] Administration of oral contraceptives with or without growth factors or antiresorptive agents (i.e., bisphosphonates) frequently are attempted to improve BMD, but the results are not conclusive.[210,215-221] The most useful therapeutic modality remains the gradual weight gain with persistent and/or recurrent psychiatric intervention, including counseling.[210,216-220]

Miscellaneous Causes

Several other rare causes of osteoporosis exist. (*See Table 2.*) Multiple myeloma as well as lytic metastatic disease secondary to various malignancies are thought to be caused by secretion of humoral substances i.e. osteoclast activation factors, PTH related peptide, various growth factors, etc., promoting bone resorption.[221-224] Osteogenesis imperfecta and hypophosphatasia are congenital in origin with several gene mutations.[225-229] The exact mechanism in osteogenesis imperfecta is less well defined, whereas lack of bone-specific alkaline phosphatase is the obvious cause in hypophosphatasia since this enzyme is required for promoting osteoblastic activity with facilitation of bone formation. Administration of bisphosphonates, oral and parenteral, have been attempted in these disorders with limited success.[221-233]

Conclusion

The major attention has been afforded to postmenopausal osteoporosis for several decades. However, recently osteoporosis secondary to other etiologies in both men and women is being increasingly recognized. Osteoporosis secondary to several disorders as well as iatrogenic causes can be anticipated. However, special attention must be afforded to etiologies that frequently are iatrogenic, such as hypogonadism, glucocorticoid-induced osteoporosis, organ transplantation, gastric bypass surgery, thyroid hormone suppression, etc. Prevention of onset or progression can be achieved with appropriate screening and prompt interventions such as adequate calcium intake, appropriate vitamin D supplementation including administration of active forms, and use of medications with proven efficacy, with the mainstay being antiresorptive agents. The major dilemmas still faced by providers include the dose, the frequency, and the duration of administration of these drugs, especially in the light of the data that BMDs plateau after 3-5 years of their use, and the effects and cost-efficacy of life-long use are unknown.

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Physician CME Questions

8. Osteoporosis in elderly men is attributed to:
   A. loss of lean body mass.
   B. declining testosterone concentrations.
   C. insulin resistance.
   D. osteogenesis imperfecta.

9. Which of the following is associated with a reduction in bone density and increased fracture rates?
   A. Hypercalciuria secondary to renal leak
   B. Hypercalciuria secondary to enhanced GI absorption of calcium
   C. Hypophosphatasia
   D. Familial hypocalciuric hypercalcemia

10. Osteoporosis associated with organ transplantation can be prevented or decelerated by:
   A. immunosuppressive therapy.
   B. treatment with bisphonates.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

C. high protein diet.
D. calcium carbonate 1500 mg/day.

11. Glucocorticoid-induced osteoporosis is:
A. the most common form of secondary osteoporosis.
B. seen with similar frequency in both men and women.
C. occurs irrespective of age and race.
D. All of the above.

12. Factors contributing to low BMD in chronic renal failure include:
A. low magnesium intake.
B. hypophosphatemia.
C. lack of formation of 1 25 OH vitamin D_3.
D. low protein intake.

CME Answer Key: 8. B; 9. A; 10. B; 11. D; 12. C

In Future Issues:

Smoking Cessation

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. 'In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■