Metabolic bone disease is common among patients with chronic liver disease. Osteoporosis accounts for the majority of cases whereas osteomalacia is rare in the absence of advanced liver disease and severe malabsorption. In this review, we will consider hepatic osteodystrophy primarily as osteoporosis and rarely osteomalacia. The reported prevalence of osteoporosis among patients with chronic liver disease ranges from 20% to 100%, depending on patient selection and diagnostic criteria. The pathogenesis is unclear and likely is multifactorial. Regardless of the etiology of bone disease in these patients, they have an increased incidence of bone pain and fractures, a major source of morbidity preceding and following liver transplantation.

PATHOGENESIS

The etiology of hepatic osteodystrophy remains undefined. Histologically, hepatic osteodystrophy is similar to postmenopausal and aging-related bone loss in that trabecular (cancellous) bone is more rapidly and severely affected than cortical bone. Potential inciting factors that either directly or indirectly alter bone mass include insulin growth factor-1 (IGF-1) deficiency, hyperbilirubinemia, hypogonadism (estrogen and testosterone deficiency), alcoholism, excess tissue iron deposition, subnormal vitamin D levels, vitamin D receptor genotype, osteoprotegerin deficiency, and immunosuppressive therapy preceding and following liver transplantation.

Maintenance of skeletal integrity involves a sequential coupling of osteoclast-induced bone resorption with osteoblast-mediated bone formation and subsequent osteoid mineralization at remodeling sites termed basic multicellular units. For bone loss to take place, a negative remodeling balance must occur with the amount of bone resorbed exceeding the amount formed. Dynamic histomorphometry, employing double tetracycline labeling followed by iliac crest bone biopsy, lends some insight into the mechanism of low bone mass formation in chronic liver disease patients. Several studies suggest that reduced bone formation in patients with chronic liver disease is the primary abnormality (“low turnover” osteoporosis), whereas others report reduced or normal formation coupled with increased resorption (“high turnover” osteoporosis).

Low turnover osteoporosis is characterized by a reduced synthesis of collagen matrix and a low rate of mineralization. Osteoblast dysfunction has been implicated and may result from reduced trophic factors such as IGF-1 or the presence of excess putative growth inhibitors, e.g., bilirubin. IGF-1 production by the liver and bone is stimulated by circulating growth hormone and insulin. IGF-1, in turn, stimulates osteoblast proliferation and differentiation. In a rat model of hepatic osteodystrophy, low-dose IGF-1 increased bone mass and bone density. Patients with cirrhosis and osteoporosis have been found to have significantly lower serum IGF-1 levels than patients with cirrhosis without osteoporosis or “normal” controls. Nonetheless, the exact role of IGF-1 deficiency in patients with hepatic osteodystrophy has not been established. Substances retained in plasma resulting from cholestasis may also contribute to osteoblast dysfunction. In vitro, unconjugated bilirubin (but not bile salts) from the plasma of patients with jaundice caused by hepatocellular and cholestatic chronic liver disease or ductal malignancies inhibits human osteoblast proliferation. This suggests that depressed osteoblast function may be related to jaundice, independent of etiology.

Hypogonadism is an established risk factor for osteoporosis. Chronic liver disease accelerates the development of hypogonadism due to both reduced hypothalamic release of gonadotrophins and primary gonadal failure. A decline in circulating estrogen may be a mediator of bone loss in women and men with chronic liver disease. Primary biliary cirrhosis (PBC) patients with premature menopause have lower bone mass than those with normal menopause age. Men with advanced chronic liver disease develop hypogonadism, and with cirrhosis, a further reduction in serum testosterone occurs. Because testosterone is metabolized to estrogen, this results in a relative decline in blood estrogen levels. A histomorphometric study among men with alcohol-induced cirrhosis revealed an impaired bone formation rate and increased osteoclast eroded surfaces that correlated with reduced testosterone levels. Serum estradiol levels were not assessed. Factors such as chronic alcohol ingestion and excess pituitary iron deposition (genetic hemochromatosis) may also contribute to the development of hypogonadism independent of the cirrhotic process. Furthermore, chronic alcohol use and an increased iron burden have been associated with impaired osteoblast activity in vitro and in vivo, respectively.

In the case of high turnover osteoporosis, synthesis of matrix and its mineralization are normal, but osteoblasts are unable to fill the numerous resorption cavities. High turnover osteoporosis has been described among 20% to 30% of patients with chronic cholestatic liver disease, PBC, and primary sclerosing cholangitis. The observed increase in osteoclast...
activity remains unexplained, but may be related to hypogonadism as described above, or vitamin D deficiency. Subnormal serum concentrations of 25-hydroxyvitamin D among patients with chronic cholestatic liver disease have also been reported. This is not believed to result from reduced hepatic hydroxylation, but may result from malabsorption, increased urinary excretion, or reduced enterohepatic circulation of vitamin D. However, many studies have confirmed the lack of a relationship between low 25-hydroxyvitamin D levels and the presence or severity of osteoporosis. Moreover, recent clinical trials that evaluated treatment with vitamin D and/or 25-hydroxyvitamin D have been largely unsuccessful in reversing or halting the progression of osteoporosis as assessed by histomorphometry, bone mineral density, and fracture incidence.

Although vitamin D deficiency per se is likely not implicated in the development of hepatic osteodystrophy, reduced tissue sensitivity to circulating vitamin D due to altered vitamin D receptor genotypes may play a role. In normal individuals and patients with postmenopausal osteoporosis, vitamin D receptor allelic polymorphisms, designated B/b, A/a, and T/t alleles on the basis of restriction enzyme sites, correlate with bone mineral density in some populations. The physiologic effect of vitamin D receptor allelic polymorphisms is unknown, but may be related to altered intestinal calcium absorption or tissue-specific variations in response to 1,25-dihydroxyvitamin D. In general, the degree of osteopenia correlates with the severity of liver disease. However, several studies of patients with PBC have reported subgroups of patients with osteopenia before the development of advanced liver disease, suggestive of a potential genetic predisposition to bone loss. In a cohort of patients with PBC, vitamin D receptor genotype correlated with lumbar spine bone mineral density, with an allele dose effect. Indeed, the risk of developing a vertebral fracture increased 2- to 3-fold with the presence of a T allele in this one study.

Factors other than gonadal hormones, vitamin D, and vitamin D receptor genotypes likely play a role in the development of high turnover bone disease in patients with hepatic osteodystrophy. Osteoprotegerin (OPG), a member of the tumor necrosis factor receptor superfamily, has recently been found to regulate bone turnover. Produced by the liver, OPG inhibits osteoclast differentiation in vitro and in vivo. In a transgenic mouse model, increased hepatic expression of OPG resulted in osteopetrosis, or increased bone density. The role of OPG in hepatic osteodystrophy is speculative; a decline in liver function may be associated with reduced production of OPG and increased osteoclast-mediated bone resorption.

Corticosteroid therapy is the primary therapy for autoimmune hepatitis and has been the mainstay of immunosuppression after liver transplantation. Trabecular bone loss is most rapid during the first 12 months of corticosteroid use and usually occurs with prednisone doses exceeding 7.5 mg/d. Corticosteroids enhance osteoclast activity via the production of interleukin 1 and interleukin 6 while paradoxically suppressing osteoblast function by decreasing differentiation, recruitment, and life span as well as indirectly through reduced synthesis of type 1 collagen and reduced production of IGF-1. In addition, corticosteroids alter intestinal calcium absorption, increase urinary calcium excretion with resultant secondary hyperparathyroidism, and precipitate hypogonadism. The net result is clinically significant bone loss with an increase in fracture risk by greater than 2-fold.

Because of the deleterious metabolic effects of prolonged high dose corticosteroid use, alternative immunosuppressive medications in conjunction with reduced dosages of corticosteroids are used in all patients immediately after liver transplantation. After liver transplantation, bone loss typically follows a biphasic course. Accelerated bone loss occurs with up to 24% deterioration in lumbar spine bone mineral density (measured by quantitative computed tomography) within the initial 3 to 6 months after transplantation. Stabilization and improvement of bone mineral density occurs during the ensuing 12 months and may continue for years. Indeed, reversal of bone loss after liver transplantation correlates with good hepatic allograft function, suggestive that hepatic osteodystrophy results from the physical and metabolic changes associated with the progressive deterioration of hepatic function. Early bone loss after liver transplantation is not only attributed to corticosteroids, but also to immunosuppressive agents such as the calcineurin inhibitors. In rats, cyclosporin and tacrolimus have been found to stimulate bone turnover by increasing trabecular bone remodeling sites resulting in an increase in bone resorption.

In addition, in this rat model, increased interleukin 1 synthesis, and reduced gonadal function occurred in response to cyclosporine use and contributed to bone loss. Because calcineurin inhibitors are used in conjunction with corticosteroids, the independent effects of these agents on bone metabolism in humans is difficult to ascertain.

RECOGNITION OF HEPATIC OSTEODYSTROPHY

Osteoporosis is a histologic diagnosis; however, clinical recognition relies on noninvasive imaging studies such as bone mineral density measurements and radiography, which enable an assessment of bone mass and fracture risk. The World Health Organization defines osteoporosis as a bone mineral density 2.5 standard deviations below the young normal mean (T score). Severe or “established” osteoporosis refers to individuals who meet the World Health Organization definition and have radiographic evidence of one or more fractures.

Dual energy x-ray absorptiometry is the method most commonly used to measure bone mass because it is accurate and can measure multiple skeletal sites. The primary hindrance to the widespread and routine use of dual energy x-ray absorptiometry among patients with chronic liver disease is cost (and potential lack of insurance coverage for screening) coupled with limited pharmacologic intervention data. A less expensive bone mass measurement technique such as quantitative ultrasound may serve as a useful screening tool to identify affected individuals. Cancellous bone sites, i.e., the axial skeleton, are preferred sites of evaluation because of their more rapid change over time and with therapeutic intervention data on treatment efficacy. Skeletal radiographs are useful adjuncts to bone mineral density measurements, as the risk of future vertebral fracture is predicted by the presence of preexisting spinal fractures.

Studies using noninvasive measurements of bone mass in unselected individuals report an osteoporosis prevalence rate of 29% to 43%. However, the vertebral fracture threshold among patients with chronic liver disease has been found to be significantly higher (124-128 g/cm² by quantitative computed tomography [QCT]) than the generally accepted threshold of 98 g/cm² in postmenopausal women. The prevalence of atro-
mastic spinal and peripheral fractures ranges from 8% to 32%, with a higher frequency noted among patients with cirrhosis. Furthermore, the presence of osteoporosis before liver transplantation is an important determinant of fracture development after transplantation. Fractures of the vertebrae, ribs, and long bones have been reported in 24% to 65% of patients in the early (3 to 6 months) postoperative period. Such fractures occur primarily among patients with a preoperative bone mineral density below the fracturing threshold.

Accordingly, patients with cirrhosis or those receiving long-term corticosteroid therapy should be screened for metabolic bone disease with a bone mineral density study. If the patient reports loss of height, a thoracolumbar spine radiograph may be obtained. In addition, several biochemical tests may be useful to ascertain calcium metabolism and gonadal hormone status: serum calcium, phosphate, thyroid function tests, intact parathyroid hormone, 25-hydroxyvitamin D, free testosterone (men), serum estradiol, and luteinizing hormone (women). Major abnormalities in parathyroid function or vitamin D metabolism warrant referral to an endocrinologist or metabolic bone specialist. The majority of patients will have abnormalities of bone mineral density alone; those who meet the World Health Organization definition of osteopenia, osteoporosis, or “established” osteoporosis are candidates for pharmacologic therapy.

MANAGEMENT OF HEPATIC OSTEODYSTROPHY

General Measures

Potentially reversible factors that may effect bone loss should be eliminated whenever possible. These include tobacco and alcohol cessation, reduction of caffeine ingestion, as well as loop diuretic (i.e., furosemide) and corticosteroid dosages. Regular weight-bearing exercise is integral to the maintenance of skeletal integrity by maintaining both muscle and bone mass. Exercise in combination with adequate dietary intake of calcium has been shown to be effective for delaying the progression of bone loss in postmenopausal women and may prevent bone loss in liver disease patients. For those patients with advanced liver disease, physical therapy with a focus on strengthening of the back muscles may be beneficial. After liver transplantation, physical therapy to facilitate early mobility is imperative. Patients with symptomatic vertebral fractures or bone pain should receive analgesics, muscle relaxants, and a spinal brace (in the case of vertebral fractures) to facilitate mobility.

Nutritional Therapy

Varying degrees of calcium malabsorption may occur in patients with chronic liver disease due to malnutrition, vitamin D deficiency, the use of cholestyramine, and/or corticosteroids. Early calcium supplementation is important because of its bone-protective effects. Furthermore, a study of osteoporotic women with PBC revealed an independent positive effect of oral calcium on bone mineral density. Age-specific guidelines for calcium requirements have been put forth by the NIH: adults at risk for osteoporosis should ingest 1,500 mg of elemental calcium per day. Calcium carbonate and calcium citrate are generally well tolerated and absorbed. Calcium supplementation is especially warranted in the post-transplantation setting during which there is a period of increased bone resorption followed by rapid formation.

In the United States, overt vitamin D deficiency with osteomalacia is rare; nonetheless, derangements of calcium and vitamin D often accompany chronic liver disease. However, early trials of vitamin D administration in osteoporotic patients with cholestatic liver disease failed to delay the progression of osteoporosis as assessed by bone mineral density and fracture incidence. In a subsequent small randomized, controlled trial of vitamin D–deficient patients with alcohol-induced liver disease and osteoporosis, treatment with vitamin D (ergocalciferol, 50,000 IU three times weekly or 25-hydroxycholecalciferol, 20 to 50 mg daily) significantly increased bone mineral density compared with the controls. In addition, patients with PBC and viral-induced cirrhosis obtained a similar beneficial effect with calcitriol (0.5 mg twice daily) on bone mineral density. However, baseline histomorphometry was not performed to exclude underlying osteomalacia. Thus, routine administration of pharmacologic doses of vitamin D in patients with chronic liver disease is controversial.

Initial studies suggested that pharmacologic doses of calcitriol may improve calcium absorption and stabilize bone mineral density in patients receiving corticosteroids. However, the routine use of calcitriol among patients treated with long-term corticosteroids fell out of favor because of a negligible impact on fracture incidence and the potential for associated toxicities (hypercalcemia). In a large randomized, controlled study, patients with rheumatoid arthritis receiving calcium and vitamin D (500 IU, equivalent to one multiple vitamin a day) as well as low-dose prednisone exhibited increased bone mineral density by comparison with those receiving placebo. In the absence of histomorphometry suggestive of osteomalacia, there is little evidence to support the routine administration of vitamin D beyond the recommended daily allowance contained in 1 to 2 standard multivitamins (400 to 800 IU).

Antiresorptive Therapies

Hormone Replacement. A gradual decline in serum testosterone and free testosterone levels occurs with advancing age. This decline is accelerated by the presence of chronic liver disease. Few data exist regarding the efficacy of hormone replacement therapy in osteoporotic men with chronic liver disease. In a small study of hypogonadal men with hemochromatosis, monthly testosterone injections resulted in a significant improvement in bone mineral density. The degree of liver disease in these patients was not well defined. Furthermore, there are no data regarding the effect of testosterone repletion on the rate of bone loss in men after liver transplantation. Nonetheless, in the absence of clear contraindications (prostate cancer, elevated prostate specific antigen, uncontrolled hyperlipidemia), symptomatic hypogonadal men may be candidates to receive injectable or transdermal testosterone preparations with the dosage adjusted to maintain high normal serum testosterone levels. This form of therapy must take into account the risks and benefits of testosterone.

It is well established that hormone replacement therapy during menopause prevents postmenopausal bone loss and reduces the incidence of fractures. Concern regarding the cholestatic potential of estrogen because of a decrease in bile flow and the lack of large randomized trial data have limited the use of estrogen replacement among women with chronic liver disease. Nonetheless, the safety and efficacy of this therapy in women with chronic liver disease are reported in patients with autoimmune hepatitis as well as in two small studies of postmenopausal women with PBC. In a case-
control study, a significant increase in lumbar spine and total body bone mineral density occurred in PBC patients with osteoporosis treated with estrogen for 2 years versus controls. Similarly, in a retrospective analysis of 16 women with PBC who received oral estrogen supplementation, a significant increase in lumbar spine bone mineral density occurred compared with controls. No study reported clinical or biochemical worsening of cholestasis in association with estrogen use. A large randomized trial evaluating the effect of hormone replacement therapy on bone mineral density in patients with PBC is ongoing. The efficacy and safety of hormone replacement therapy in female liver transplant recipients have also not been determined. Improved bone mineral density in women with glucocorticoid-induced osteoporosis receiving estrogen therapy offers some encouragement. Furthermore, in animal models, estrogen curtails cyclosporine-induced bone loss, suggestive of a benefit for the transplant recipient.

At this time, hormone replacement therapy in postmenopausal women and premenopausal women with hypothyroid amenorrhea caused by chronic liver disease should be administered cautiously with close monitoring of hepatic function. Transdermal estrogen has less hepatotoxic potential than oral preparations and should be considered as first line therapy. Individuals with an intact uterus will also require a progestin supplement. Premenopausal women with hypothyroid amenorrhea may be managed with oral contraceptives or very low doses of oral estrogen. Women with hypothyroid amenorrhea may have a spontaneous recovery of menses within 6 months after liver transplantation, allowing cessation of hormone replacement therapy.

Calcitonin. Calcitonin, administered via nasal inhalation or subcutaneous injection, decreases bone resorption by inhibiting osteoclast activity and number. In postmenopausal women with osteoporosis, calcitonin not only reduces bone loss in the spine and hip, but reduces the incidence of vertebral fractures. In addition, the injectable form has demonstrable analgesic effects in 50% of individuals. Current data regarding the use of calcitonin for the treatment of hepatic osteodystrophy are limited to patients with PBC. In a cross-over design study of vitamin D–replete PBC patients treated with calcitonin (40 IU subcutaneously every other day) or placebo for 6 months with a 3-month washout period, there was no difference in bone mineral density. Of note, an initial transient improvement in lumbar spine bone mineral density resulted from calcium supplementation alone. However, in an uncontrolled study of patients with osteoporosis and PBC, sequential therapy with 1,25 dihydroxyvitamin D followed by calcium and calcitonin therapy (40 IU intramuscularly three times weekly) delayed the progression of bone loss over a 3-year period. A beneficial effect of calcium therapy alone could not be excluded due to the study design. The effect of calcitonin on fracture incidence or bone pain in patients with hepatic osteodystrophy has not been evaluated.

Calcitonin is effective for the treatment of corticosteroid-induced osteoporosis and in animal models it is reported to prevent cyclosporine A–induced bone loss. Therefore, it is regarded as a promising agent for the prevention of bone loss after organ transplantation. In a small randomized study in which liver transplant recipients received injectable calcitonin (40 IU intramuscularly, daily), a significant increase in bone mineral density (6%) occurred with calcitonin versus untreated controls. The effect on fracture incidence or bone pain was not reported. Side effects are few and include flushing and nausea. The intranasal form is relatively easy to use and is the preferred method of drug delivery. There are currently no data regarding the efficacy of intranasal calcitonin in liver transplant recipients.

Bisphosphonates. Bisphosphonates are phosphate derivatives that attach to the surface of bone and thereby prevent osteoclast-mediated resorption. Etidronate, one of the first bisphosphonates available for oral use, reduces fracture incidence but must be administered cyclically to prevent bone mineralization defects. Pamidronate, a second generation parenteral bisphosphonate, is more potent than etidronate and may be administered every 3 to 6 months as a single infusion. Alendronate and risedronate, oral amino-bisphosphonates, have been shown to increase vertebral bone mineral density and reduce the incidence of vertebral fractures in postmenopausal women when ingested daily.

Bisphosphonates are effective for preventing corticosteroid-induced bone loss. Cyclical etidronate has been shown to prevent corticosteroid-induced bone loss in at least 2 randomized trials. Similarly, a recent multicenter, randomized trial revealed an increase in bone mineral density with alendronate and risedronate in patients treated with corticosteroids. The potential for ulcerative esophagitis with daily oral bisphosphonates has hindered its routine use in patients with advanced liver disease and esophageal varices because of concerns of precipitating esophageal variceal hemorrhage. In a small trial of patients with PBC receiving azathioprine and corticosteroids, treatment with cyclical etidronate (400 mg daily for 2 weeks) versus calcium alone resulted in a cessation of progressive bone loss as assessed by lumbar spine bone mineral density 3 and 12 months after initiation of therapy.

Preliminary data regarding the use of these agents in liver transplant recipients are also encouraging. In a randomized trial, cyclic oral etidronate resulted in a significant increase (8%) in vertebral bone mineral density after 1 year of therapy in liver transplant recipients versus untreated controls. Moreover, intravenous pamidronate, administered at 3-month intervals before and for 9 months after liver transplantation, has been shown to prevent vertebral fracture incidence in liver transplant recipients (0% treated vs. 38% untreated) with low pretransplant bone mineral densities. Further studies evaluating the efficacy and safety of these agents, including alendronate, in liver transplant patients are underway.

Bisphosphonates are approved for use in postmenopausal osteoporosis as well as for the prevention and treatment of corticosteroid-induced osteoporosis. These agents are generally referred to as “anti-resorptive” agents because they uniformly decrease bone remodeling and allow for the remodeling spaces to fill in, resulting in a modest increase in bone mass. In patients with high remodeling space, anti-resorptive agents may increase bone mass up to 2%. By contrast, “anabolic agents,” such as fluoride and parathyroid hormone-related fragments increase bone mass to a greater degree than simply filling in the remodeling space.

Anabolic Agents

Fluoride. Sodium fluoride stimulates osteoblast proliferation and increases bone formation. Fluoride use may increase bone mineral density in corticosteroid-induced osteoporosis. However, excessive exposure to fluoride may result in reduced bone strength and quality with an increased poten-
tial for fractures. In a large randomized study of high-dose fluoride (75 mg/d) for the treatment of postmenopausal osteoporosis, lumbar spine bone mineral density increased 35% over a 4-year period without an impact on the incidence of vertebral fractures. However, peripheral bone fracture rates were increased in the fluoride-treated group, suggesting that the new bone formation was structurally defective. A subsequent randomized trial investigating the use of low dose (50 mg/d) cyclic slow-release sodium fluoride with calcium supplementation for 4 years resulted in a substantial increase in lumbar spine bone mineral density and a significantly reduced incidence of vertebral fractures, implying that the newly formed bone was qualitatively normal.

Accordingly, low dose sodium fluoride has been studied in patients with hepatic osteodystrophy. In a small randomized study of patients with PBC receiving calcium and vitamin D supplementation, sodium fluoride (50 mg/d) prevented a progressive loss of bone mineral density compared with controls. The effect on fracture incidence was not determined, as no new fractures occurred in fluoride-treated patients or controls. A subsequent study evaluating the effect of sodium fluoride (25 mg/d) in patients with chronic liver disease receiving calcitriol (0.5 μg) and calcium revealed a significant increase in lumbar spine bone mineral density, 25% at 2 years versus a 13% increase in those receiving calcitriol alone and a 5% increase in untreated controls. No fractures occurred in treated patients; untreated patients had a fracture incidence of 13%. The efficacy and safety of fluoride in liver transplant recipients has not been evaluated and fluoride is currently not FDA approved.

GENERAL RECOMMENDATIONS

Multiple factors contribute to the development of hepatic osteodystrophy. The best course of management for these patients is to review the individual risk factors for osteoporosis, obtain a bone mass measurement, and prescribe age and disease-specific therapies. The dosage, route, and frequency of administration, cost of available therapies, and our treatment recommendations are outlined in Table 1.

**REFERENCES**


