AMERICAN GASTROENTEROLOGICAL ASSOCIATION

American Gastroenterological Association Medical Position Statement: Osteoporosis in Hepatic Disorders

This document presents the official recommendations of the American Gastroenterological Association (AGA) on Osteoporosis and Hepatic Disorders. It was approved by the Clinical Practice Committee on March 1, 2003, and by the AGA Governing Board on July 25, 2003.

Metabolic bone disease occurring in individuals with chronic liver disease, known as hepatic osteodystrophy, is a potential complication of long-standing hepatic disease. Special care is required to prevent the development of fractures in individuals with advanced hepatic disease and following liver transplantation. This position statement summarizes the graded findings and recommendations of a systematic technical review of osteoporosis in these states. The general biology and pathogenesis of osteoporosis, including its relationship with inflammatory states, diagnostic tools, and clinical utility of bone densitometry, has been reviewed elsewhere in the AGA Technical Review on Osteoporosis in Gastrointestinal Diseases.[1]

Complex metabolic changes in liver disease create multiple mechanisms for alterations in bone metabolism, and in any given patient it is likely that multiple factors are operating simultaneously. Bone loss in women with cholestatic and noncholestatic liver diseases is more rapid than in healthy controls, and hypogonadism is a contributing factor. Nutritional deficiencies are very common in advanced cirrhosis, and the medications used in the treatment of liver disease can also have an adverse effect on bone and calcium metabolism. Although the liver has an essential role in vitamin D absorption and metabolism, osteoporosis (and not osteomalacia) is the primary skeletal disorder.

There is marked heterogeneity in bone mineral density (BMD) findings in chronic liver disease, ranging from no effect to a large BMD deficit. Technical factors and differences in study populations may contribute to this. On average, a mild BMD deficit appears to be present. Although cholestatic disorders (primary biliary cirrhosis and primary sclerosing cholangitis) are stated to show a greater reduction than noncholestatic liver disease in some studies, the differences are probably not clinically significant. Osteoporosis may appear more striking in primary biliary cirrhosis because the disease usually affects elderly women, who are naturally prone to osteoporosis.

Established cirrhosis is generally associated with lower BMD than noncirrhotic liver disease, but duration of liver disease does not correlate with BMD. Among cirrhotic patients, more advanced clinical and histologic stages generally show progressively more severe skeletal deficit. As expected, women showed reductions in age- and sex-matched BMD that are equal to or greater than in men. Menopause (especially premature menopause) and male hypogonadism adversely affected BMD in some series. Greater body mass and weight may be associated with greater BMD, but the correlation is inconsistent. Corticosteroid use in mixed liver disorders has been associated with reduced BMD in some, but not all, studies.

Most longitudinal studies of BMD in chronic liver disease have focused on cholestatic disorders, and many of these have been limited by small patient numbers, short follow-up, measurement at peripheral sites with poor site-responsiveness, and instrumentation with suboptimal precision. Most of the available data concerns the lumbar spine, and the paucity of hip data is a significant shortcoming. In general, rates of bone loss are similar to expected, although some studies of women with primary biliary cirrhosis or viral cirrhosis have shown accelerated bone loss.

Vertebral and nonvertebral fracture rates are increased in chronic liver disease, especially in postmenopausal women. Population differences in terms of age, sex, and corticosteroid exposure probably contribute to the wide reported range (3%–44%) in prevalent vertebral fracture rates. Fracture rates increase dramatically in healthy older subjects, and this expected pattern is seen in patients with chronic liver disease. In the largest cohort to date, prevalent vertebral and peripheral fracture rates among a group of patients with mixed liver disorders were approximately twice the rate of matched controls. Postmenopausal women are probably at much greater risk than men or younger women. In regression analysis, vertebral fractures have been independently related to lower spine BMD, severity of liver dysfunction, and

hypogonadism. Peripheral fractures were related to established cirrhosis, hypogonadism, and alcohol abuse. Fracture rates are minimal in eugonadal noncirrhotic patients. Incident fracture rates have been less well characterized, but reduced lumbar spine BMD appears to be a marker for increased risk of vertebral fracture.

As the long-term survival of patients undergoing orthotopic liver transplantation (OLT) increases, osteoporosis is becoming a major cause of morbidity. The etiology is multifactorial, and pretransplant bone disease and posttransplant factors both contribute to the problem. Of these, the single most important factor in the development of posttransplant bone disease is the degree of osteopenia at the time of OLT. The use of high-dose corticosteroids and other immunosuppressive agents such as cyclosporin A and tacrolimus (FK506), immobility, and poor nutrition are believed to contribute to the excessive bone loss after OLT. Postoperative regimens are changing, and patients now spend much less time immobilized in the hospital. Newer immunosuppressive regimens are also less reliant on corticosteroids. An important but unanswered question is whether these undesirable effects of liver transplantation on bone can be avoided.

Bone loss after OLT follows a biphasic course, with the greatest decrease during the first 3–6 months and then spontaneous stabilization or even improvement after 6–12 months. Measurement of predominantly cortical peripheral sites appears to be relatively insensitive in detecting loss in bone mass compared with the lumbar spine and hip. Some studies suggest that the hip is reduced to a greater extent than the lumbar spine and shows less spontaneous recovery. Long-term follow-up data even suggest the possibility of continued recovery of BMD for as long as 7 years after OLT. The small but statistically significant decrease in BMD after OLT is insufficient to completely account for the high early fracture risk and does not usually worsen over time. Immunosuppressive therapy used to prevent rejection of the transplanted liver undoubtedly contributes to rapid loss of bone mass after OLT. The deleterious effect of high-dose corticosteroids is well known, and maximum bone loss occurs during the first 3–6 months, when the corticosteroid dose is the highest. Bone loss decreases as corticosteroids are tapered to maintenance levels. A similar temporal relationship holds for cyclosporine and tacrolimus.

Pre-OLT bone histomorphometry most commonly shows a low turnover pattern with reduced bone formation rate, reduced osteoid area and osteoblast surface, and osteoporosis without osteomalacia. Histologic studies performed 3 months after OLT show an increase in osteoblast surface and bone formation with a parallel increase in serum bone Gla protein (osteocalcin). Vitamin D insufficiency is present in up to 96% of patients before OLT. Postoperative bone loss is accompanied by a decrease in lean body mass, which can predispose to falls and may contribute to the increase in frequency of fractures after OLT.

Many cross-sectional studies confirm that patients undergoing assessment for OLT have a significant reduction in BMD and a high prevalence of frank osteoporosis, but no consistent factors have been identified to predict reduced pretransplant BMD. Whether the specific liver diagnosis is an important factor is uncertain. Primary cholestatic disorders may show more severe reductions in pretransplant and posttransplant BMD than parenchymal disorders, but this is far from a uniform finding.

Most fractures develop in the first year after OLT, and very few fractures occur after the first 3 years. The spine is the most common fracture site in most studies but may go undetected unless x-rays of the spine are performed. Pre-OLT prevalent vertebral fractures are the single strongest predictor of post-OLT vertebral fractures, but BMD is also important because reduced BMD pre-OLT and post-OLT has been associated with higher fracture rates. Women were significantly more likely than men to sustain fractures, and postmenopausal status (for women) or age older than 45 years (for men) identified most fractures.

Summary of Bone Disease in Chronic Liver Disease

1. On average, there is a mild BMD deficit in chronic liver disease, but considerable patient heterogeneity exists (level B evidence).
2. In the absence of concurrent corticosteroid therapy, rates of BMD loss are similar to predicted (level B evidence).
3. Vertebral and nonvertebral fracture rates are increased in chronic liver disease, especially in postmenopausal women (level A evidence).
4. Markers of greater osteoporosis and fracture risk include older age, hypogonadism, corticosteroid therapy, and established cirrhosis (level B evidence).
5. Eugonadal noncirrhotic patients generally have a low incidence of osteoporotic fractures (level A evidence).
6. Patients with primary biliary cirrhosis are at increased risk for osteoporosis due to predominant female sex and older age, but cholestatic disease per

se does not differ significantly from noncholestatic disorders in terms of osteoporosis and fracture risk (level A evidence).
7. Prediction rules relying on multiple variables (such as body mass index, corticosteroid history, age, and sex) may be a useful aid in predicting the presence of osteoporosis and for risk stratification (level B evidence).

Summary of Bone Disease After Liver Transplantation

1. All pre-OLT patients should be evaluated for osteoporosis and disorders of bone metabolism: history and physical examination with attention to risk factors for osteoporosis, thoracolumbar spine x-rays, serum calcium, phosphate, 25-hydroxyvitamin D, and free testosterone (for men). Thoracolumbar spine radiographs should be repeated if the patient reports loss of height or severe back pain (level D evidence).
2. Bone loss after OLT follows a biphasic course, with the greatest decrease during the first 3–6 months and then spontaneous stabilization or even improvement (level A evidence).
3. Most fractures develop in the first year, and very few fractures occur after the first 3 years (level A evidence).
4. The small but statistically significant decrease in BMD after OLT is insufficient to completely account for the high early fracture risk and usually does not worsen over time (level A evidence).
5. Posttransplant BMD can recover to above baseline, and this seems to be more common with cholestatic liver disease (level B evidence).
6. Pretransplant insufficiency fractures and low BMD are markers of high fracture risk after OLT (level A evidence).

Bone Density Testing and Therapy in Liver Disease

The general approach to osteoporosis therapy, including corticosteroid-induced osteoporosis, has been discussed in the AGA Technical Review on Osteoporosis in Gastrointestinal Diseases.[1] There is a paucity of therapeutic intervention studies specifically aimed at bone health in hepatic diseases. Most well-powered treatment studies are in populations of postmenopausal women or corticosteroid-treated patients who do not have gastrointestinal or hepatic disease. Studies are required that assess interventions directed at bone health in these disorders specifically and that use fracture prevention as the primary end point. Although there is much enthusiasm to address bone disease in hepatic diseases, there is a pressing need for prospectively conducted research to define the magnitude of the problem and the interventions required.

Summary of Bone Density Testing and Therapy in Liver Disease

The following outlines a possible approach to managing osteoporosis in hepatic disorders.

1. Patients who have experienced a fragility fracture, who are postmenopausal, and who require long-term treatment with corticosteroids (>3 months) should undergo BMD testing. BMD should also be assessed when the diagnosis of primary biliary cirrhosis is first made, in patients with cirrhosis, and before liver transplantation (level D evidence).
2. Patients with risk factors and a normal initial BMD result should be retested after 2–3 years to exclude significant bone loss. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy (level D evidence).
3. Osteoporosis can be the first clinical manifestation underlying cholestatic liver disease, and it may be worthwhile to screen for anti-mitochondrial antibody in osteoporotic patients with both an elevated γ-glutamyltransferase and serum alkaline phosphatase level (level D evidence).
4. All patients require education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation) as well as vitamin D and calcium supplementation (level D evidence).
5. All patients should receive 1000–1200 mg of elemental calcium daily (depending on their age) and at least 400–800 IU of vitamin D daily. Vitamin D deficiency should be corrected by increasing serum 25-hydroxyvitamin D levels to at least 25–30 ng/mL (level D evidence). In patients with malabsorption, higher doses of calcium and vitamin D may be necessary.
6. If female hypogonadism or early menopause (before age 45 years) is evident, hormone replacement therapy (best via the transdermal route in patients with malabsorption or liver disease) is advised for the prevention of osteoporosis (level D evidence in hepatic disease, level A evidence for vertebral and nonvertebral fracture risk reduction in generally healthy postmenopausal women). Es-

trogen therapy is approved by the Food and Drug Administration for the prevention of osteoporosis in postmenopausal or hypogonadal premenopausal women but must be balanced against the significant risks. Non–estrogen-based therapy is generally preferred for older postmenopausal women.

7. Raloxifene, a selective estrogen receptor modulator, is approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women (level D evidence in hepatic disease, level A evidence for vertebral fracture risk reduction in osteoporotic postmenopausal women). A bone disease specialist should participate in the decision to choose raloxifene in patients with a hepatic disorder.
8. Testosterone should be used to treat hypogonadism in men (level D evidence).
9. Bisphosphonates should be considered in patients with known osteoporosis, with vertebral fractures, or who cannot withdraw from corticosteroids after 3 months of use (level D evidence). Bisphosphonates are approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in patients with known osteoporosis, with fragility fractures, or on prolonged corticosteroid therapy (level D evidence in hepatic disease, level A evidence regarding vertebral and nonvertebral fracture risk reduction in postmenopausal women, level A evidence regarding vertebral fracture risk reduction in osteoporotic men and corticosteroid-treated patients).
10. Nasal or subcutaneous calcitonin can be considered as an alternative when the preceding antiresorptive agents are contraindicated or poorly tolerated (level D evidence in hepatic disease, level A evidence regarding fracture risk reduction in osteoporotic postmenopausal women).
11. As in other organ transplant recipients, bone loss occurs rapidly, so therapy is optimally started before or at the time of OLT. There is conflicting evidence that intravenous administration of a bisphosphonate at the time of transplantation may reduce bone turnover and fractures, but its use should be directed by a bone disease specialist (level C evidence).
12. Parathyroid hormone is approved by the Food and Drug Administration for the treatment of severe osteoporosis (level D evidence in hepatic disease, level A evidence in osteoporotic postmenopausal women). Its use should be directed by a bone disease specialist.
13. Fluoride is not recommended for the treatment of osteoporosis associated with a hepatic disorder (level D evidence in hepatic disease, no consistent evidence for fracture risk reduction in other groups).

References

1. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology 2003;124:795–841.

Address requests for reprints to: Chair, Clinical Practice Committee, AGA National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

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