Bone Disease in Cirrhosis

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Bone disease (BD) is an important and common complication of cirrhosis because of its negative effect on quality of life in the form of chronic pain and immobility. In addition, its association with a high morbidity warrants timely identification and therapy. BD is most commonly seen in those of advanced age, smokers, postmenopausal women, individuals with alcoholism, malnourished individuals, and in liver disease of cholestatic etiology (Table 1). The prevalence of BD in patients with cirrhosis has been reported between 12%-55%.¹ A higher prevalence is noted in patients with primary biliary cirrhosis (PBC), likely related to the concurrence of two additional risk factors: chronic cholestasis and female gender. About 60% of patients with PBC and primary sclerosing cholangitis (PSC) have osteoporosis or osteopenia prior to orthotopic liver transplantation (OLT).² It is crucial to identify and treat BD before OLT, because BD worsens during the first 6-12 months after OLT, leading to a high incidence of traumatic fractures (25%-35%). The rapid bone loss after OLT is thought to result from the intense immunosuppressive therapy. However, by the second year post-OLT, bone mass has generally recovered and bone fractures are less common.³

Pathophysiology

Bone is a dynamic connective tissue maintained by the opposing yet coordinated actions of osteoblast-mediated bone formation and osteoclast-mediated bone resorption. With aging, bone resorption exceeds formation, resulting in a negative bone balance. Osteopenia and osteoporosis subsequently develop in older patients. Some data suggest decreased bone formation as the critical mechanism of osteoporosis in liver disease. Experimental data showed a dose-dependent decrease in the proliferative capacity of

osteoblasts with increasing bilirubin levels.⁴ Patients with cirrhosis and osteoporosis also have a correlation between low levels of insulin-like growth factor and reduced bone formation, but the exact mechanism for this association is not well defined. Nonetheless, increased resorption may also contribute to the development of BD in liver disease. This observation is specific to the subset of postmenopausal patients with advanced liver disease. In these patients, calcium and vitamin D deficiency may lead to secondary hyperparathyroidism causing increased bone turnover. Genetic polymorphisms of the vitamin D receptor gene, collagen 1 α -1 gene, osteoprotegerin, and its ligand RANKL may also be involved, but the specific role of these factors remains incompletely understood.

Diagnosis and Management

Patients with chronic liver disease, especially those with established cirrhosis, should be screened for BD, given the noteworthy prevalence (Table 2). If normal on initial evaluation, bone mineral densitometry (BMD) should be repeated every 2 to 3 years thereafter. However, in patients at risk for rapid bone loss such as in cholestatic liver disease and with multiple risk factors for osteoporosis, surveillance for BD should be considered at shorter intervals, even annually. Certainly, BD screening should be undertaken as part of the standard preoperative liver transplantation evaluation. In addition to bone densitometry, a comprehensive assessment of risk factors and conditions contributing to BD should be completed (Table 1). Several secondary causes of osteoporosis have specific therapies; therefore, it is necessary to screen patients with cirrhosis for these conditions prior to diagnosing or treating osteoporosis on the basis of a BMD analysis alone. The Fracture Risk Assessment Tool (FRAX)

Abbreviations: BD, bone disease; BMD, bone mineral densitometry; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

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is a helpful algorithm endorsed by the World Health Organization developed to evaluate the risk of fractures in individual patients (Table 3).⁵ FRAX allows the clinician to estimate the 10-year probability of a hip fracture or a major

osteoporotic fracture based on femoral neck BMD and the following clinical risk factors: age, gender, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol >3 units per day, low BMD. Although, the FRAX model has not been specifically studied in patients with cirrhosis, it may serve as a guidance in the office

TABLE 1 Risk factors of bone disease. The presence of these risk factors in a patient with cirrhosis should prompt consideration for bone mineral density testing.

Risk Factors of Osteoporosis
Age
Previous fragility fracture
Oral glucocorticoid therapy
Body mass index <19
Alcohol intake >3 units/day
Maternal history of hip fracture
Poor nutrition
Smoking history
Malnutrition
Hypogonadism

TABLE 3 The FRAX tool endorsed by the World Health Organization to evaluate the fracture risk.

Clinical Risk Factors Included in the FRAX Tool	
Current age	Rheumatoid arthritis
Gender	Secondary cause of osteoporosis
A prior osteoporotic fracture	Parental history of hip fracture
Femoral neck BMD	Current smoking
Low body mass index	Alcohol intake (3 or more drinks/day)
Oral glucocorticoids >5 mg/day of prednisone for >3 months (ever)	

TABLE 2 The prevalence of osteopenia and osteoporosis in chronic liver disease of diverse etiologies. Adapted from Lopez-Larramona et al.¹¹

Ref.	n	Etiology	Prevalence of osteopenia/osteoporosis	Pathogenic mechanisms/associated factors
Goral et al, 2010 ¹²	55	Child A-B-C cirrhosis Mixed etiology	Osteoporosis 37%	Increased TNF α and IL-6 Decreased IGF-1 levels
Wariaghli et al, 2010 ¹³	64	Cirrhosis Mixed etiology	Osteoporosis 45.3%	Female sex Cholestasis Lower weight and height
Loria et al, 2010 ¹⁴	35	Cirrhosis Viral and alcoholic		Not specified
George et al, 2010 ¹⁵	72	Cirrhosis Viral and alcoholic	Low BMD 68%	Low level of IGF-1
Sokhi et al, 2004 ¹⁶	104	Cirrhosis Mixed etiology	Osteoporosis 11.5% Osteopenia 34.6%	Child B-C stage Female
Gallego-Rojo et al, 1998 ¹⁷	32	Viral cirrhosis	Osteoporosis 55%	Child stage IGF-1 serum levels
Auletta et al, 2005 ¹⁸	30	Chronic viral hepatitis	Osteopenia 44% Osteoporosis 20%	Chronic hepatopathy
Diamond et al, 1989 ¹⁹	22	Hemochromatosis	Osteoporosis 45%	Hypogonadism Low free testosterone levels
Sinigaglia et al, 1997 ²⁰	32		Osteoporosis 28%	Cirrhosis and iron overload
Mounach et al, 2003 ²¹	33	Primary Biliary Cirrhosis	Osteoporosis 51.5%	Low BMI Menopausal status Duration of liver disease Vitamin D deficiency
Lindor et al, 1995 ²²	88	Primary Biliary Cirrhosis	Osteoporosis 35%	Not specified
Guañabens et al, 1990 ²³	20	Primary Biliary Cirrhosis	Osteoporosis 35%	Duration of liver disease Post Menopause Malabsorption of calcium
Angulo et al, 1998 ²⁴	81	Primary Sclerosing Cholangitis	Osteoporosis 17%	Stage of liver disease Associated advanced inflammatory bowel disease
Malik et al, 1998 ²⁵	57	Alcoholic	Low BMD (z-score $\leq$ 2.0) 17.5%	Vitamin D deficiency
Kim et al, 2009 ²⁶	18	Alcoholic	Osteoporosis 22% Osteoporosis 50%	Cumulative alcohol intake
Gonzalez-Calvin et al, 1993 ²⁷	39	Alcoholic	Osteopenia 23%	Cumulative alcohol intake Impairment of osteoblastic activity by ethanol

Abbreviations: BMD, bone mass density; BMI, body mass index; IGF-1, insulin-like growth factor; IL-6, interleukin-6; TNF, tumor necrosis factor.

Figure 1 Bone disease management algorithm in cirrhosis. Timely diagnosis and treatment is crucial for fracture prevention.

setting to determine how often to assess the bone density in a given patient (Table 3).⁵

Treatment

Studies defining efficacy of treatment in osteoporosis of liver disease are inconsistent. There is no clear antifracture effect established for various potential therapeutic measures. Furthermore, there is no agreement on the most appropriate time to initiate treatment. However, several general prevention measures and treatment options are reasonable considerations (Fig. 1).

General prevention of bone disease such as elimination of alcohol, smoking, and initiation of a well-balanced diet are primary recommendations. In addition, the following measures are reasonable and should be considered: home safety assessment, limit central nervous system depressants, careful dose adjustment of antihypertensive agents, visual correction, and calcium and vitamin D supplementation. Corticosteroids and immunosuppressive agents should be reduced to the lowest doses required for therapeutic effect in order to prevent further decline of BMD.

Calcium and Vitamin D

There are few studies looking at optimal dosing and timing of initiation of calcium and vitamin D in patients with chronic liver disease. AASLD guidelines suggest the use of calcium 1.0-1.5 g and vitamin D 1000 IU daily for prevention of BD.

Bisphosphonates

Bisphosphonates are antiresorptive agents that increase bone mass and reduce the occurrence of fractures as validated by many studies in postmenopausal osteoporosis. These agents should be considered, in addition to calcium and vitamin D, at the time of diagnosis of significant BD in patients with liver disease. Etidronate and alendronate in patients with PBC prevent bone loss with minimal adverse effects after 1 and 2 years of treatment.⁶ Although there are

no large studies assessing safety and efficacy of bisphosphonates in the setting of cirrhosis, bisphosphonates are generally well tolerated when given in weekly dosing. The parenteral form is preferred in those with esophageal varices due to risk of esophageal ulceration with oral formulations.⁷ Patients treated with the parenteral form should be monitored for signs of osteonecrosis of the jaw.

Hormonal Therapy

Many studies have shown bone loss prevention and even increased bone mineral density in patients on transdermal hormone replacement therapy. Despite these positive results, the overall consensus remains that hormonal treatments are second-line therapy. Other nonhormonal agents with fewer side effects can be used in the treatment of osteoporosis instead.

Other Treatment Options

Raloxifene, a selective estrogen receptor modulator has been insufficiently studied to reach firm conclusions regarding bone loss prevention and fracture reduction rate. Sodium fluoride, which acts by increasing bone formation, has been used in certain forms of osteoporosis. However, when compared to etidronate, sodium fluoride appeared to have lower efficacy.⁸ Calcitonin inhibits bone resorption but its effect in patients with liver disease is not clear. In a study on PBC patients who underwent combination therapy with calcitonin, calcium, and vitamin D for 12 months, improvement in bone loss was noted.⁹ However, another 6-month study using calcitonin was unable to prevent bone loss and decrease fracture rate 1 year after OLT in patients with decreased BMD at baseline.¹⁰ ■

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