Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)

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INTRODUCTION

Hepatic osteodystrophy refers to the structural and metabolic bone changes seen in patients with chronic liver disease and includes both osteoporosis and osteomalacia. Osteoporosis is a skeletal condition characterized by low bone mass, whereas osteomalacia is a disorder of decreased bone mineralization of newly formed osteoid at sites of bone turnover. Both disorders increase the risk for fracture. (See "Pathogenesis of osteoporosis" and "Clinical manifestations, diagnosis, and treatment of osteomalacia in adults".)

This topic will review the evaluation of low bone mass in patients with primary biliary cholangitis (previously referred to as primary biliary cirrhosis). The discussion that follows is generally consistent with guidelines regarding osteoporosis in patients with liver disease [1-3].

Other related issues, including bone disease following liver transplantation and a discussion of treatment approaches for osteoporosis, are discussed elsewhere.

- (See "Prevention and treatment of osteoporosis after solid organ or stem cell transplantation".)
- (See "Overview of the management of osteoporosis in postmenopausal women".)
- (See "Evaluation and treatment of premenopausal osteoporosis".)
- (See "Treatment of osteoporosis in men".)

EPIDEMIOLOGY

Low bone density is common in patients with primary biliary cholangitis (PBC), with prevalence estimates ranging from 20 to 50 percent [4-7]. In observational studies, age, weight, height, histologic stage, menopausal status, vitamin D deficiency, and severity and duration of liver damage were identified as risk factors for osteoporosis [4,6,8-10]. Only 20 percent of patients with advanced stages of PBC have normal bone mass [11].

The prevalence of fractures among patients with PBC is approximately 10 to 20 percent [2,8]. When compared with the general population, the absolute increase in fracture risk is moderately increased. In a population-based study, patients with primary biliary cholangitis had a twofold increased risk of any fracture compared with the general population, with an absolute excess fracture rate of 12.5 per 1000 person-years [12]. In one study, fractures were associated with bone density, menopause, age, and height but not with severity of PBC [8].

Osteomalacia, characterized by decreased bone mineralization, is rarely seen in PBC [7]. When present, it is typically associated with vitamin D deficiency, with or without concomitant fat malabsorption. (See "Clinical manifestations, diagnosis, and treatment of osteomalacia in adults".)

PATHOGENESIS

The mechanism of osteoporosis in patients with primary biliary cholangitis is not well understood. The plasma concentration of calcium is usually normal. Patients with cholestatic liver disease may be at increased risk for malabsorption of fat-soluble vitamins due to decreased bile acid secretion, and deficiency of vitamin D is seen in approximately 15 to 30 percent of patients with PBC [5,13]. However, chronic cholestasis leading to malabsorption of vitamin D does not fully explain bone disease in patients with primary biliary cholangitis (PBC) because the plasma concentrations of calcidiol (25-hydroxyvitamin D) and calcitriol (1,25 dihydroxyvitamin D) are normal in some patients with PBC and osteoporosis [2]. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment", section on 'Defining vitamin D sufficiency'.)

Studies suggest that patients with PBC have low-turnover osteoporosis (bone resorption and formation reduced), possibly due to one or more of the following mechanisms [7,14]:

- Reduced levels of specific growth factors (eg, insulinlike growth factor 1) are seen in patients with cirrhosis and this negatively affects osteoblast function and bone formation [7].

- Unconjugated bilirubin or serum from jaundiced patients negatively affects osteoblast viability and differentiation in experimental models [15].

- Lithocholic acid impairs osteoblast activity and is associated with Vitamin K deficiency which also impairs osteoblast formation in experimental models [16,17].

The pathogenesis of osteoporosis is reviewed in detail separately. (See "Pathogenesis of osteoporosis".)

EVALUATION

The evaluation for low bone mass in a patient with PBC is similar to that in any patient at risk for osteoporosis and includes assessment of clinical risk factors for fracture, bone mineral density testing, and laboratory evaluation.

- (See "Osteoporotic fracture risk assessment", section on 'Assessment of fracture risk'.)
- (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women".)
- (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in men".)

Clinical risk factors for fracture — Chronic liver disease, including PBC, is a risk factor for low bone density and fracture. Patients with PBC may have additional risk factors for fracture independent of bone mineral density and PBC (table 1). Bone mineral density (BMD) and clinical risk factors combined may provide a better estimate of fracture risk than BMD or clinical risk factors alone. (See "Osteoporotic fracture risk assessment", section on 'Clinical risk factor assessment'.)

Bone mineral density testing — The majority of patients with osteoporosis do not have symptoms related to their bone disease. At the time of diagnosis of PBC, we obtain BMD testing in patients with PBC who have at least one additional risk factor for osteoporosis (table 1 and algorithm 1) [1,4]. (See "Screening for osteoporosis in postmenopausal women and men", section on 'Bone mineral density' and "Overview of dual-energy x-ray absorptiometry".)

Osteoporosis in postmenopausal women and in men age 50 years and older is defined by a bone mineral density that is ≥2.5 standard deviations below the average value of young adults (T-score), whereas low bone mass is defined by a value more than one standard deviation but less than 2.5 standard deviations below the average (table 2). (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in men".)

In premenopausal women and in men under the age of 50 years, a clinical diagnosis of osteoporosis should not be made on the basis of BMD alone. Osteoporosis can be diagnosed when the bone density is below the expected range for age (Z-score ≤-2), in the presence of other risk factors for fracture (eg, PBC, long-term glucocorticoid use, hypogonadism). (See "Epidemiology and etiology of premenopausal osteoporosis", section on 'Definitions' and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in men", section on 'Diagnosis of osteoporosis'.)

In addition, any patient with a fragility fracture is regarded as having osteoporosis. A fragility fracture is due to any fall that occurs from a standing height or less that results in a fracture, and common sites for fragility fracture are the hip, spine and wrist. The most common fractures are vertebral fractures, two-thirds of which are asymptomatic and are diagnosed as incidental findings on a chest or abdominal radiograph. (See "Osteoporotic thoracolumbar vertebral compression fractures: Clinical manifestations and treatment", section on 'Clinical manifestations'.)

Laboratory tests — We obtain the following laboratory tests as part of the initial evaluation for low bone mass:

- 25-hydroxyvitamin D (25[OH]D)
- Complete biochemistry profile (including calcium, phosphate, alkaline phosphatase, creatinine)
- Complete blood count
- Testosterone in men

Patients with osteoporosis usually have normal serum levels of calcium, phosphate, and alkaline phosphatase. Although 25-hydroxyvitamin D levels may be low in patients with osteoporosis, 25-hydroxyvitamin D levels rarely are below 10 ng/mL (25 nmol/L). Patients with serum 25(OH)D levels <10 ng/mL are at risk for developing osteomalacia and require further evaluation. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment", section on 'Evaluation'.)

MANAGEMENT

Overall approach — The approach to the prevention and treatment of low bone mass in patients with primary biliary cholangitis depends upon factors such as the patient's bone mineral density, age, and whether the patient has hypogonadism (algorithm 1) [1]. Lifestyle measures should be adopted universally to reduce bone loss in patients with PBC. Lifestyle measures include

adequate calcium and vitamin D, exercise, smoking cessation, counseling on fall prevention, and avoidance of heavy alcohol use.

- (See "Overview of the management of osteoporosis in postmenopausal women".)
- (See "Evaluation and treatment of premenopausal osteoporosis".)
- (See "Treatment of osteoporosis in men".)
- (See "Prevention and treatment of glucocorticoid-induced osteoporosis".)
- (See "Calcium and vitamin D supplementation in osteoporosis".)

Patients who are candidates for pharmacologic therapy — Pharmacologic therapy with a bisphosphonate is preferred for most patients with primary biliary cholangitis who have fragility fractures, osteoporosis on BMD, or who have T-scores between -1 and -2.5 and high risk for fracture. (See 'Evaluation' above and "Osteoporotic fracture risk assessment", section on 'Assessment of fracture risk'.)

The management of such patients is similar to that for other patients who have osteoporosis, and oral bisphosphonates are considered initial pharmacologic therapy for most patients at risk for fracture. Vitamin D deficiency should be corrected prior to initiation of bisphosphonates. (See "Bisphosphonate therapy for the treatment of osteoporosis", section on 'Pretreatment evaluation' and "Risks of bisphosphonate therapy in patients with osteoporosis".)

Oral bisphosphonates should not be used as initial therapy in patients with esophageal disorders (eg, achalasia, esophageal stricture, esophageal varices, Barrett esophagus) or with an inability to follow the dosing requirements (eg, stay upright for at least 30 minutes). These patients can be treated instead with intravenous bisphosphonate therapy or other approved agents. Additional therapies for patients with contraindications to oral bisphosphonates are reviewed elsewhere. (See "Overview of the management of osteoporosis in postmenopausal women".)

For patients with osteoporosis who are on therapy, we repeat BMD testing in two years. In a trial of 42 postmenopausal women with PBC with two year follow-up, improvements in bone mineral density were similar in women receiving weekly alendronate compared with monthly ibandronate (mean percentage change 4.5 versus 5.7 percent) [18]. Neither treatment adversely affected liver function or cholestasis. Two small studies of oral bisphosphonate treatment in women with PBC have also suggested improvement in bone mineral density following approximately two years of treatment [19,20].

Patients not requiring pharmacologic therapy — For patients with PBC who do not have osteoporosis on initial testing or who do not have increased risk of fracture based on clinical risk assessment, we perform follow-up bone mineral density testing after two to three years, but acknowledge that data are lacking regarding the optimal testing interval [1,21].

Patients following liver transplantation — Patients with chronic liver disease who undergo liver transplantation may show improvement in bone mineral density in the long term [22]. The management of osteoporosis in patients undergoing liver transplantation is discussed separately. (See "Prevention and treatment of osteoporosis after solid organ or stem cell transplantation".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Primary biliary cholangitis".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Patients with primary biliary cholangitis (PBC) are at risk for osteoporosis and fracture for several reasons, including age, menopausal status, and cholestasis contributing to vitamin D deficiency. Low bone density is common in patients with PBC, with prevalence estimates ranging from 20 to 50 percent. When compared with the general population, the absolute increase in fracture risk is approximately twofold higher. (See 'Epidemiology' above.)

- **Bone mineral density testing** – The majority of patients with osteoporosis do not have symptoms related to their bone disease. At the time of diagnosis of PBC, we obtain bone mineral density testing in patients with PBC who have at least one additional risk factor for osteoporosis (table 1 and algorithm 1). (See 'Bone mineral density testing' above.)

- **Laboratory testing** – For all patients with PBC and low bone mass, we obtain the following laboratory tests as part of the initial evaluation (see 'Laboratory tests' above):

  - 25-hydroxyvitamin D (25[OH]D)
  - Complete biochemistry profile (including calcium, phosphate, alkaline phosphatase, creatinine)
  - Complete blood count
  - Testosterone in men

- **Management** – The management of patients with PBC and osteoporosis is similar to that for other patients who have osteoporosis:

  - (See "Overview of the management of osteoporosis in postmenopausal women".)

- (See "Evaluation and treatment of premenopausal osteoporosis".)
- (See "Treatment of osteoporosis in men".)

Lifestyle measures should be adopted universally to reduce bone loss in patients with PBC. Lifestyle measures include adequate calcium and vitamin D, exercise, smoking cessation, counseling on fall prevention, and avoidance of heavy alcohol use. (See 'Overall approach' above.)

For most patients with PBC who have osteoporosis, pharmacologic therapy with a bisphosphonate is suggested. Oral bisphosphonates should not be used as therapy in patients with esophageal disorders (eg, esophageal varices) or with an inability to follow the dosing requirements (eg, stay upright for at least 30 minutes). These patients can be treated instead with intravenous bisphosphonate therapy. (See 'Patients who are candidates for pharmacologic therapy' above.)

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GRAPHICS

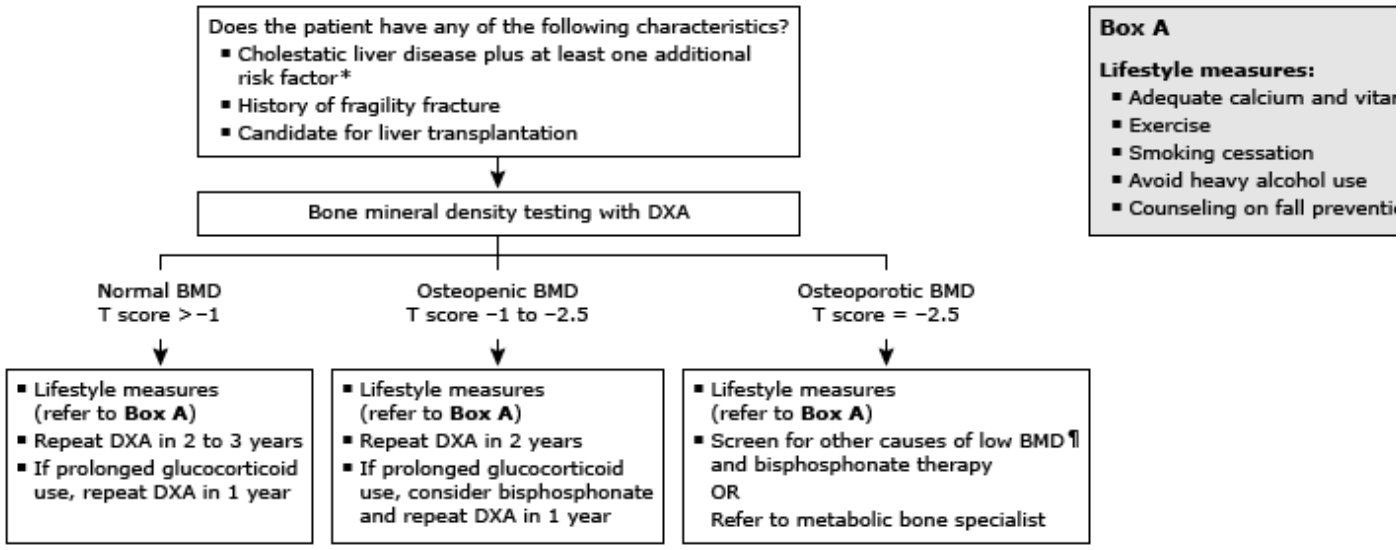
Clinical risk factors for fracture independent of bone mineral density

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Data from: Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005; 16:581.

Graphic 76445 Version 4.0

Management of low bone mass in patients with liver disease



Refer to UpToDate content on Evaluation and treatment of low bone mass in patients with primary biliary cholangitis (primary biliary cirrhosis)

DXA: dual-energy x-ray absorptiometry; BMD: bone mineral density

* Risk factors for fracture include advancing age, tobacco use, significant alcohol consumption, low body weig and early menopause.

¶ Laboratory screen for other causes of low BMD: complete blood count, serum calcium, alkaline phosphatas creatinine, 25-OH vitamin D, protein electrophoresis, and testosterone (in men).

Original figure modified for this publication. Leslie WD, Bernstein CN, Leboff MS. AGA technical review on osteoporosis in hepatic disord Gastroenterology 2003; 125:941. Illustration used with the permission of Elsevier Inc. All rights reserved.

Graphic 52724 Version 4.0

Bone mineral density T-score criteria for osteoporosis and low bone mass

Diagnosis	T-score
Normal	≥-1.0
Low bone mass (osteopenia)	Between -1.0 and -2.5
Osteoporosis	≤-2.5
Severe (established) osteoporosis	≤-2.5 and fragility fracture

Adapted for clinical use from the World Health Organization: http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf (accessed November 9, 2010).

Graphic 53999 Version 3.0

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