Metabolic Bone Disease in Primary Biliary Cirrhosis

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KEYWORDS

• Primary biliary cirrhosis • Metabolic bone disease • Osteoporosis
• Antiresorptive agents

KEY POINTS

- Primary biliary cirrhosis (PBC) is a liver-specific autoimmune disease that primarily affects women (female-to-male ratio, 10:1) between 40 and 60 years of age.
- Metabolic bone disease is a common complication of PBC, affecting 20% to 52% of patients, depending on the duration and severity of liver disease.
- The osteoporosis seen in PBC seems mainly due to low bone formation, although increased bone resorption may contribute.
- Treatment of osteoporosis consists primarily of the antiresorptive agents that are typically used to treat postmenopausal patients with osteoporosis without liver disease. Bisphosphonates appear to be the most promising given their efficacy, as well as the lack of potential adverse side effects that are associated with other agents such as HRT.
- Additional large prospective, long-term studies in patients with PBC are needed in order to determine efficacy in improving bone density as well as reducing fracture risk.

OVERVIEW OF PRIMARY BILIARY CIRRHOSIS

PBC is a liver-specific autoimmune disease that primarily affects women between the ages of 40 and 60 years, although there are rare patients diagnosed in their teens or even into their 90s.[1,2] Although some epidemiologic studies have reported a rising incidence over the past 2 decades, others report stable numbers. A systematic review of data from Europe, North America, and Australia reports an incidence of 0.9 to 5.8 per 100,000 people. Disease prevalence varies from 1.9 to 40.2 per 100,000 people, depending on geographic location, with increased rates of disease in North America and Northern Europe,[3] likely due to earlier recognition of the disease.

The exact pathophysiology of PBC is unknown, but, as with other autoimmune diseases, both genetic and environmental factors are involved. The prevalence of PBC in

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Gastroenterol Clin N Am 45 (2016) 333–343
http://dx.doi.org/10.1016/j.gtc.2016.02.009 **gastro.theclinics.com**
0889-8553/16/$ – see front matter Published by Elsevier Inc.

first-degree relatives is more than 10 times higher than in the general population.[4] Genetic studies have shown an association between the HLA alleles DRB1*08, DR3, and DPB1*0301 and increased risk of disease, whereas DRB1*11 and DRB1*13 confer protection from PBC.[5] The advent of genome-wide association studies have uncovered many potential pathways affected in PBC, including B-cell function, antigen presentation, and T-cell differentiation.[5] Several potential environmental exposures include various bacteria (in particular, *Escherichia coli* and *Mycobacterium gordonae*), viruses, and toxic compounds, but none is definitive.[4] PBC is characterized by T-cell–mediated inflammation of the intralobular bile duct epithelium, which leads to their damage and subsequent loss. The resultant cholestasis leads to retention of toxic bile acids and eventual cirrhosis.[4]

Approximately 90% to 95% of patients with PBC are women. As with most other autoimmune diseases, the etiology of such female predominance in PBC is unclear; however, based on more recent genetic research, pathogenesis may include a combination of sex hormone abnormalities and X chromosome instabilities and defects. The X chromosome contains genes that control sex hormone levels and that are critical in maintaining immune tolerance.[6] Furthermore, preliminary data have shown there is an increased frequency of X monosomy in the circulating leukocytes of women with PBC compared with controls and that this frequency increases with patient age.[7] Although the relationship between these associations and disease pathogenesis remains to be fully understood, the findings are intriguing.

Patients can present with fatigue and pruritus or they are diagnosed on further investigation of an elevated alkaline phosphatase found on routine liver chemistries. The serologic hallmark of the disease is an elevated antimitochondrial antibody (AMA), which is present in 95% of PBC cases and in less than 1% of the normal population.[8] Liver biopsy is not always required to make the diagnosis if both alkaline phosphatase and AMA levels are elevated, but it would confirm the diagnosis if laboratory tests are inconclusive as well as stage the extent of liver disease.

The only approved treatment of PBC in the United States is ursodeoxycholic acid (UDCA). Treatment response is associated with increased survival and decreased liver transplantation, especially in long-term follow-up of patients with early-stage disease.[9–12] Proposed beneficial effects of UDCA include its ability to stimulate ductular secretions and to protect against injury from toxic bile acids as well as to downregulate B cells and AMA production.[13] Response to treatment is measured by improvement in alkaline phosphatase and bilirubin.[12] Normalization of liver tests is seen in just over half of patients at 5 years.[9]

BONE DISEASE IN PRIMARY BILIARY CIRRHOSIS

Hepatic Osteodystrophy

The term, *hepatic osteodystrophy*, refers to metabolic bone disease that can accompany advanced liver disease, in particular cholestatic liver diseases, such as PBC and primary sclerosing cholangitis, and includes both osteomalacia and osteoporosis[14] (**Table 1**). Both disorders weaken bones and increase the risk of low-trauma fractures, particularly of the vertebrae, proximal femur, and distal forearms. Osteoporosis is a skeletal bone disorder of decreased bone mass with a normal ratio of mineral and osteoid matrix, whereas osteomalacia causes softening of the bone because of defective mineralization of newly formed osteoid, which results in a decreased ratio of mineral to osteoid matrix.[15]

Osteomalacia

Osteomalacia, or decreased bone mineralization, is not as common as osteoporosis in patients with PBC and is usually associated with vitamin D deficiency, which can arise