Chronic Complications of Cholestasis

Evaluation and Management

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KEYWORDS

• Primary biliary cholangitis • Cholestasis • Malabsorption
• Fat-soluble vitamin deficiency • Metabolic bone disease • Hyperlipidemia
• Portal hypertension • Hepatocellular carcinoma

KEY POINTS

- Chronic cholestasis increases the risk of fat-soluble vitamin deficiency, most commonly vitamin A and D, particularly in patients with serum bilirubin greater than 2 mg/dL.
- Therapy to prevent osteoporosis and bone fractures should be considered in patients with primary biliary cholangitis (PBC) and a T score less than −1.5.
- Hyperlipidemia is common in PBC; however, coexisting cardiovascular risk should be addressed and the effect of emerging PBC therapies on lipids should be closely monitored.
- Although uncommon, patients with PBC have an increased risk of variceal bleeding from portal hypertension at precirrhotic stages and risk-prediction strategies are indicated.
- The risk of hepatocellular carcinoma is increased in patients with PBC who do not achieve biochemical response to treatment, particularly in men.

INTRODUCTION

Long-term complications of chronic cholestasis not only increase the risk of morbidity and mortality but also have a significant impact on the patient's quality of life. Despite the increasing number of effective therapies for the treatment of primary biliary cholangitis (PBC), cholestatic complications will continue to be present and therefore remain relevant priorities for the discovery and delivery of high-quality care. In addition, the study of new therapies for PBC should include proactive assessment and measurement of their impact on complications of cholestasis. This proactive assessment is important because emerging new therapies for management of cholestasis may or may not impact these manifestations in a beneficial manner.

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Complications of chronic cholestasis in patients with PBC include fat-soluble vitamin deficiency, metabolic bone disease, hyperlipidemia, portal hypertension (cirrhotic and precirrhotic), and hepatocellular carcinoma (HCC). The goals of this article are to address these common chronic complications for patients with PBC and to highlight evidence-based best practices for evaluation and effective management of these disorders. Please see Andres F. Carrion and colleagues' article, "Understanding and Treating Pruritus in Primary Biliary Cholangitis," in this issue for detailed information on pruritus.

MALABSORPTION AND FAT-SOLUBLE VITAMIN DEFICIENCY

Definition and Diagnosis

Before the development and subsequent widespread use of ursodeoxycholic acid (UDCA) for treatment of PBC, the natural history of the disease was notable for a significant acceleration in the rate of morbidity and mortality following the onset of symptoms. A key study from the early 1980s highlighted this point, demonstrating that although the 5- and 10-year survival in asymptomatic patients with PBC was comparable to the healthy US population, those who developed any symptoms of disease, including malabsorption, jaundice, or pruritus, had a markedly reduced survival.[1]

Before the existence of any effective therapy for PBC, management primarily focused on the complications of prolonged cholestasis, including steatorrhea, fat-soluble vitamin deficiency, and pruritus.[2] Early studies from the 1960s demonstrated that patients with PBC experienced significant steatorrhea and weight loss, quantified as up to 10 g of fecal fat loss per day after intake of 70 g per day.[3] The steatorrhea was highly associated with decreased availability of bile salts to aid in the absorption of nutrition.

Fortunately, steatorrhea and severe fat-soluble vitamin deficiency have become less common in the past 2 decades. Most patients with clinically measurable fat-soluble vitamin deficiency also have advanced liver disease, especially with prolonged jaundice. One study of 52 patients reported that 17 had measurable deficiency in vitamin A, and one was symptomatic.[4] A larger study from 2001 with nearly 180 patients with PBC stratified the group according to histologic stage of fibrosis.[5] The investigators reported that vitamin A was the most frequently encountered fat-soluble vitamin deficiency (33.5%), followed by deficiencies of vitamin D (13.2%), vitamin K (7.8%), and vitamin E (1.9%). Vitamin A deficiency was associated with the stage of fibrosis (11.1% in stage I and 52.2% in stage IV) in addition to Mayo risk score and total cholesterol level. The only association with vitamin D deficiency occurred with serum albumin levels. The investigators concluded that fat-soluble vitamin deficiency is relatively uncommon in patients with PBC.

However, it is likely that micronutrient deficiency persists in patients with milder degrees of chronic cholestasis. Indeed, despite an appropriate and similar macronutrient diet in both cholestatic patients including PBC and Primary Sclerosing Cholangitis (PSC) and healthy controls, Floreani and colleagues[6] reported significant reductions of both micronutrients and antioxidants specifically in the cholestatic group. Their findings included reduced levels in retinols and α-tocopherols. Furthermore, in the PBC subgroup there was a negative correlation between carotenoids and serum markers of cholestasis, including alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT), albeit at a modest degree ($r = -0.27$, $P<.013$ and $r = -0.26$, $P<.018$, respectively). Interestingly, the investigators did not find a correlation between antioxidant levels and the histologic stage of disease. These findings clearly suggest that reduced micronutrient levels are readily found in cholestatic patients despite an adequate macronutrient diet and correlate with cholestatic markers.