

Bone and liver diseases

Who thinks about osteoporosis when evaluating patients with chronic liver disease?

Well, I dare say that very few of the physicians who care for these patients do, and the same occurs in the context of research, since very few groups have rigorously analyzed its prevalence and pathogenic mechanisms. Therefore, it is important to disseminate information regarding the prevalence and incidence of osteoporosis in the major liver diseases, as well as to analyze the underlying mechanisms. The most extensively studied liver diseases have been cholestatic disorders, specifically primary biliary cholangitis (PBC) and end-stage liver disease. The prevalence of osteoporosis in PBC is around 35 % in the most significant studies, and depends on diagnostic criteria and the severity of liver damage, since its development is associated with age, postmenopausal status, duration of liver disease, and advanced histological stage (1). The prevalence of fractures is around 15 % in PBC and is even higher, approximately 22-36 %, in end-stage liver disease (2). These figures, however, correspond to studies published more than 10 years ago, and therefore may currently be lower due to improved control of cholestasis after the introduction of ursodeoxycholic acid and changes in the profile of patients awaiting liver transplantation. Nevertheless, this hypothesis has not been confirmed, since recent studies from the Swedish national registry and the Korean national health service, including between 4,000 and 5,000 patients with PBC, indicate a significantly higher incidence rate of fractures in patients with PBC vs controls (3,4). Similarly, analyses evaluating whether bone disease in patients awaiting liver transplantation had changed over a 20-year period showed that the prevalence of osteoporosis and fractures remained similar, although patients were older and had less severe liver damage in more recent years (5). However, other chronic liver diseases should not be overlooked, such as hemochromatosis, alcoholic liver disease, and nonalcoholic fatty liver disease. Both hemochromatosis and alcoholic liver disease are associated with an increased risk of osteoporosis and fractures; in hemochromatosis, it remains unclear whether osteoporosis is due to iron overload directly affecting bone tissue or occurs through complications such as liver cirrhosis or hypogonadism, while excessive alcohol consumption is an independent risk factor for osteoporosis and falls (6,7).

The mechanisms involved in osteoporosis associated with chronic liver disease are poorly understood, but most studies suggest that osteoporosis is mainly due to low bone formation. For this reason, it has been investigated whether sclerostin, which regulates osteoblastogenesis, plays a role in the low bone formation associated with chronic cholestasis. Serum sclerostin levels have been found to be elevated, and furthermore, sclerostin is expressed in the bile ducts of patients with PBC, especially in the early stages of the disease when inflammation/cholangitis is present (8). Additionally, and probably in more advanced stages of liver disease, substances retained during cholestasis, such as bilirubin and bile acids, may participate in reducing bone formation by decreasing proliferation, differentiation, and mineralization and by increasing apoptosis of osteoblastic cells, as observed in *in vitro* studies (9,10). Based on clinical and histological observations, it has been proposed that bone resorption increases as cholestasis worsens (11). Recently, *in vitro* studies have demonstrated that bilirubin may contribute to osteoporosis in advanced cholestatic liver disease by increasing osteoclast viability and decreasing apoptosis (2).

There are other factors involved in liver-bone interactions. Vitamin K, which is necessary for osteocalcin carboxylation, may be reduced in patients with severe cholestasis, representing an additional contributing factor. In this regard, undercarboxylated osteocalcin has been found to be elevated in a small group of patients with PBC, and its values decreased after administration of vitamin K1 (13). On the other hand, reduced IGF-1 levels have been described in liver cirrhosis (14), as well as a high prevalence of hypogonadism in hemochromatosis, chronic alcoholism, cirrhosis, and end-stage liver disease (15). Vitamin D deficiency, poor nutrition, and sarcopenia, which are frequent in most advanced liver diseases, complete the spectrum of bone disease in chronic liver diseases (15).

The treatment of osteoporosis associated with liver disease has been poorly investigated. In addition to adequate calcium intake and vitamin D supplementation to achieve serum 25OHD levels ≥ 30 ng/mL, different drugs used in postmenopausal osteoporosis have been tested, although studies are scarce and involve a limited number of patients. Most studies have been conducted in PBC and in patients before and after transplantation, with data focused on bone mineral density rather than fracture outcomes. Thus, hormone replacement therapy and raloxifene have been tested in very small series of patients with PBC, while more studies have been performed with oral bisphosphonates and zoledronate (16,17). Currently, 3 trials with denosumab have been published, again involving a limited number of patients (18,19), and one case report with romosozumab (20). All of these studies have shown stability or increases in bone mineral density, of varying magnitude, with few adverse effects.

The final takeaway is that patients with chronic liver disease may develop osteoporosis during the course of their illness due to a profound imbalance between bone formation and resorption caused by liver dysfunction, cholestasis, vitamin D deficiency, poor nutrition, and hypogonadism, with the magnitude depending on the type of liver disease and the severity of the condition.

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Conflict of interest: The author declares no conflict of interest.

Artificial intelligence: The author declares not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

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DOI: 10.20960/RevOsteoporosMetabMiner.00112