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Hepatic osteodystrophy-An underrecognized metabolic bone disease

Pramanik *et al.* Hepatic Osteodystrophy

Abstract

Hepatic osteodystrophy (HO) is a common and frequently untreated complication, manifested as osteoporosis or osteopenia, encountered in the evolution of chronic liver diseases (CLD). In addition to patients with chronic cholestasis and cirrhosis, patients with CLD from other etiologies may be affected. Several studies have reported an increased prevalence of osteoporosis/osteopenia in patients with CLD. The pathogenesis varies according to etiology and is multifactorial, involving genetic factors, vitamin deficiencies, proinflammatory cytokines, hypogonadism, hyperbilirubinemia, antiviral therapy, corticosteroids, and lifestyle factors. The approach to management should include individualized assessment for fracture risk factors and bone mineral density. Prevention of osteoporosis in CLD relies on the mitigation of risk factors, treatment of underlying hypogonadism, and encouraging a healthy diet and weight-bearing exercise. Treatment trials specific to HO are small, and the primary medical intervention for the treatment of osteoporosis in CLD remains bisphosphonates though a benefit in terms of fracture reduction has not consistently been shown. Further research is necessary to better define the management and specific treatment of hepatic osteodystrophy for the prevention of fragility fractures and to improve the quality of life. This article provides an updated review of hepatic osteodystrophy considering all these aspects.

Key Words: Hepatic osteodystrophy; chronic liver disease; pathogenesis; management; vitamin D; bisphosphonates

Core Tip: Hepatic osteodystrophy is a common complication, manifested as osteoporosis or osteopenia, encountered in the evolution of chronic liver diseases. Despite being clinically significant, it often represents an underappreciated and underdiagnosed complication of chronic liver disease as systematic screening and management remain suboptimal. The general biology of hepatic osteodystrophy, including its pathogenesis, diagnostic tools, and rationale for treatment, has been

determined largely empirically from studies of postmenopausal women with osteoporosis. The treatment of hepatic osteodystrophy is limited, reflecting an unmet need for the best possible management of this disorder. Bisphosphonates have been shown to be effective in selected group of patients with chronic liver disease.

INTRODUCTION

¹ Bone disease is a common complication of chronic liver disease (CLD). The term hepatic osteodystrophy (HO) refers to all metabolic bone complications encountered in CLD. However, osteoporosis is now widely accepted as the primary metabolic bone disease in primary biliary cholangitis (PBC) and likely CLD as a whole¹[1]. Despite being a clinically significant, it often represents as an underappreciated and underdiagnosed complication of CLD as systematic screening and management remain suboptimal[2]. Alterations in calcium phosphate homeostasis, vitamin D Deficiency, hypogonadism, chronic inflammation, nutritional and genetic factors contribute to its pathogenesis[3,4]. Despite its significant contribution to morbidity in CLD patients, therapeutic strategies are often extrapolated from osteoporosis guidelines. These guidelines are based on data on general population excluding patient with CLD and thus limits its applicability in this population[5]. This review provides a critical analysis of the current knowledge on the epidemiology, molecular and cellular mechanisms, clinical presentation, diagnostic challenges, and unmet therapeutic needs of HO. It summarizes recent advancements in bone biology related to liver disease and highlights the current and emerging interventions.

Prevalence

In patients with CLD, significant variability in skeletal alterations was observed, influenced by the etiology, duration, and stage of the liver condition[6]. Initially osteoporosis was described only with cholestatic live diseases (Primary biliary cirrhosis and primary biliary cholangitis), but recent data suggests ⁹ approximately every second patient with viral hepatitis, hemochromatosis, and Wilson's disease has osteoporosis or

osteopenia[7]. A recent trial showed the prevalence of osteoporosis and osteopenia in cirrhotic patients was 29.2% and 28.3%, respectively[8]. Bone related changes are more common in patients with alcoholic liver diseases (up to 55%) as compared to non-alcoholic steatohepatitis (NASH) (up to one third patients)[9,10]. The poor bone quality endangers CLD individuals at substantial risk for non-traumatic bone fractures with a prevalence between 7% and 35% which is significantly higher than normal individuals[11]. Another recent meta-analysis of 21 studies found that cirrhotic patients had significantly higher odds of osteoporosis (OR = 1.93) and fracture (OR = 2.30) compared to control patients[12]. Liver transplant leads to poorer bone health due to steroid use and perioperative bone loss. In a prospective study by Haagsma *et al.*, 38% of patients developed vertebral fractures within the first six months post-transplantation[13]. Prevalence of hepatic osteodystrophy according to the aetiologies of liver disease is provided in table 1⁹[7,9,14-16]. The high prevalence of bone disease and fracture in this group significantly adds to morbidity and increases economic burden.

Pathogenesis

The pathogenesis of development of hepatic osteodystrophy is complex and multifactorial[17]. Several interactive physiological effects that contribute to the pathogenesis of hepatic osteodystrophy. Both hepatokines (functional proteins secreted from hepatic tissue) like bone morphogenic protein 9, FGF 21, IGF1, hepcidin, feutin A *etc*, and osteokines (secreted from osseous tissue) like osteocalcin, osteopontin, sclerostin *etc*, interact together and can affect both hepatic tissue as well as bone. This physiological crosstalk is collectively referred as liver- bone axis[18]. This liver-bone interaction plays the pivotal role in the pathogenesis of HO. Initial studies for exploring the pathogenesis of HO were mainly done in cholestatic diseases. However, recent studies also evaluated extensively the possible factors behind the development of HO in other hepatic diseases including advanced chronic liver disease, metabolic dysfunction associated steatotic liver disease (MASLD) and alcoholic liver disease. Though there is evidence of significant heterogeneity in possible, most of the studies found that the

primary factor behind the low bone mass in HO is low bone formation rate in these patients. In addition, increased bone resorption rate and nutritional factors also play an important role in development of HO. The summary of the unifying mechanisms of pathogenesis is outlined in **Figure 1**.

Impaired bone formation

Initial studies done in patients with primary biliary cirrhosis (PBC) showed impaired osteoblastic function as suggested by decreased mean trabecular bone volume, mean wall thickness, mean osteoid seam width along with defective matrix synthesis[19]. Similar finding of low bone formation rate was also reported in other histomorphometric analysis studies done in cholestatic liver disease[20,21]. Low serum level of bone formation markers like osteocalcin were also reported in patients with primary biliary cirrhosis[22]. There are multiple hypothesis which can explain the low turn-over state of HO. Low insulin like growth factor 1 (IGF1) had been reported in patients with chronic liver disease[23]. Decreased synthesis of IGF-1, IGFBP-3 and growth hormone resistance play a role in the genesis of low BMD in these patients[24,25]. Sclerostin, a key negative regulator of the Wnt/ β -catenin signalling pathway, inhibits bone formation by reducing osteoblastic activity[26]. Sclerostin binds to the LRP5/6 receptor and thus prevents the interaction of this LRP5/6 receptor with the WNT ligands and further activation of osteoblastic pathway[27]. Moreover, WNT signalling pathway also inhibits key mediators of osteoclastogenesis like RANKL, leading to inhibition of bone resorption[28]. Thus, sclerostin can also increase osteoclastogenesis by inhibiting this WNT signalling pathway. In histopathological examination of hepatic tissue of PBC, sclerostin was found to be expressed in the epithelium of the bile ducts and the expression level was higher in the presence of cholangitis or granuloma[29]. Moreover, serum level of sclerostin was reported to be higher in advanced liver disease[30]. Increased expression of sclerostin in osteocytes had also been reported in patient of alcoholic liver disease (ALD)[31]. Thus, sclerostin is possibly one of the major mediators of low bone mass leading to the development of

HO. In more advanced stage of cholestasis, the elevated levels of bilirubin and bile acids can also suppress the bone formation by inducing apoptosis of osteoblastic cells in patients with cholestatic liver disease[32,33].

Increased bone resorption

In a few bone morphometric studies done in advanced liver disease, evidences of increased bone resorption had also been reported[34,35]. Decreased bone wall thickness and increased bone turnover were reported in patients with PBCs[35]. Secondary hyperparathyroidism due to vitamin D deficiency or alteration of vitamin D metabolism had been associated with PBC[36]. Osteoprotegerin (OPG)/receptor activator ratio of nuclear factor kappa ligand (RANKL) can also play a pivotal role in activating osteoclast mediated bone resorption in chronic liver diseases[37]. Hyperbilirubinemia per se can also activate RANKL/OPG mediated osteoclastogenesis[33].

Other factors

Among the other factors nutritional and genetic factor can also increase the risk of development of HD. Activation of osteocalcin is dependent of Vitamin K activity and increase in uncarboxylated osteocalcin had been associated with reduced BMD and increased in fracture risk[38]. Vitamin K deficiency is common in cholestatic disorders and it can be another factor behind the low bone mass in liver diseases[39].

Alteration of Vitamin D metabolism can also be one of the factors behind the deterioration bone metabolism in liver disease. In the skin 7-dehydrocholesterol is converted into vitamin D₃. In cirrhosis, there is increased expression of 7-dehydrocholesterol reductase which leads to increased degradation of 7-dehydrocholesterol[40]. Vitamin D binding protein (VDBP) is essential for proper circulation of vitamin D. Rodent studies have reported that VDBP levels are decreased with advancing chronic liver disease resulting in impairment of circulation of vitamin D and its metabolites in chronic liver disease[40]. Hydroxylation of Vitamin D are impaired as the expression of both vitamin D 25-hydroxylase and sterol 27-hydroxylase

enzymes are reduced in cirrhosis[40,41]. This leads to decreased production of 25-hydroxy vitamin D (Calcidiol)[42]. Moreover, enhanced degradation of vitamin D because of increased 24-hydroxylase activity has also been reported in cirrhosis[43]. In addition to these mechanisms, vitamin D deficiency in chronic liver disease is caused by poor dietary intake, malabsorption, inadequate sunlight exposure and jaundice related reduced cutaneous synthesis of vitamin D[44]. Vitamin D deficiency can result in bone loss *via* increased bone turnover and secondary hyperparathyroidism[45].

Hypogonadism can be seen in alcoholic liver disease (ALD), advanced cirrhosis, and hemochromatosis due to effect on both hypothalamic-pituitary and gonadal level and can cause bone loss by mainly reducing osteoblastic activity[46,47].

Variou genetic studies have explored the possible role of genetic mutations or polymorphism in development of HO. Genetic polymorphism of VDR gene had been reported to be associated with HO in PBC[48]. In a study from Spain, *COLIA1 Sp1 and VDR* polymorphism were reported to reduce bone mass in patients with PBC[49]. The polymorphism of IGF1 microsatellite repeat and CLDN14 genes were also reported to be associated with low bone mass in cholestatic liver disease[50,51].

Liver diseases are inflammatory conditions, and different pro-inflammatory cytokines can affect bone health in advanced liver diseases. CLD causes elevation of Transforming growth factor b (TGF b) levels. Increased levels of TGF-b alters the composition of extracellular matrix thereby affecting bone flexibility. TGF-b shifts the extracellular matrix towards fibronectin which increases osteoclast activity. Oncofetal fibronectin, a O-glycosylated form of fibronectin is induced by TGF-b which directly interferes with formation of bone[17]. Similarly, vimentin expression is increased by TGF-b which suppresses the maturation of osteoprogenitor cells. Further, TGF-b interferes with bone morphogenetic protein signalling and blocks osteoblast maturation[17]. Proinflammatory cytokines like tumour necrosis factor α (TNF α) is increased in NAFLD and it can increase osteoclast activity as well as can suppress osteoblast recruitment from progenitor cells[52]. Various other cytokines like interleukin 1 (IL-1), IL 8 were found to be associated in development of HO in cirrhotic

patients[53]. The summary of effect of the various inflammatory cytokines are shown in the **Figure 2**.

In addition to CLD per se, etiological factors behind the development of chronic liver disease can directly affect bone metabolism. Alcohol associated bone disease is a multifactorial disease[54]. Alcohol causes bone disease by direct effects on bone and mineral metabolism in addition to causing hepatic damage, nutrient deficiencies, hypogonadism and hypercortisolism[55,56]. In hemochromatosis, excess iron deposition can directly suppress bone formation by inhibiting the osteoblasts and can also increase bone resorption rates[46,57,58]. The specific pathophysiological factors for different aetiologies like alcoholic liver disease, cholestatic liver disease, MASLD and viral hepatitis have been summarized in **table 2** [52,59-72].

Other general risk factors like increasing age, low body mass index, malnutrition, lack of exercise, muscle wasting and smoking can also be responsible for significant bone loss in chronic liver disease[17]. Medications used in various liver diseases like corticosteroids, anti-viral agents (ribavirin), Cholestyramine, Calcineurin inhibitors and chemotherapeutic agents also have detrimental effects in the bone health [5,73-75].

Diagnosis

High risk factors

High risk factors for osteopenia and osteoporosis can be classified into traditional risk factors and liver specific factors. Traditional risk factors such as older age, female gender, post-menopausal status, physical inactivity, alcohol consumption, smoking, and low vitamin D levels are linked to poor bone quality. However, the type and duration of liver disease and concurrent steroid use may have a more significant impact on bone quality in patients with chronic liver disease. More advance disease correlates with poorer bone quality and liver transplant candidates often shows more severe bone disease due to more prolonged liver condition[12]. Alcoholic liver disease, cholestatic liver disease and concomitant steroid use are associated with higher odds of poor bone health.

Bone mineral density (BMD)

The gold standard for diagnosing HO is to assess ¹⁷ bone mineral density (BMD) with ¹⁹ dual X-ray absorptiometry (DXA) at the lumbar vertebrae and femoral neck. The World Health Organization (WHO) defines osteoporosis as a T-score below ² -2.5, indicating bone mineral density (BMD) more than 2.5 standard deviations below the average for young adults. Osteopenia is defined as a T-score between -1 and -2.5. For individuals aged less than 50 years, the Z-score is recommended to compare BMD with age-, race-, and sex-matched controls^[76]. WHO also created the Fracture Risk Assessment Tool (FRAX[®]) to assess individual risk ¹⁵ based on clinical factors and BMD at the femoral neck. FRAX estimates the 10-year probability of hip and major osteoporotic fractures. However, presence of fragility fracture needs immediate treatment, without the need for BMD measurement. These cut offs are derived from general osteoporosis guidelines, where CLD patients are underrepresented. Dedicated studies to determine treatment threshold for CLD patients are lacking.

In cirrhotic patients with ascites, paracentesis should be done before BMD measurements as fluid can falsely lower lumbar spine BMD values during a DXA scan^[77]. ⁶ In 2003, the American Gastroenterological Association (AGA) released guidelines addressing osteoporosis in patients with liver and gastrointestinal diseases^[78]. The AGA recommends evaluating vitamin D levels and BMD in all individuals diagnosed with cirrhosis.

Biochemical evaluation

Given the high prevalence of HO, it is imperative that all patients with CLD undergo a comprehensive assessment of bone health. This should include the measurement of vitamin D and blood calcium levels. Additionally, thyroid and gonadal functions should be evaluated to exclude other potential causes of osteoporosis.

Bone turnover marker

Bone turnover markers are derivatives of the bone remodelling process detected in the blood and urine of patients with bone disorders. The most commonly utilized markers of osteogenesis include osteocalcin, alkaline phosphatase (bone specific), and procollagen type 1 carboxyterminal propeptide. Resorption markers include urinary pyridinoline, deoxypyridinoline, type 1 collagen amino-terminal telopeptide, and hydroxyproline. Till date, there is no consensus regarding their use in clinical practice in CLD patients, However, they can be used to monitor therapy when antiresorptive therapy is initiated.

It is essential to recognise that liver dysfunction can influence serum concentrations of bone turnover markers (BTMs), revealing an increased degradation of bone matrix. Consequently, the evaluation of BTMs provides limited conclusions for individuals with CLD[79].

Management

Osteoporosis screening in chronic liver disease

Limited guidelines are available for screening for osteoporosis in patients with CLD. A higher prevalence of osteopenia and osteoporosis has been observed in individuals with PBC have compared to age and sex-matched controls[2]. In Generally, evaluation of BMD should be conducted in cirrhotic patients and in patients with cholestatic liver disorders, those on long-term corticosteroid therapy, and as part of the liver transplantation evaluation[80]. In conditions associated with rapid bone loss, like in cholestatic patients with multiple risk factor for osteoporosis, and in whom high-dose corticosteroid treatment has been started recently, it is advisable to repeat DXA in a shorter interval of around one year. For patients with advanced cirrhosis, the same schedule is also recommended[80]. In individuals within normal BMD, DXA may be repeated after 2-3 years, as is suggested in the non-cirrhotic population. A flow chart for diagnosis and treatment of bone disease in CLD patients is provided in Figure 3.

Management of osteoporosis- General measures

The current treatment of osteoporosis in CLD mainly focuses on alleviation of risk factors, treatment of primary liver disease, and optimization of nutritional status. Caloric intake recommendations vary between 35-50 kcal/kg/d, with daily protein intake of 1.2-1.5 g/kg actual body weight, depending on the severity of malnutrition[81]. Supplements of calcium (1,000-1,500 mg/d) and vitamin D (400-800 IU/d) or the dose required to preserve normal levels should be provided to all CLD patients as primary prevention[80,82]. However, the role of calcium and vitamin D supplementation in preventing HO has not been established[83] and clinical trials addressing this issue are needed. Vitamin D levels should be assessed in all patients with CLD, specifically in those with advanced disease[84], non-alcoholic fatty liver and cholestatic diseases[85]. In absence of any specific recommendations in patients with CLD barring those with chronic cholestasis, it seems rational to supplement all patients with CLD with 25(OH)D levels < 20 ng/mL with oral vitamin D until a serum 25(OH)D level of above 30 ng/mL is achieved[80,86]. Additionally, vitamin D levels should be monitored annually in perimenopausal and postmenopausal women with PBC.

Specific antiosteoporotic therapy

There is no universal agreement regarding the appropriate time to initiate treatment, however, people with established osteoporosis, and consequently with fragility fractures, should receive treatment to reduce the risk of future fractures. PBC patients with a T-score below -1.5 have a high risk of hip and vertebral fractures, supporting this T-score as a guide in practice for starting specific therapy in these patients[87] [Figure 3]. It is logical to consider specific treatment in these patients and in all osteoporosis patients prior to transplantation. Although commonly recommended as first-line treatment for osteoporosis[2], effectiveness of bisphosphonates (BP) in CLD is not as clear because of the limited number of studies with small sample size and short-term follow-up. Studies on in CLD have mostly been done in patients with PBC[88]. In particular, alendronate and ibandronate have been found to be effective in improving bone mass in PBC patients[56]. In a study of post-menopausal women with PBC and

osteoporosis, ibandronate was compared to alendronate. Patients were randomized to receive i.v ibandronate (monthly) or oral alendronate (weekly). At the end of 2 years, there was no significant difference in BMD between the 2 groups. However, a significantly better compliance was observed in the ibandronate group[89]. In spite of concerns for bisphosphonate use in CLD, serious adverse events have not been reported. In patients with severe esophagitis and esophageal varices, use of oral BPs is usually avoided, with parenteral BP such as zoledronic acid may be an alternative therapy. Due to its annual administration, compliance can be improved[81]. A recent trial from India revealed zoledronic acid improved lumbar spine BMD in men with HO as compared with placebo by reducing bone resorption as evident by significant decrease in plasma beta-C-terminal telopeptide (β -CTX) levels in the treatment arm[90]. However, there are no long-term studies of BPs in preventing fractures in patients with CLD. A selective estrogen receptor modulator, raloxifene, has shown some benefits in increasing BMD in PBC patients[91]; nevertheless, limited data are there on its efficacy and safety in patients with cirrhosis. More recently, denosumab, a RANK ligand inhibitor, has emerged as a potential option for the treatment of osteoporosis in CLD. A recent study examined the safety and efficacy of denosumab for osteoporosis in CLD patients and reported that irrespective of age, gender, and the presence of cirrhosis, the median BMD at the lumbar spine, femoral neck, and total hip improved by 4.44%, 3.71%, and 4.03%, respectively, from baseline to one year[92]. Until more conclusive data comes, use of third-generation BPs is recommended as first-line therapy in CLD patients with osteoporosis[1].

Current understanding of PBC-related osteoporosis indicates that it results from decreased bone formation, which may explain the attenuated effect of traditional antiresorptive agents. In this context, anabolic agents like parathyroid hormone (PTH) analogues, teriparatide or abaloparatide, may be more efficacious than BPs. In one study involving rats that underwent biliary ductal ligation, use of recombinant human PTH 1-34 showed a significant improvement in BMD compared to untreated controls[93], but has not been specifically evaluated in humans with CLD.

Figure 4 illustrating contributing factors to the development of osteoporosis in CLD, probable preventive strategies, and treatment of osteoporosis.

Hormone replacement

Initially, concerns over worsening of cholestasis restricted estrogen use in CLD but randomized controlled trials (RCTs) found no deterioration in liver disease[94,95]. Hormone replacement therapy (HRT) may be effective in increasing BMD in PBC, however no improvement in fracture risk has been demonstrated and adverse effects limit the use[96]. Considering available agents with less side effects, HRT is not recommended for treatment of osteoporosis in CLD patients without primary hypogonadism[1]. It seems sensible to screen for and treat hypogonadism with testosterone replacement particularly in high-risk groups, for example, hemochromatosis, ALD, and cirrhosis.

Liver-directed therapies

Effectiveness of therapies aimed at the primary liver disease depends on the etiology. Treatment of PBC with ursodeoxycholic acid or obeticholic acid did not improve BMD or decrease risk of fracture. On the other hand, abstinence from alcohol improved BMD. Excluding the early post-transplant period, liver transplantation improves BMD eventually as well[1].

CONCLUSION

HO remains a highly prevalent, yet underrecognized complication of chronic liver disease. Its unique pathogenesis, spanning disturbances in mineral metabolism, chronic inflammation, endocrine dysfunction and genetic factors necessitates a disease specific approach to its diagnosis and management. Unfortunately, despite the increased recognition, current screening and therapeutic regimen are predominantly adapted from general osteoporosis guidelines which usually lacks validation in hepatic cohorts. Early and systematic screening for bone disease should be incorporated in standard of

care for CLD patients to enable timely intervention which can prevent bone related complications. Dedicated clinical trials with newer agents like denosumab and teriparatide are needed to establish their benefits and long-term safety. Finally, ongoing research elucidating the molecular mediators between hepatic injury and bone manifestations offers promising avenues for targeted therapies.

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