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Bone loss in chronic liver diseases: Could healthy liver be a requirement for good bone health?

Bone loss in chronic liver disease

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Abstract

Given that liver is involved in many metabolic mechanisms, it is not surprising that chronic liver disease (CLD) could have numerous complications. Secondary osteoporosis and increased bone fragility are frequently overlooked complications in CLD patients. Previous studies implied that up to one-third of these individuals meet diagnostic criteria for osteopenia or osteoporosis. Recent publications indicated that CLD-induced bone fragility depends on the etiology, duration, and stage of liver disease. Therefore, the increased fracture risk in CLD patients puts a severe socio-economic burden on the health system and urgently requires more effective prevention, diagnosis, and treatment measures. The pathogenesis of CLD-induced bone loss is multifactorial and still insufficiently understood, especially considering the relative impact of increased bone resorption and reduced bone formation in these individuals. It is essential to note that inconsistent findings regarding bone mineral density measurement were previously reported in these individuals. Bone mineral density is widely used as the "golden standard" in the clinical assessment of bone fragility, while also it is not adequate to predict individual fracture risk. Therefore, micro-scale bone alterations (bone microstructure, mechanical properties, and cellular indices) were analyzed in CLD individuals. These studies further support the thesis that bone strength could be compromised in CLD individuals, implying that an individualized approach to fracture risk assessment and subsequent therapy is necessary for CLD patients. However, more well-designed studies are required to solve the bone fragility puzzle in CLD patients.

Key Words: Chronic liver disease; Fracture risk; Hepatic osteodystrophy; Osteoporosis; Bone strength

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Core Tip: Secondary osteoporosis and increased bone fragility are frequently overlooked complications in patients with chronic liver disease (CLD). Recent publications agree that CLD-induced bone fragility depends on the etiology, duration, and stage of liver disease, but certain ambiguities are still present. Importantly, etiopathogenetic mechanisms leading to CLD-induced bone loss are still insufficiently clarified. Given that available clinical tools for fracture risk assessment are not entirely reliable, evaluating small-length structural bone properties could improve understanding of the multifactorial nature of bone fragility in CLD patients, which could set a base for the development of more effective preventive and therapeutic strategies.

INTRODUCTION

The importance of a wide range of liver functions in the human body becomes the most visible in chronic liver disease (CLD). The most commonly known CLD complications are portal hypertension, hepatic encephalopathy, ascites, hepatorenal syndrome, variceal bleeding, and hepatocellular carcinoma[1,2]. However, CLD is also associated with changes in the skeleton, previously known as hepatic osteodystrophy[3,4]. Among CLD patients, substantial heterogeneity of skeletal changes was noted depending on the etiology, duration, and stage of the liver disorder[5,6]. Pioneer studies indicated that hepatic osteodystrophy is a frequent complication of cholestatic liver diseases[7], while these skeletal changes were later described in non-cholestatic hepatic disorders[8,9]. It has been reported that approximately every second patient with viral hepatitis, hemochromatosis and Wilson disease has osteoporosis or osteopenia[10–12], while up to 55% of patients with alcoholic liver cirrhosis have osteoporotic bone changes[3,13,14]. Interestingly, bone alterations in non-alcoholic fatty liver disease or non-alcoholic steatohepatitis have recently drawn researchers' attention, revealing that up to one-third of these individuals could develop bone alterations[15,16].

Consequently, CLD individuals are at substantial risk for non-traumatic bone fractures[17–19], with a prevalence between 7% and 35%[20]. Recent data revealed a two to three-times higher risk of fracture in patients with end-stage hepatic disorder than in

control individuals[19,21], while other research teams described an eight times higher fracture risk in these patients [22]. Regarding fracture localizations, data suggest that vertebral fractures are most common in patients with end-stage CLD[19,23–26], given that more than one-third of these individuals experienced at least one vertebral fracture during their lifetime[8,23,27]. Moreover, CLD contributes to the age-associated increase in the risk of femoral fracture and, subsequently, its life-threatening complications[22]. Recent data highlighted that occurrence of fragility fractures is shifted toward younger age in CLD patients[22], given that the fracture risk in CLD patients younger than 45 years corresponds to the fracture risk noted in controls over 75 years of age[22]. It is important to emphasize that CLD likely changes the sex distribution of fracture risk in the aged population, considering that CLD is more frequent in male patients[28], while osteoporosis and osteoporosis-related bone fractures are more probable to develop in older women[29]. Despite the significant number of studies that have assessed various characteristics of bone deterioration in CLD individuals, many unknowns should be elucidated to understand this topic entirely.

OSTEODENSITOMETRY FINDINGS IN CLD PATIENTS

Most contemporary studies dealing with bone changes in CLD patients used dual-energy X-ray absorptiometry (DXA) as the most valuable tool in the clinical assessment of fracture risk [30]. Interestingly, opposite results were yielded. Namely, significantly lower DXA-obtained bone mineral density (BMD) was noted in patients with end-stage CLDs of viral, autoimmune, and biliary origin[31–33]. At the same time, other authors failed to show a significant BMD decrease in CLD of the same etiology[34,35]. Multiple studies showed reduced DXA-obtained BMD values in the lumbar spine and femoral neck of patients with alcohol-induced CLDs[36–38], while other research teams failed to show these bone alterations in individuals prone to chronic alcohol abuse[17,39,40]. Given that the primary source of these contradictory data could be in the study design (cross-sectional study design), selection criteria, and the number of participants included in the study,

future well-designed prospective studies are required to fully understand BMD alterations in CLD patients.

BONE TURNOVER BIOMARKERS (BTMS) IN PATIENTS WITH CLD

As a non-invasive and cost-effective tool for indirect assessment of bone remodeling dynamics, BTMs are a complementary method in the clinical management and follow-up of the treatment effects in patients with osteoporosis and osteoporosis-related bone fragility[41]. Automated or manual immunoassays using blood or urine samples are utilized to measure a specific combination of these protein or protein-derivative biomarkers[42], which are considered indicative of the dynamic relation between osteoblast activity (bone formation markers) and osteoclast activity (bone resorption markers)[41,43]. The most frequently investigated bone formation markers are osteocalcin (OC), bone alkaline phosphatase (BALP), and N-propeptide of type I collagen (PINP)[41]. On the other side, commonly interpreted bone resorption markers are deoxypyridinoline (DPD), C- and N-terminal telopeptides of type I collagen (CTX and NTX), and tartrate-resistant acid phosphatase isoform 5b (TRAP)[41]. The interpretation of BTM levels has been of clinical utility in age-related osteoporosis[43], while its role in the clinical management of CLD-induced bone loss is still modest. Some data suggest that serum levels of OC and BALP are decreased in individuals with CLD[25,36,44], while others failed to show significant differences between individuals with CLD and the control group[45,46]. Moreover, contradictory data regarding the level of β-CTX and DPD were noted in CLD patients[36,45,47,48]. It is important to note that liver dysfunction could affect serum concentrations of BTMs which reveal excessive bone matrix degradation, indicating that its assessment allows only limited conclusions in CLD individuals[10,49]. Multiple limitations of BTM assessment are among the reasons why CLD-induced bone changes are recognized and treated after patient experiences non-traumatic fracture[10], suggesting that further investigation is required to elucidate the role of BTMs in developing novel, adequate preventive and treatment strategies.

ASSESSMENTS OF MICRO-SCALE BONE PROPERTIES IN CLD INDIVIDUALS

The World Health Organization recommended BMD as the primary parameter for the diagnosis of osteopenia and osteoporosis and for clinical fracture risk assessment[50]. However, increased bone fragility could not be solely explained by BMD decrease[51,52], considering that the occurrence of fragility fractures primarily involves the mutual interaction of several bone-strength determinants (Figure 2). In other words, low BMD should be considered an applicable and non-invasive clinical predictor of bone fragility rather than its synonym[52,53]. Namely, it has been known that only up to one-third of non-traumatic fractures are attributable to low BMD values, indicating that many individuals with bone fractures have BMD in the referent range[54]. Moreover, various bone properties are recognized as important determinants affecting bone strength (ability to resist fracture)[55]. Thus, current studies suggested that multiscale analysis of various bone properties (with respect to the hierarchical structure of the bone, Figure 2) could contribute to a better understanding of increased bone fragility in elderly individuals with chronic comorbidities, including a variety of CLDs[56]. The importance of assessing these bone properties is highlighted by the fact that some pharmaceutic agents were proven to improve bone strength and reduce fracture risk without increasing BMD[57,58], indicating the potential for developing new and effective treatment strategies[52].

Initially, histomorphometry studies using optic microscopy assessment of iliac bone biopsies proved deteriorated trabecular bone architecture in CLD patients[59,60]. In addition, some novel clinical studies confirmed these results on the tibia and radius of CLD patients, using a more newel methodology - peripheral quantitative computed tomography[33,61,62]. Since osteoporosis is not uniform throughout the skeleton[63], it was crucial to assess CLD-induced micro-structural decline in lumbar vertebrae and proximal femora[38,64]. Similarly to previous findings, our research group used micro-computed tomography with an isotropic resolution of 10 μm to observe impaired micro-architectural integrity of lumbar vertebrae and proximal femora collected from CLD individuals[9,38,64]. On the trace of altered trabecular and cortical micro-architecture, we demonstrated reduced mechanical bone competence in these individuals[38,65], indicating

that altered bone matrix content could be involved in CLD-induced bone fragility. Still, future state-of-the-art studies should focus on a precise nano-scale morpho-structural estimate of the inorganic (mineral) and organic component of the bone extracellular matrix (collagen fibers) to elucidate its role in increased bone fragility among CLD individuals (Figure 2). Finally, the long-term benefit of small-length bone studies could be developing a specific diagnostic algorithm that will help to reliably predict bone strength based on the information available in the clinical context of each patient.

THE MOLECULAR MECHANISMS INVOLVED IN ETIOPATHOGENESIS OF CLD-INDUCED BONE LOSS

Bone loss in CLD patients is commonly described as a consequence of bone remodeling disturbance[8], but the particular contribution of increased bone resorption and decreased bone formation still needs to be thoroughly explained. Nowadays, a common understanding is that the etiopathogenetic mechanisms of bone loss are dependable on the liver disease's etiology[3,8]. Previous data revealed that osteoblast dysfunction and decreased bone formation play a central role in the etiopathogenesis of low-turnover osteoporosis in patients with various forms of CLDs (for example, cholestatic liver disease, hemochromatosis, and Wilson's disease)[7,12,48,66]. Conversely, viral CLD displays a more dominant effect on increased osteoclast activity, inducing high-turnover osteoporosis[21,32,67].

On a molecular level, low-turnover osteoporosis in CLD patients is commonly associated with toxic effects of biliary stasis and copper/iron accumulation on differentiation, maturation, and proliferation of osteoblasts (Figure 3)[68–70]. Also, previous studies suggested that osteoblast dysfunction in patients with cholestatic forms of CLD could be mediated by insulin growth factor-1 or oncofetal fibronectin[66,70,71], while direct toxic effects of alcohol on osteoblastic function contribute to bone loss among patients within alcohol-induced CLD[72,73]. During the process of bone formation, osteoblasts become embedded within the bone matrix, continuing to function as bone remodeling orchestrators - osteocytes[74]. Osteocytes form a global network throughout

the bone tissue by intercellular channels (gap junctions), most frequently formed by connexin 43[75]. Reduction in osteocytic expression levels of connexin 43 and minor disruptions in the osteocyte lacunar network was noted in CLD individuals (Figure 3), suggesting that the mechanosensing potential and molecular transduction might be defective in those patients with CLD[65,76]. In addition, increased bone expression levels of sclerostin (an osteocyte-derived negative regulator of bone formation) were noted in CLD individuals[65,76], which was in accordance with previous clinical studies[77,78]. These data indicate that treatment targeting sclerostin may be an interesting strategy to fight osteoporosis in CLD patients[10]. Still, possible therapeutical utilities in CLD patients are yet to be thoroughly investigated in the years ahead.

Previous studies revealed that bone loss in CLD individuals could be explained by a strong link between systemic hyperproduction of inflammatory mediators and increased bone resorption (Figure 3)[21,32,67]. Most commonly, it is understood that factors produced by immune cells (tumor necrosis factor-α, interleukins (IL)-1, IL-6, IL-7, IL-11, IL-15, and IL-17) could directly activate osteoclast precursors or display indirect effect by osteoblasts[8,10,72]. Namely, increased levels of receptor activator for nuclear factor kappa B ligand (RANKL), the disturbed ratio between RANKL and osteoprotegerin (OPG) levels, matrix metalloproteinases activity, and cathepsin K are described as contributing factors in CLD-induced bone loss *via* increased bone resorption (Figure 3)[10,79–81]. The recent recommendation for therapy targeting RANKL advocates the importance of the RANK-RANKL-OPG system in bone loss among CLD patients[20,82]. In addition, increased circulating macrophage colony-stimulating factor 1 (M-CSF1) in CLD patients could promote bone resorption due to its role in directing monocytes to form a larger number of osteoclasts in these patients[6].

Lastly, unbalanced nutritional habits (low calcium and protein intake), malabsorption, low levels of vitamin D levels, disruption in the homeostasis of the intestinal microbiome, coupled with a variety of hormonal and metabolic disruptions (such as increased PTH levels, hypogonadism, and hypercorticism) are identified as factors that contribute to bone loss in CLD individuals[20,72,83]. Based on these data, new

nutritional support guidelines were recently introduced by the European Association for the Study of the Liver[20,84]. However, given that bone changes in CLD patients are undoubtedly present, it is vital to further investigated more direct etiopathogenetic mechanisms involved in the relationship between liver and bone disorders.

CONCLUSION

Bone alterations are a common complication in patients with CLD, especially in those with liver cirrhosis. Over the previous period, numerous studies have contributed to understanding bone fragility in CLD patients. However, numerous ambiguities are still present due to the modest reliability of clinical diagnostic methods, which could lead clinicians to doubt whether or when it is necessary to start treating CLD-induced skeletal alterations. Thus, evaluating small-length structural bone properties could improve understanding of the multifactorial nature of bone fragility in CLD patients. All these data could set a base for developing a patient-specific diagnostic algorithm that will reliably predict bone strength based on the information available in a clinical context. Additionally, specific clinical guidelines for preventing, diagnosing, and treating skeletal disorders in patients with CLD need to be established in the near future.

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