

Hepatic osteodystrophy: An important matter for consideration in chronic liver disease

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Abstract

Hepatic osteodystrophy (HO) is the generic term defining the group of alterations in bone mineral metabolism found in patients with chronic liver disease. This paper is a global review of HO and its main pathophysiological, epidemiological and therapeutic aspects. Studies examining the most relevant information concerning the prevalence, etiological factors, diagnostic and therapeutic aspects involved in HO were identified by a systematic literature search of the PubMed database. HO generically defines overall alterations in bone mineral density (BMD) (osteoporosis or osteopenia) which appear as a possible complication of chronic liver disease. The origin of HO is multifactorial and its etiology and severity vary in accordance with the underlying liver disease. Its exact prevalence is unknown, but different studies estimate that it could affect from 20% to 50% of patients. The reported mean prevalence of osteoporosis ranges from 13%-60% in chronic cholestasis to 20% in chronic viral hepatitis and 55% in viral cirrhosis. Alcoholic liver disease is not always related to osteo-

penia. HO has been commonly studied in chronic cholestatic disease (primary biliary cirrhosis and primary sclerosing cholangitis). Several risk factors and pathogenic mechanisms have been associated with the loss of BMD in patients with chronic liver disease. However, little information has been discovered in relationship to most of these mechanisms. Screening for osteopenia and osteoporosis is recommended in advanced chronic liver disease. There is a lack of randomized studies assessing specific management for HO.

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Key words: Hepatic osteodystrophy; Liver disease; Osteoporosis; Osteopenia

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INTRODUCTION

Hepatic osteodystrophy (HO) is the generic term defining the group of alterations in bone mineral metabolism found in patients with chronic liver disease^[1]. These individuals have been described as having a higher rate of osteopenia and osteoporosis and the different studies performed in this connection have shown that the rates vary. HO is therefore a common complication throughout the progression of chronic hepatopathy and involves dete-

rioration in quality of life which affects the patient's long-term prognosis^[2]. Consequently, a detailed bone mineral density (BMD) and bone metabolism evaluation should be performed in all patients with chronic liver disease in order to prevent fractures and chronic pain. This article aims to provide a general review of HO.

CHRONIC LIVER DISEASE AND ITS ASSOCIATION WITH OSTEOPENIA AND OSTEOPOROSIS

The prevalence of osteoporosis and fracture risk in patients with chronic liver disease

Metabolic bone disease is a significant disorder which appears in patients with chronic hepatopathy (also known as HO), especially in those affected by chronic cholestasis^[3,4]. Its etiology is complex and multifactorial and manifests as osteopenia and osteoporosis. This bone disorder must be evaluated and detected early in all patients with chronic liver disease in order to minimize the risk of fractures and improve their clinical progression and quality of life^[5]. Various studies have been conducted on the prevalence of osteoporosis in these patients and in patients with chronic cholestasis (Table 1). In most of this research, bone density is calculated using a bone densitometry. However, the authors use different methods to analyze mineral density in order to select patients and even have different definitions of osteoporosis^[6-8].

Patients with chronic liver disease harbor additional risk factors for developing osteoporosis, such as hypogonadism, vitamin D deficiency, alcohol consumption, chronic steroid treatment and a low body mass index^[9]. With osteoporosis, the patient is predisposed to suffering bone fractures and increased morbimortality. Vertebral fractures are most frequent in these patients, ranging from 3% to 18%^[10,11].

Cirrhosis: Different authors consider that the prevalence of osteoporosis in cirrhotic patients is related to the severity of liver disease expressed by the Child-Pugh index^[12,13]. This prevalence ranges from 20% to 56% and inter-individual variations are observed in relationship to bone density. The fracture rate ranges from 5% to 20%^[14].

Chronic cholestatic disease: A high prevalence of osteoporosis is associated with both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). This is one of the most widely studied groups of patients with chronic hepatopathy in terms of bone mineral metabolism pathologies. Its prevalence among different groups is estimated to range from 13% to 60%^[15].

PBC

Various studies have been conducted on the BMD of patients with PBC. The predominant alteration in these patients is osteoporosis and osteomalacia is very rare^[16].

Reduction in bone density is related to the severity of cholestatic disease, although not all patients with PBC develop osteoporosis and the rate of bone mass loss varies from one individual to another^[17,18].

Other factors linked to osteoporosis in PBC are the time to progression of the disease and the degree of cholestasis, as a reflection of the stage of chronic hepatopathy. Post menopause and malabsorption of calcium in the intestine have also been suggested as predisposing factors in these patients^[19].

Generally, research on bone pathology in PBC coincides with indicating cholestasis as an independent risk factor for developing osteoporosis. Nevertheless, studies to see if there was an improvement in BMD following treatment with ursodeoxicolic acid did not show significant changes compared to untreated patients. Regarding this aspect, cirrhosis co-existing with advanced cholestatic disease can significantly contribute to alterations in BMD^[9,20].

PSC

PSC patients harbor various risk factors for developing osteoporosis: cholestasis, co-existing cirrhosis and corticosteroid treatment in the presence of associated inflammatory bowel disease. Individuals with PSC showed a decrease in the BMD of the lumbar vertebrae compared to healthy controls^[10].

Hemochromatosis: Certain studies have described a link between hemochromatosis and low BMD by relating co-existing hypogonadism and iron overload with the development of osteoporosis^[21]. The prevalence of the latter is approximately 30%^[22].

Alcoholism: Alcoholism is an independent risk factor of the development of osteoporosis and osteoporotic fractures and has been especially studied in male patients. BMD of the lumbar vertebrae in these individuals is lower than in healthy controls^[23] and the risk of fractures is independent from existing cirrhosis or associated hypogonadism^[24,25]. Alcohol abuse in women who do not have cirrhosis and hypogonadism does not appear to be linked to osteopenia and osteoporosis^[26].

Non-cholestatic and non-cirrhotic hepatopathy: The exact prevalence of osteoporosis in patients with chronic hepatopathy but who do not have cirrhosis, cholestasis and hypogonadism is unknown. The approximate prevalence of osteoporosis measured at the lumbar vertebrae in this group of patients ranges from 16% to 50%^[27] with a fracture rate ranging from 12% to 18%^[28].

PHYSIOPATHOLOGY OF BONE MASS LOSS IN PATIENTS WITH CHRONIC LIVER DISEASE

Bone mass increases from childhood, approximately

reaching maximum levels in one's thirties. From one's forties onwards, it starts to decrease in both genders but with a faster loss in women following the menopause. Peak bone mass is determined by genetic and hormonal factors, type of diet and physical activity. The rate of osteoporosis increases in the elderly as the loss of bone mineral mass is a phenomenon associated with aging.

Bone mass loss occurs as a result of an increase in bone turnover and/or an imbalance in bone remodeling. The latter can be caused by decreased osteogenesis, increased bone resorption or by a combination of both. Certain studies have shown increased bone resorption in the context of chronic liver disease, even in patients without osteoporosis. Other research has shown decreased bone formation^[12,29]. A study of bone histomorphometric parameters performed on 50 patients with PBC and PSC showed decreased bone formation (osteoblast dysfunction) in men and women and a significant increase in bone resorption due to osteoclast activation, especially in women. According to the authors, the duration of cholestasis or other associated factors seem to be more important than the severity of the disease itself, expressed by levels of serum bilirubin in the development of osteodystrophy^[30].

The risk of osteoporotic fracture is determined not only by BMD but also by trabecular architecture, bone geometry, bone turnover and risk factors which are not associated with the skeleton such as postural instability and the risk of falls.

The main risk factors for developing osteoporosis and, therefore, bone fractures in patients with chronic liver disease include: low body mass index (< 19 kg/m²), excessive alcohol consumption, prolonged steroid treatment (5 mg/d of prednisolone for over 3 mo), sedentary lifestyle, hip fractures in the mother at a young age (< 60 years), hypogonadism and early menopause (under 45 years)^[9].

PATHOGENIC MECHANISMS INVOLVED IN BONE MASS LOSS IN PATIENTS WITH CHRONIC LIVER DISEASE

Genetic factors

Certain genetic polymorphisms have been described which may play a secondary role in the development of osteoporosis in chronic cholestatic hepatopathy. These include the vitamin D receptor gene, the collagen type 1 α 1 gene and insulin-like growth factor (IGF-1) polymorphisms^[31].

Anomalies of calcium and vitamin D metabolism

Vitamin D is produced by endogenous synthesis in the skin, aided by sunlight, from which cholecalciferol is synthesized (vitamin D₃). Both cholecalciferol and ergocalciferol or vitamin D₂ can also be obtained from food. Vitamin D undergoes 25-hydroxylation in the liver tissue, a process which is affected by advanced liver disease.

Vitamin D deficiency is associated with secondary hyperparathyroidism, an increase in bone turnover and ac-

celerated loss of bone mass. Various studies have shown low serum 25-hydroxyvitamin D levels in individuals affected by chronic liver disease, which continue decreasing as cirrhosis develops^[32-34]. The main factors triggering vitamin D deficiency in chronic hepatopathy are believed to be limited exposure to ultraviolet radiation and nutritional deficiency. Intestinal malabsorption, alterations in the enterohepatic circulation of vitamin D and decreased skin synthesis in individuals with jaundice also contribute to vitamin D deficiency. However, no significant correlation between osteopenia and decreased vitamin D levels has been demonstrated in patients with chronic cholestasis^[35].

Vitamin K deficiency

Vitamin K is an essential cofactor for osteoblasts to synthesize osteocalcin - bone matrix protein. Vitamin K deficiency contributes to osteopenia in patients with PBC and supplementing it can prevent them from losing bone mass^[36].

IGF-1 deficiency

IGF-1 is involved in osteoblast differentiation and proliferation. Low serum levels of IGF-1 were observed in a study with bile duct-ligated rats, suggesting that cholestasis deeply affects its activity^[37]. Therefore, its deficiency observed in cirrhosis and cholestatic hepatopathies may cause osteoblast dysfunction and osteopenia^[14,15].

Hyperbilirubinemia

In vitro studies on animal models show that the increase in unconjugated bilirubin impairs osteoblast function in a dose-dependent and reversible effect^[38,39]. The results of research on humans are inconsistent. For some authors, osteopenia progresses at the same rate as jaundice does in patients with PBC and PSC^[40], while this correlation is insignificant for others^[41].

Receptor activator of nuclear factor κ B ligand and osteoprotegerin

The receptor activator of nuclear factor κ B ligand/osteoprotegerin (RANKL/OPG) system regulates bone metabolism by modulating osteoclast activity, to the extent that OPG is a factor which inhibits that activity while the RANKL ligand activates it. Various research has shown that the OPG/RANKL ratio is high in patients with chronic liver disease compared to control subjects, which shows that there is ligand consumption that activates osteoclastic activity, and an excess OPG as a compensating mechanism which tries to prevent the loss of bone mass^[42-44]. Other cytokines involved in the pathogenesis of chronic liver disease such as interleukin (IL)-1, IL-6 and tumor necrosis factor α can activate this system^[37]. Additionally, circulating mononuclear cells could have a higher capacity to differentiate into osteoclasts in patients with chronic liver disease and osteopenia^[45].

Hypogonadism

Hypogonadism associated with chronic hepatopathy has

Table 1 Prevalence of osteopenia and osteoporosis in chronic liver disease of various etiologies

Ref.	n	Etiology	Prevalence of osteopenia/osteoporosis	Pathogenic mechanisms/ associated factors
Goral <i>et al</i> ^[44] , 2010	55	Child A-B-C cirrhosis Mixed etiology	Osteoporosis 37%	Increased TNF α and IL-6 levels Decreased IGF-1 levels
Wariaghli <i>et al</i> ^[53] , 2010	64	Cirrhosis Mixed etiology	Osteoporosis 45.3%	Female sex Cholestasis Lower weight and height Not specified
Loria <i>et al</i> ^[67] , 2010	35	Cirrhosis Viral and alcoholic	Osteoporosis 14% Osteopenia 26%	Not specified
George <i>et al</i> ^[34] , 2010	72	Cirrhosis Viral and alcoholic	Low BMD 68%	Low levels of IGF-1
Sokhi <i>et al</i> ^[66] , 2004	104	Cirrhosis Mixed etiology	Osteoporosis 11.5% Osteopenia 34.6%	Child B-C stage and female female
Gallego-Rojo <i>et al</i> ^[12] , 1998	32	Viral cirrhosis	Osteoporosis 53%	Child stage IGF-1 serum levels
Auletta <i>et al</i> ^[72] , 2005	30	Chronic viral hepatitis	Osteoporosis 20% Osteopenia 44%	Chronic hepatopathy per se
Diamond <i>et al</i> ^[11] , 1989	22	Hemochromatosis	Osteoporosis 45%	Hypogonadism Low free testosterone levels
Sinigaglia <i>et al</i> ^[22] , 1997	32	Hemochromatosis	Osteoporosis 28%	Cirrhosis and iron overload
Mounach <i>et al</i> ^[73] , 2008	33	Primary biliary cirrhosis	Osteoporosis 51.5%	Low BMI Menopausal status Duration of liver disease Vitamin D deficiency
Lindor <i>et al</i> ^[20] , 1995	88	Primary biliary cirrhosis	Osteoporosis 35%	not specified
Guañabens <i>et al</i> ^[74] , 1990	20	Primary biliary cirrhosis	Osteoporosis 35%	Duration of liver disease Post menopause Malabsorption of calcium
Angulo <i>et al</i> ^[10] , 1998	81	Primary sclerosing cholangitis	Osteoporosis 17%	Stage of liver disease Associated advanced inflammatory bowel disease
Malik <i>et al</i> ^[23] , 2009	57	Alcoholic	Low BMD (z-score \leq -2.0) 17.5%	25-hydroxy-vitamin D deficiency
Kim <i>et al</i> ^[24] , 2003	18	Alcoholic	Osteoporosis 22% Osteopenia 50%	Cumulative alcohol intake
Gonzalez-Calvín <i>et al</i> ^[25] , 1993	39	Alcoholic	Osteopenia 23%	Cumulative alcohol intake Impairment of osteoblastic activity by ethanol

BMD: Bone mass density; BMI: Body mass index; IGF-1: Insulin-like growing factor 1; IL-6: Interleukin-6; TNF: Tumoral necrosis factor.

been proposed as a factor which favors the loss of BMD. Low levels of estradiol, luteinizing hormone and follicle-stimulating hormone have been observed in postmenopausal women with cirrhosis, with normal testosterone and sex hormone binding globulin^[46]. However, in males with advanced liver disease, there is an increase in the level of estrogen due to peripheral aromatization, which does not seem to protect against bone mass loss in individuals with alcoholic liver disease^[47].

Medication

Glucocorticoid-based treatments in autoimmune liver disease and chronic cholestatic liver diseases accelerate the loss of bone mass, although their contribution is difficult to estimate due to the effect of liver disease *per se* on the bone^[48]. The adverse effect of cholestyramine on the intestinal absorption of vitamin D has also been reported^[15].

Lifestyle

Alcohol consumption and smoking aggravate osteopenia/osteoporosis, together with a sedentary lifestyle, malnutrition and a low body mass index^[49].

DIAGNOSTIC AND THERAPEUTIC ASPECTS OF OSTEOPENIA AND OSTEOPOROSIS IN CHRONIC LIVER DISEASE

Diagnosis of osteopenia and osteoporosis

The main objective for assessing and treating HO is to prevent bone fractures. BMD is measured using dual energy X-ray bone absorptiometry performed on the lumbar vertebrae and femoral neck. The results of the measurement are classified on a scale by the World Health Organization, the *t-score* being the basic parameter for diagnosis. Osteoporosis is therefore defined as a BMD of less than 2.5 standard deviation compared to the normal average score for young adults (*t-score* of less than -2.5). Similarly, osteopenia is defined as having a *t-score* of between -1 and -2.5^[50]. Prospective studies show how the risk of fractures increases progressively in proportion to the decrease in BMD, with between a two-fold and three-fold increase per standard deviation decrease therein^[51].

Assessment of all patients with chronic liver disease and suspected osteoporosis should include a hemogram

and basic biochemistry, including liver function, phosphocalcium metabolism and gonadal and thyroid profile. A simple X-ray of the dorsal and lumbar vertebrae is indicated if there is a clinical suspicion of spinal fracture as this is an indication for treatment, irrespective of bone density.

During the bone remodeling process, enzymes and non-enzymatic peptides reach the bloodstream and/or are eliminated through urine. Their concentration in blood and urine is related to the total bone turnover rate. These products, or bone turnover markers (BTM), are divided into two groups: resorption markers and formation markers. The main osteosynthesis markers are procollagen type I carboxyterminal propeptide and procollagen type I aminoterminal propeptide, osteocalcin and alkaline phosphatase bone isoenzyme. Noteworthy among the resorption markers are the urinary excretion of deoxypyridinoline, pyridinoline, type 1 collagen amino-terminal telopeptide and hydroxyprolinuria, the latter being less specific. These markers are usually expressed in relationship to the urinary excretion of creatinine.

BTM are higher in patients with osteoporosis and there is an inverse relationship between their levels and BMD. Until now, there has been no particular consensus regarding the most appropriate strategy for their use in clinical practice, although it is thought that they could be useful for monitoring bone mass loss in response to treatment for osteoporosis and for predicting fracture risk. However, this extreme is yet to be verified, because there have been only a few studies with patients suffering from chronic liver disease carried out^[52,53]. It would seem that BTM levels are influenced by the extent of hepatic fibrosis and by the intrahepatic metabolism of collagen in these individuals which could make it difficult to interpret the results obtained^[9].

Treatment of osteoporosis in chronic liver disease

There are very few randomized-controlled intervention studies on the prevention of osteoporosis and fractures in chronic liver disease. Most of available data relate to studies performed on patients with PBC^[6-8] and do not evaluate the effective reduction in fracture rates.

General non-pharmacological measures and specific antiosteoporotic drugs are available to treat HO.

General measures: These include lifestyle and nutritional measures aimed at correcting the reversible risk factors, such as alcohol consumption, smoking and making lifestyle changes by introducing regular moderate physical exercise.

Extensive studies have provided no evidence on the effect of calcium and vitamin D in preventing OP and fractures in these patients. Research has been performed on small groups yielding inconsistent BMD results^[16,32,51]. However, it seems reasonable to recommend supplements by taking a daily dose of 800 UI of vitamin D3 and 1 g of calcium^[9,54].

Specific drugs in the treatment of HO: Bisphosphonates are powerful anti-resorptive drugs that selectively inhibit osteoclast activity. These agents have been shown to reduce the risk of vertebral and non-vertebral fractures and increase BMD in postmenopausal women with osteoporosis who do not have liver disease^[47]. They have also been effective in preventing steroid-induced osteoporosis in patients with PBC^[6]. However, there are no long-term controlled studies developed to evaluate the efficiency of bisphosphonates in fracture-prevention in individuals with chronic liver disease. A study with 80 postmenopausal women with osteoporosis and chronic liver disease secondary to hepatitis virus B and C suggests that a cyclic etidronate treatment could be effective to reduce the incidence of bone fracture^[55].

Alendronate improves BMD of patients with PBC^[56,57], although it should be used with caution because of potential esophageal side effects^[9]. Risedronate seems to have a less toxic effect on the esophageal mucosa, which could be useful for treating patients with esophageal varices.

Consequently, bisphosphonates are the main pharmacological agents used in the treatment of HO nowadays, despite the fact that limited data on bisphosphonates-therapy in chronic liver disease are available^[38,58,54].

Raloxifene is a selective estrogen receptor modulator. It has positive effects on the lumbar bone mass and femoral neck and reduces vertebral fracture risk in postmenopausal osteoporosis. In a small study of patients with PBC, raloxifene led to significant improvement in lumbar BMD after 1 year of treatment, while no improvement was observed in the femoral neck^[59]. Evaluation by a bone disease specialist is recommended before using raloxifene in individuals with hepatic disease^[54].

Parathyroid hormone (PTH) is a bone-forming drug that is administered subcutaneously in dosages of 20 to 40 µg per day, achieving an increase in BMD and a decrease in vertebral fracture risk in postmenopausal osteoporosis. Few data are published on its usefulness in osteoporosis secondary to chronic liver disease. A study in rats with induced biliary cirrhosis showed that intermittent administration of human PTH increases BMD and could be effective to prevent loss of bone mass^[60].

Treatment of hypogonadism in patients with chronic liver disease and HO remains controversial. Hormone replacement with testosterone in hypogonadic males without chronic liver disease was efficient and increased BMD^[61]. Hormone replacement therapy (HRT) with estrogen and progesterone was proposed as a safe treatment for women with chronic hepatopathy, administered either orally or transdermally and sequentially or continuously^[62,63]. Following the publication of the HERS II^[64] and WHI^[65] studies questioning the safety of HRT, its use is currently not recommended. The increased risk of hepatocellular carcinoma related to this treatment should be taken into account by weighing up its benefits and risks and it should be better administered transdermally^[9,37,59].

Orthotopic liver transplantation and bone metabolism: A high prevalence of low BMD among patients with chronic liver disease just before liver transplantation has been observed. Estimated rates range from 26% to 34% and from 11.5% to 14% for osteopenia and osteoporosis, respectively^[66,67].

Immediately after orthotopic liver transplantation (OLT), there is a loss of BMD and fracture risk increases. However, in the long term, osteopenia improves in transplant patients, as shown by a prospective study of patients with PBC and PSC who underwent OLT^[68]. Thus, liver transplantation is an efficient long-term treatment for osteoporosis in chronic cholestatic liver disease. Bisphosphonates have also shown to be useful to avoid bone loss in transplant patients^[69,70] but there is no evidence to consider one single agent among this group of drugs as first line therapy^[71].

CONCLUSION

Osteopenia and osteoporosis are important and common complications of chronic liver disease, receiving the generic definition of HO. Their exact prevalence is unknown, ranging between 20% and 50% depending on the series. The development of HO may be due to both increased bone resorption and decreased bone formation. The etiology is multifactorial and can vary in accordance with the origin of the liver disease, having been preferentially studied in chronic cholestatic diseases (PBC and PSC). There are multiple risk factors associated with loss of BMD, the most important being chronic cholestasis and advanced cirrhosis.

Pathogenic mechanisms are diverse and very little is known about some of them: genetic factors, alterations in calcium-vitamin D metabolism, hyperbilirubinemia, vitamin K and IGF-1 deficiency, RANKL-OPG system activity and hypogonadism.

Osteoporosis can result in bone fractures with a harmful effect on morbidity and quality of life. Therefore, an assessment of bone metabolism and risk factors for bone loss and a BMD measurement are recommended in patients with chronic liver disease. An early diagnosis of HO is essential to correct reversible risk factors which predispose to bone mass loss.

Treatment and prevention strategies include general measures, dietary and lifestyle, calcium and vitamin D3 supplementation and bisphosphonates. However, advanced HO is difficult to treat and special care is required to prevent bone loss in individuals with severe hepatic disease. Further research is needed since there are no large randomized controlled trials of intervention in chronic liver disease and osteoporosis. In the same way, there is lack of randomized studies in areas like fracture prevention with available therapeutic agents and potential usefulness of new treatments for osteoporosis.

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