# Hepatic osteodystrophy

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**Summary**

**Metabolic disturbances of bone are frequent in patients with chronic liver disease. The prevalence of osteoporosis among patients with advanced chronic liver disease is reported between 12% and 55%; it is higher in primary biliary cirrhosis. All patients with advanced liver disease should be screened for osteoporosis with a densitometry, especially if the etiology is cholestatic and in the presence of other risk factors. Clinical relevance of hepatic osteodystrophy increases after liver transplantation. After liver transplant, a rapid loss of bone mineral density can be detected in the first 6 months, followed by stabilization and slight improvement of the values. At the time of transplantation, bone density values are very important prognostic factors.**
**Therapy of hepatic osteodystrophy is based primarily on the control of risk factors: cessation of tobacco and alcohol assumption, reduction of caffeine ingestion, exercise, supplementation of calcium and vitamin D, limitation of drugs such as loop diuretics, corticosteroids, cholestyramine.**
**Bisphosphonates have been proposed for the therapy of osteoporosis in patients with liver disease, particularly after liver transplantation. The possible side effects of oral administration of bisphosphonates, such as the occurrence of esophageal ulcerations, are of particular concern in patients with liver cirrhosis and portal hypertension, due to the risk of gastrointestinal hemorrhage from ruptured esophageal varices, although this risk is probably overestimated.**

*KEY WORDS: hepatic osteodystrophy; liver cirrhosis; liver transplantation; vitamin D.*

## Introduction

Metabolic disturbances of bone are frequent in patients with chronic liver disease (1), especially those who are affected by cholestatic diseases (primary biliary cirrhosis and primary sclerosing cholangitis) (2, 3). Hepatic osteodystrophy commonly manifests with osteoporosis and osteopenia (4), depending on the impairment of bone mineral density (BMD), while osteomalacia is rare (5). Many etiological factors are assumed as part of the process leading to hepatic osteodystrophy, even if its origin is still far to be completely defined (6).

## Osteoporosis and chronic liver disease

The prevalence of osteoporosis among patients with advanced chronic liver disease is reported between 12% and 55% (7-9), depending on the criteria used for diagnosis, etiology and degree of disease (Table 1).
Osteoporosis and fractures are more frequent in patients with cirrhosis than in the general population, even in the absence of factors such as cholestasis or alcohol abuse (10).
The prevalence is higher in chronic cholestatic diseases, namely primary biliary cirrhosis (PBC) (11) and primary sclerosing cholangitis (PSC) (12). In patients affected by PBC, the reduction in bone density is usually related to the severity of cholestatic disease (13), postmenopause and malabsorption of calcium in the intestine (14). Risk factors for the development of osteoporosis in patient with PSC are cholestasis itself, the degree of liver cirrhosis, the use of corticosteroids, the presence of inflammatory bowel disease (15). The most valuable strategy for the management of hepatic osteodystrophy is primary prevention: all patients with advanced liver disease should be evaluated for bone densitometry screening, especially if the etiology of the disease is cholestatic and in the presence of other risk factors (6).

## Pathogenesis of hepatic osteodystrophy

The pathogenesis is not completely defined and is probably multifactorial (6). There is no full agreement on the main pathophysiological mechanism leading to osteoporosis in chronic liver diseases.
In patients with liver disease, the factors that contribute to the onset of osteoporosis are similar to those that favor the loss of trabecular bone in post-menopausal osteoporosis and in the elderly (2) (Table 2). Low levels of insulin-like growth factor-1 (IGF-1), a bone collagen and osteoblast stimulator synthesized in the liver (11, 16-19), and increased unconjugated bilirubin (20, 21) have inhibitory effects on osteoblast differentiation and proliferation. Low body mass index (BMI) (22), alcoholism (23, 24), malnutrition (25, 26), sedentary lifestyle with physical inactivity (27) are behavioral factors often present in patients with chronic liver disease,

Table 1 - Prevalence (%) of osteopenia/osteoporosis/fractures in chronic liver disease.

| Disease | Osteopenia | Osteoporosis | Fractures | Authors |
|---|---|---|---|---|
| **Chronic liver disease (various etiologies)** | | 30-48 | 36.5 | Diamond et al. 1990 |
| | | 43 | 22 | Monegal et al. 1997 |
| | | 39 | 35 | Ninkovic et al. 2000 |
| | 34.6 | 11.5 | | Sokhi et al. 2004 |
| | 37.8 | 12.8 | | Moschen et al. 2005 |
| | 68 | | | George et al. 2010 |
| | | 37 | | Goral et al. 2010 |
| | 26 | 14 | | Loria et al. 2010 |
| | | 45.3 | | Wariaghli et al. 2010 |
| | 35 | 38 | 36.3 | Wibaux et al. 2011 |
| | 22-43 | 4-23 | | Alcalde Vargas et al. 2012 |
| **Cirrhosis (in general)** | | 20-56 | 5-20 | Goral et al. 2010 |
| **Viral cirrhosis** | | 53 | | Gallego-Rojo et al. 1998 |
| | 44 | 20 | | Auletta et al. 2005 |
| | | 43 | | González-Calvín et al. 2009 |
| **Alcohol-induced cirrhosis** | | | 30 | Diamond et al. 1990 |
| | 23 | | | González-Calvín et al. 1993 |
| | 50 | 22 | | Kim et al. 2003 |
| | 17.5 | | | Malik et al. 2009 |
| **Chronic cholestatic disease (PBC, PSC)** | | 45 | 13 | Guañabens et al. 1994 |
| | | 21 | 13 | Parés et al. 2001 |
| | | 31 | 14 | Guañabens et al. 2005 |
| | | 32 | 21 | Guañabens et al. 2010 |
| **PBC** | | 35 | | Guañabens et al. 1990 |
| | | 35 | | Lindor et al. 1995 |
| | | 31 | 6 | Newton et al. 2001 |
| | | 21 | 13 | Parés et al. 2001 |
| | | 31 | 14 | Guañabens et al. 2005 |
| | | 51.5 | | Mounach et al. 2008 |
| **PSC** | | 17 | | Angulo et al. 1998 |
| **Hemochromatosis** | | 45 | | Diamond et al. 1989 |
| | | 28 | | Sinigaglia et al. 1997 |
| | | 25 | | Valenti et al. 2009 |
| **Non-cholestatic non-cirrhotic hepatopathy** | | | 12-18 | Diamond et al. 1990 |
| | | 16-50 | | Schiefke et al. 2005 |

**PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis*

and are connected with reduced BMD, development of osteopenia/osteoporosis, and increased fracture risk.

Bone remodeling and osteoclastogenesis are also regulated by the system of the receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG), in which RANKL is a promoter of osteoclast differentiation and activation, while OPG, a member of the tumor necrosis factor (TNF) superfamily, is an inhibitor (28, 29). In osteopenic/osteoporotic patients with chronic liver disease, as compared with patients with chronic liver disease and normal bone mineral density, serum RANKL levels are significantly lower and OPG levels are higher (30). This may be caused by a consumption of RANKL activating osteoclasts and an exceeding amount of compensatory OPG, leading to a significant increase of the OPG/RANKL ratio in cirrhotic patients with decreased BMD, independently from the etiology of the underlying liver disease (31-33). Moreover, a low serum level of RANKL is known to be an independent predictor of non-traumatic fracture (34). Cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) are also involved in the modulation of the OPG/RANKL system in patients with chronic liver disease (17, 35-38). On the other hand, the increased OPG/RANKL ratio might partly represent a compensatory mechanism to prevent bone loss and to maintain bone mass in chronic liver disease (31, 32).

Corticosteroids are the standard therapy for autoimmune and chronic colestatic liver disease, in addition to being the base for immunosuppression after liver transplantation. Long-term administration of glucocorticoid therapies, especially in association with immunosuppressive agents, such as calcineurin inhibitors, are responsible for a significant bone loss, with reduction of bone mineral density (BMD), increased osteoclastic action (39, 40) and lack of osteoblasts differentiation (18, 41-43).

Hypogonadism is another key factor related to the loss of bone mass in patients with chronic liver disease: both testosterone and estrogen deficiency are involved in increasing life span of osteoclasts and decreasing life span of osteoblasts, with consequent progressive bone resorption without adequate bone rebuilding (44-46).

The reduction of bone synthesis is defined as “low turn-over” osteoporosis and it is characterized by a severely impaired

Table 2 - Risk factors for osteoporosis.

| | |
|---|---|
| **Clinical factors** | Advanced age (>65)<br>Low peak bone mass (T-score)<br>Hyperthyroidism/hyperparathyroidism<br>Gastrointestinal, hematological and chronic liver disease<br>COPD<br>Diabetes<br>Rheumatoid arthritis<br>Hypogonadism (both testosterone and estradiol) |
| **Drugs** | Glucocorticoids<br>Anticonvulsivants<br>Benzodiazepines<br>Heparin<br>Immunosuppressants |
| **Behavioral factors** | Cigarettes smoke<br>Alcohol<br>Caffeine<br>Sedentary lifestyle |
| **Nutritional factors** | Low body weight (Low body fat) with BMI <19 Kg/m$^2$<br>Low calcium/vitamin D intake<br>Poor nutrition<br>Total parenteral nutrition |
| **Genetic factors** | Female gender<br>White and Asian race<br>Maternal fractures<br>Vitamin D and IGF-1 receptor gene polymorphisms |

activity of bone remodeling units, the so-called basic multicellular units (BMU) (18). In this kind of osteoporosis, typically seen in parenchymal liver disease, both bone quality and quantity are defective: bone resorption induced by osteoclast is not followed by adequate bone formation induced by osteoblast and this disequilibrium leads to low synthesis of collagen matrix and insufficient osteoid mineralization (2, 18). On the contrary, "high turn-over" osteoporosis represents a minor mechanism of hepatic osteodystrophy, being described among about 20-30% of patients with cholestatic liver disease (2, 47). In this case, a normal level of collagen matrix and osteoid mineralization is associated with an increased activity of osteoclast at the BMU (18).
Vitamin K deficiency is related to a lack of inhibition of osteoclasts differentiation (via expression of RANKL, normally inhibited by vitamin K2) (48, 49) and to an impaired osteoblasts ability to synthesize osteocalcin and osteonectin, proteins of the bone matrix. Through these ways, vitamin K deficiency causes osteopenia and bone loss (50, 51).

## Hepatic osteodystrophy and vitamin D

Vitamin D deficiency is widely distributed among patients with chronic liver disease, regardless of its etiology (52-57). It correlates with the severity of liver failure, measured by Child-Pugh and MELD scores (52, 58), it has a multifactorial origin and it appears more common among cirrhotic patients (52). Low serum levels of vitamin D are associated with osteoporosis, increased bone turnover and high risk of bone fractures (22, 59), especially in elderly patients (60). Osteomalacia is rare except in advanced hepatic disease with severe malabsorption (2, 5). The deficit of 25-OH-vitamin D is probably due not to a deficient hepatocyte capability of hydroxylating vitamin D, but rather to intestinal malabsorption, increased urinary excretion and altered enterohepatic circulation of vitamin D (18, 47). Indeed, in patients with liver disease, oral vitamin D supplementation increases blood levels of 25-OH vitamin D (61), suggesting that the hydroxylating capability of hepatocytes is maintained. The role of vitamin D deficiency in the development of hepatic osteodystrophy is not defined yet: probably it does not have a direct effect on the development of osteoporosis, considering that secondary hyperparathyroidism and vitamin D receptor polymorphisms are more relevant factors (19, 52, 62, 63). Moreover, many drugs, such as antibiotics, diuretics and non-steroidal anti-inflammatory drugs interfere with calcium absorption (64). In addition, studies that have evaluated the efficacy of vitamin D supplementation in patients with chronic cholestatic liver diseases have not shown an effect on the progression of osteoporosis, as shown by BMD and incidence of fractures (2, 65, 66). On the other hand, the correction of vitamin D levels in patients with liver disease may have other beneficial effects besides that on osteodystrophy. In patients with recurrent hepatitis C virus infection after liver transplantation, serum vitamin D level positively correlates with sustained virological response after antiviral therapy, suggesting that a better response is obtained with cholecalciferol supplementation (58). Bitetto et al. (67) demonstrated a predisposition to rejection episodes in patients with low serum vitamin D levels before liver transplantation, speculating that its supplementation could improve immune tolerance and prevent acute cellular rejection. On the other hand, a recent study of Corey et al. (68) failed to demonstrate the role of vitamin D in the progression of chronic liver disease: no difference in vitamin D level was found between patients with and without progression of hepatitis C-associated liver disease over 4 years.

## Hepatic osteodystrophy and liver transplantation

Hepatic osteodystrophy is particularly relevant in liver transplantation, because of the extension of life expectancy of patients with liver disease and, therefore, increased likelihood of clinical manifestations of hepatic osteodystrophy, and because of corticosteroid and immunosuppressive post-intervention therapy (69, 70).
For a prognostic assessment, the bone health of candidates, in terms of density and homeostasis, should be evaluated before transplantation. In these patients, bone densitometry (via dual energy X-ray absorptiometry, DXA), spinal X-ray for the diagnosis of prevalent fractures, vitamin D levels and renal, parathyroideal and gonadal function assessment are recommended (71-73). A significant decrease in bone mass is typical of patients with end-stage cirrhosis: this condition is related to reduced bone formation, impaired bone metabolism (regarding vitamin D and parathyroid hormone levels) and hypogonadism (74). Moreover, in patients referred for liver transplantation, both severity and etiology of the liver disease (alcoholic) are main risk factors for the development of bone loss and mineral metabolism disorders (74). Treatment of transplantation-related bone loss is indicated regardless of the after-graft BMD, since in that period a quick and considerable bone loss occurs (75). Therapy with calcium,

active vitamin D and bisphosphonates (both oral and intravenous) reduces bone loss after liver transplantation and increases BMD in patients with osteoporosis (73, 76). Alendronate inhibits bone loss in osteoporotic and osteopenic patients, increasing BMD within two years after liver transplantation (76), significantly as compared with calcium and calcitriol alone (77). Repeated endovenous infusions of pamidronate are effective in preventing bone loss (72, 78, 79) and decreasing bone turn-over, especially in trabecular bone (80). Risendronate reduces bone loss and turn-over, and increases BMD at spine at 12 months after liver transplantation (81). Moreover, zoledronic acid improves BMD at spine, femoral neck and hip, by reducing bone loss at 12 months after liver transplantation (82, 83) and turnover after liver transplantation (84). Alendronate, pamidronate and risendronate do not seem to give protection against skeletal fractures (77, 79, 81). Misof et al. (85) demonstrated that zoledronate improves mineralization density in cortical and trabecular bone at 6 months, and significantly reduces fracture incidence at 2 years after liver transplantation.

After orthotopic liver transplantation, bone loss continues, reaching the maximal level during the first 3 months after transplantation (86-88). In many studies, the frequency of fractures after liver transplantation is reported around 20-40% (89-91). After liver transplantation, risk factors for bone loss and fractures are the use of glucocorticoids and immunosuppressive agents, vitamin D deficiency and secondary hyperparathyroidism, hypogonadism, previous bone disease (72). Glucocorticoids suppress bone synthesis and increase bone resorption by inhibiting osteoblast differentiation and activity (43), reducing osteoclast apoptosis and often causing avascular necrosis (39, 92), a serious complication also in pediatric patients (56, 93). Immunosuppressive therapies with calcineurin inhibitors, such as FK506 (Tacrolimus) and Cyclosporine A and G, induce elevated bone resorption and turn-over, with reduction in bone mass and BMD (94, 95), independently of the association with glucocorticoid drugs (89). An adequate serum vitamin D level is a key factor for the management of post-transplantation bone loss. Vitamin D insufficiency is a common condition associated with chronic liver disease (74, 96) and is a predisposing factor for osteoporosis after liver transplantation (69, 72, 97-101).

Hypogonadism is a common finding in patients with chronic liver disease (102): even if serum levels of testosterone partially improve after liver transplantation, they do not usually reach the normal range (101, 103). Vitamin D deficiency, hypogonadism and glucocorticoids are major risk factors for osteoporosis before liver transplantation: a preexisting reduction of bone mass and previous fractures are related to a higher incidence of bone fractures after liver transplantation (72, 104, 105). There is clear evidence that bone mass recovers from bone loss during the period that follows transplantation: BMD returns to the pre-transplantation level at around 85 months after liver transplantation (106). On the other hand, the persistence of elevated serum PTH and osteocalcin levels are markers of a maintained bone remodeling (106). As shown by Floreani et al. (97), the increase in serum osteocalcin is still present at 12 months after liver transplantation, indicating a metabolic activation of osteoblasts. This condition, probably in cooperation with immunosuppressive therapy and corticosteroids, is responsible for the high prevalence of bone fractures even many years after liver transplantation (107).

**Diagnosis and management of hepatic osteodystrophy**

Considering the high prevalence of osteoporosis in patients with chronic liver disease, every patient with this condition should undergo an evaluation of bone mass, particularly an assessment of bone mineral density (BMD) and bone homeostasis and metabolism, in order to prevent fractures and chronic bone pain (9, 11). It is noteworthy that the presence of ascites in patients with cirrhosis may affect the accuracy of bone density measurement in the spine (108). Indeed, ascites can cause a fluid artifact in the soft tissue and bone interface that can falsely lower BMD measurement, particularly in the spine (108, 109). Paracentesis modified the diagnosis of osteoporosis or osteopenia in 12% of patients (109). Therefore, in patients with ascites, BMD should be preferentially measured soon after paracentesis, to avoid over-diagnosis of osteoporosis and osteopenia, particularly in the lumbar spine (108).

In patients with chronic liver disease, particularly those who are affected by cholestatic liver disease, therapy is based primarily on the maintenance of bone mass density with control of risk factors. It is mandatory to avoid alcohol consumption and cigarettes smoke, to reduce caffeine ingestion, to make regular physical exercise, to keep an adequate intake of calcium and vitamin D, and to limit the use of drugs such as diuretics, corticosteroids and cholestyramine (2, 110).

Hormone replacement therapy (HRT) with estrogen is advantageous in postmenopausal women without chronic liver disease and in postmenopausal or hypogonadal women with chronic liver disease: in both categories, it has been demonstrated significant BMD increase and reduced fracture rate (111). In men affected by hemochromatosis and hypogonadism, administration of testosterone increased BMD (112). However, hormonal therapies should be administered cautiously because of their potential hepatotoxicity, the cholestatic effect of estrogens and the possible increased risk of hepatocellular carcinoma by testosterone (53, 113, 114).

It is known that bisphosphonates increase BMD and lower the incidence of fractures in post-menopausal women affected by osteoporosis without liver disease (115). In addition, they are effective in preventing corticosteroids-induced osteoporosis, especially alendronate for patients with primary biliary cirrhosis (116-118). Bisphosphonates, in particular zoledronate, have been proposed for the therapy of osteoporosis in patients with chronic liver disease, especially after liver transplantation (76, 84, 85). Possible side effects of oral administration of bisphosphonates, such as the occurrence of esophageal ulcerations, are of particular concern in patients with liver cirrhosis and portal hypertension, due to the risk of gastrointestinal hemorrhage from ruptured esophageal varices, although this risk is probably overestimated (53). Moreover, among all the different therapeutic regimens for hepatic osteodystrophy, bisphosphonates are the most effective in preventing the resorption of both cortical and trabecular bone in patients with chronic liver disease of viral etiology (119).

In regard to hepatic osteodystrophy, parenteral administration of calcitonin has been analyzed, especially in patients with cholestatic liver disease, even though with conflicting results. In these studies, on one hand some authors were not able to find a real benefit from the use of parenteral calcitonin even after a 6-month therapy (120), with no effect on bone loss also in patients referred for liver transplantation (121); on the other hand, other authors demonstrated a par-

tial improvement of BMD in the lumbar spine (119), especially when calcitonin was associated with cyclic therapy with vitamin D and calcium (122, 123).

## Conclusions

Hepatic osteodystrophy is a frequent condition in patients with chronic liver disease, particularly in cholestatic diseases. Hepatic osteodystrophy is mainly due to osteoporosis, which is clinically relevant especially in patients with advanced liver disease and after liver transplantation. Patients with liver disease should be investigated for the presence of hepatic osteodystrophy, to allow the identification and the correction of risk factors and the start of the therapeutic program.

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The Authors contributed equally to this work.

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