Management of osteoporosis in liver disease

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Summary  Osteoporosis resulting in a high risk for fracture is a common complication in patients with liver disease, particularly in those with chronic cholestasis and with end-stage cirrhosis. The pathogenesis of bone loss in liver patients is poorly understood but it mainly results from low bone formation as a consequence of cholestasis or the harmful effects of alcohol or iron on osteoblasts. Increased bone resorption has also been described in cholestatic women with advanced disease. The management of bone disease in liver patients is addressed to reduce or avoid the risk factors for osteoporosis and fracture. Bisphosphonates associated with supplements of calcium and vitamin D are safe and effective for increasing bone mass in patients with chronic cholestasis and after liver transplantation, though no clear achievements in decreasing the incidence of fractures have been described, probably because of the low number of patients included in the therapeutic trials. Randomized studies assessing bisphosphonates in larger series of patients, the development of new drugs for osteoporosis and the improvement in the management of liver transplant recipients may change the future.

Introduction

The term ‘hepatic osteodystrophy’, including osteoporosis and osteomalacia, was used for years to express the bone disorders in patients with liver disease. Osteomalacia, characterized by defective bone mineralization is, however, very uncommon in liver patients. It has been reported only in isolated cases with severe cholestasis and intestinal malabsorption from geographical areas with limited sunlight exposure [1]. Osteoporosis is the bone disease observed in liver patients. It is typified by loss of bone mass and strength that leads to fragility fractures [2] and therefore results in a significant impact on morbidity and quality of life. Currently the diagnosis of osteoporosis mainly lies in the assessment of bone mineral density with a T-score below −2.5. Osteopenia is diagnosed when the T-score is between −1 and −2.5 [3]. Severe or ‘established’ osteoporosis refers to individuals who meet densitometric criteria and have one or more fragility fractures.

Prevalence of osteoporosis and fractures

There is some heterogeneity regarding the prevalence of osteoporosis in patients with chronic liver disease, which partly depends on patient selection and diagnostic criteria.
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Patients with liver disease have osteoporosis, with a higher prevalence in patients with primary biliary cirrhosis. They have two additional risk factors: chronic cholestasis and female gender. The prevalence of fractures in patients with liver disease ranges from 7 to 35% [4]. Fractures are more prevalent in postmenopausal women than in males and young women [5], and in patients with autoimmune hepatitis treated with glucocorticoids [6]. In women with primary biliary cirrhosis, vertebral fractures are associated with osteoporosis and osteopenia with a T-score lower than −1.5, whereas osteoporosis and osteopenia are associated with the severity of liver damage [7]. The clear-cut correlation between vertebral fracture and a T-score lower than −1.5, observed in these patients (Fig. 1) may indicate that this densitometric measurement is a useful criteria for prescribing agents to prevent further loss of bone mass and development of new fractures.

Densitometric osteoporosis has been found in approximately one-third of patients with end-stage liver disease before transplantation [8]. Moreover, most liver transplant patients have a rapid bone loss within the first six months after transplantation, being as high as 6% in the lumbar spine at three months [9]. This is associated with an incidence of fractures between 25% and 35% within the first year of transplantation, being more frequent in women, elderly, cholestatic [10] and alcoholic patients, and particularly in those with osteoporosis and fragility fractures before transplantation [11]. The incidence of fractures in transplant patients is lower in recent years [12], probably related to changes in immunosuppressive regimens and a higher bone quality.

Pathogenesis of osteoporosis

The amount of bone mass depends on the balance between two opposite processes: bone resorption originated by osteoclasts and bone formation induced by osteoblasts. As a consequence, if resorption exceeds formation there is a negative balance which results in bone loss and osteoporosis. The mechanisms resulting in osteoporosis in liver disease have not been completely elucidated. Some studies indicate an increased bone resorption, although most point towards a decreased bone formation. Indeed, impaired osteoblast function resulting in lower mean wall thickness and a defect in matrix synthesis [13], as well as a low bone formation rate have been reported [13,14]. These data are consistent with the decreased serum levels of osteocalcin [15], a biochemical marker of bone formation. Osteoblast dysfunction with low bone formation may result from reduced trophic factors such as insulin growth factor-1 (IGF-1) or from retained substances of cholestasis, including bilirubin and bile acids. Thus, serum IGF-1 levels are decreased in patients with cirrhosis [16] and low doses of IGF-1 increase bone mass in cirrhotic rats [17]. Other alterations such as increased production of a fibronectin isoform containing the oncofetal domain during liver disease may participate in the decrease of bone formation [18]. Furthermore, unconjugated bilirubin decreases survival in cultured primary human osteoblasts and sera from jaundiced patients significantly impair differentiation in cultured osteoblasts [4]. Lithocholic acid has deleterious effects on human osteoblasts as well, not only in relation to their viability, but also regarding the potential damaging effects of this bile acid on the vitamin D pathways, through the vitamin D receptor (VDR) [19].

Despite the previous data on osteoblasts and subsequent effects on bone formation, some histomorphometric reports have revealed increased bone resorption and turnover even in the absence of osteoporosis as an early feature of bone disease in PBC [20]. Reduced trabecular wall thickness and increased bone turnover have been found to be proportional to the severity of hepatic dysfunction and cholestasis [21]. Accordingly, overt or subtle calcium and vitamin D deficiencies leading to secondary hyperparathyroidism have been proposed as the cause of increased bone turnover found in some patients with cholestasis [22]. The involvement of osteoprotegerin, a protein which inhibits osteoclast maturation and protects bone from both normal osteoclast remodeling, seems to be irrelevant since high circulating levels of this protein not related to osteoporosis have been reported in liver disease [23]. More recently, a role for proinflammatory cytokines has been suggested in the pathogenesis of bone loss in chronic liver diseases [24]. Thus, it has been shown in viral cirrhosis that serum concentrations of soluble tumor necrosis factor receptor p55 are significantly higher in patients with osteoporosis and are inversely correlated with BMD [25].

Other conditions including low vitamin D levels, hypogonadism and poor nutrition may be contributing factors to the full picture of bone disease in liver patients. Thus, hypogonadism which is frequent in hemochromatosis [26], cirrhosis and alcoholic liver disease [27], may result in increased bone remodeling and bone loss. Moreover, a reduction in bone formation has been observed in alcoholic patients, with low serum levels of osteocalcin during alcohol intake, which normalizes with abstinence [28]. Deposits of iron may be responsible for low bone formation, due to the direct lesion-producing effects of iron on osteoblast activity in hemochromatosis [29]. Vitamin K deficiency has been also considered as another ancillary factor in the pathogenesis of osteoporosis in liver disease, since vitamin K mediates the carboxylation of glutamyl residues in bone proteins such as osteocalcin.

Genetic susceptibility for osteoporosis in liver diseases and particularly PBC has been assessed, with uncertain results. One report concluded that the VDR genotype is an independent predictor of decreased BMD in PBC, whereas others failed to find this association. Collagen type Iε1 Sp1 polymorphism has been associated with reduced baseline BMD in PBC, although the impact of this polymorphism on bone mass was not directly related to the liver disease itself. The influence of IGF-1 polymorphism on osteoporosis in PBC has also been investigated, with weak results. Taken together, it can be summarized that gene polymorphisms either do not influence or have a very small effect on the development of osteoporosis in these patients [30].

Diagnosis

The risk factors for osteoporosis should be evaluated in patients with chronic liver disease, including the following: chronic alcohol intake, smoking, body mass index lower...
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<th>Osteoporosis (%)</th>
<th>Overall Fractures (%)</th>
<th>Vertebral fractures (%)</th>
<th>Peripheral fractures (%)</th>
<th>Age (years) mean ± SEM (range)</th>
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PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; ALD: alcoholic liver disease; VH: viral hepatitis DPA: dual photon absorptiometry; DXA: dual X-ray absorptiometry; QCT: quantitative computed tomography; ND: not done; NR: not reported; *: hypogonadism.
than 19 Kg/m², male hypogonadism, early menopause, secondary amenorhea of more than six months, family history of osteoporotic fracture and treatment with glucocorticoids (5 mg/d of prednisone or over for more than three months).

The indications of bone densitometry in patients with chronic liver disease are not completely accepted, although there is consensus on the fact that BMD should be evaluated in patients with previous fragility fractures, exposure to glucocorticoids and before liver transplantation [2,31]. Also, it seems suitable measuring BMD in patients with cholestatic diseases or if any of the previously described risk factors are found, and the patient has cirrhosis, as well as after transplantation (Table 2). Bone densitometry should be repeated after two to three years for those patients within the normal range to exclude significant bone loss. However, the clinical conditions associated with a rapid bone loss such as in cholestatic patients with more than one risk factor for osteoporosis, and in those recently initiating high-dose corticosteroid therapies, the screening should be performed in a shorter interval of approximately one year. This schedule is also recommended for cirrhotic patients with advanced clinical stage and those potentially eligible for liver transplantation. Densitometry should also be performed in all patients before liver transplantation.

Lateral X-rays of the dorsal and lumbar spine should also be carried out to disclose vertebral fractures [4]. In addition, circulating levels of calcium, phosphorous, 25-hydroxyvitamin D and parathyroid hormone should be assessed. Disturbances in thyroid and gonadal function should be ruled out in particular cases. Biochemical markers of bone turnover may be assessed to monitor the individual response to anti-osteoporotic treatment. The indication of undecalcified transiliac bone biopsy is suitable only if a mineralizing defect is suspected. Potential artifacts resulting in inaccuracy in BMD and bone marker measurements in patients with advanced liver disease should be taken into account. Collagen-related markers of bone turnover do not accurately reflect bone remodeling in PBC, since they are influenced by liver collagen metabolism [15]. In addition, central BMD measured by DXA in patients with ascites may be falsely reduced. Thus lumbar and total hip BMD values increase after large-volume paracentesis in cirrhotic patients [32].

Table 2  Recommendations for bone mineral density assessment.

<table>
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<tr>
<th>Previous fragility fractures</th>
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<td>Alcohol abuse</td>
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<td>Before and after liver transplantation</td>
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* Postmenopausal women, low body mass index, male hypogonadism, early menopause, secondary amenorrhea.

Management

Modification of risk factors and supportive measures for bone health

The factors contributing to bone loss should be reduced to a minimum, basically by stopping alcohol intake and smoking (Fig. 2). The dose of glucocorticoids should be adjusted to the minimum necessary. As much physical activity as possible is advised especially exercises aimed at improving the mechanics of the spine.

Since patients with advanced liver disease frequently have little appetite and are malnourished a balanced diet should be recommended. Supplements of calcium (1,000–1,500 mg/d) and vitamin D (400–800 IU/day or 260 μg every two weeks) or the dose required to maintain normal levels should be provided. Particular care should be taken with patients receiving resins, such as cholestyramine, since their administration may reduce the intestinal absorption of vitamin D [4]. Although calcium and vitamin D supplements are recommended, there are no data confirming the efficacy of these supplements in preventing bone loss in patients with liver disease.

Specific treatments

Different drugs for osteoporosis have been proposed in patients with liver disease, but most studies have included small numbers of patients, and therefore it is difficult to reach any definite conclusions. Furthermore, no clear anti-fracture effect could be demonstrated and except for osteoporosis in PBC and after liver transplantation, no consistent studies have been carried out.

There is no agreement concerning the appropriate time to start treatment, but patients with established osteoporosis, and therefore with fragility fractures, should be treated to reduce the risk of further fractures. Taking into account that patients with a lumbar or a proximal femur T-score lower than −1.5 have a high risk for vertebral fracture, it seems reasonable to consider treatment in patients with chronic cholestasis and BMD below this threshold [7], particularly if they have additional risk factors for osteoporosis (Figs. 1 and 2). Likewise, it seems rational to treat all patients immediately after liver transplantation and before transplantation if they have osteoporosis.

Bisphosphonates

Bisphosphonates are anti-catabolic drugs which increase bone mass and reduce the incidence of fractures in post-menopausal osteoporosis. Their effects in liver disease are not entirely defined, basically because of the scarce number of studies and the few number of treated patients [33–41]. Nonetheless, it has been demonstrated that cyclic administration of etidronate is able to prevent bone loss after two years of treatment and that alendronate increases bone mass in PBC, comparable to what occurs in osteoporosis due to other causes. One placebo-controlled trial of alendronate (70 mg per week) in patients with PBC also indicated that alendronate is able to increase bone mass after one year with no or with only minor adverse effects [37,38]. Our results of once-weekly 70 mg alendronate in patients...
Figure 1 Lumbar and femoral neck T-scores of patients with and without vertebral fractures. A T-score lower than $-1.5$ (dashed red line) is associated with high risk for vertebral fracture.

with PBC indicated that this regimen was more effective in increasing BMD, with a non-significant increased adherence and a better tolerability profile, than daily dosing [38]. Preliminary results comparing alendronate 70 mg weekly vs. ibandronate 150 mg monthly in PBC patients with osteoporosis or low bone mass and fragility fractures, showed that both drugs have similar effects on BMD, but the adherence to treatment was superior for monthly ibandronate, without adverse effects on liver tests [36,39]. Serious adverse events have not been observed and potential harmful effects of alendronate such as esophagitis were not detected.

Pamidronate, administered parenterally, has been assessed in patients with end-stage chronic liver disease, prior to and after liver transplantation [42–44]. There are conflicting results with respect to the efficacy of this agent on preventing bone loss and reducing the fracture rate, due to the fact the trials included few patients or were inappropriately designed to detect bone loss and the capacity for reducing incident fractures. The results of a placebo-controlled trial indicated that 90 mg of pamidronate given within the first 2 weeks and at 3 months after transplantation preserves lumbar BMD during the first year without significant side effects. However, pamidronate did not reduce bone loss in the femoral neck, nor the incidence of fractures [44].

Figure 2 Prophylaxis and treatment of osteoporosis in liver diseases according to the bone mineral density or presence of vertebral fractures.
Alendronate and zoledronic acid have also been evaluated in liver transplant recipients. In a randomized trial alendronate (70 mg per week) plus daily calcium and 0.5 μg of calcitriol significantly increased BMD during the two years after liver transplantation. The drug was well tolerated without deleterious effects on liver chemistries, but alendronate did not appear to offer protection against fractures [41]. Another study using weekly alendronate also showed that alendronate prevents bone loss associated with liver transplantation [40]. Zoledronic acid treatment in transplanted patients increases BMD although temporary hyperparathyroidism and hypocalcemia were observed after infusion in some cases. No effect on the incidence of fractures was reported [45]. Another study using zoledronic acid in patients after liver transplantation, showed that treated patients had reduced bone turnover and most importantly, a lower fracture rate [46].

Hormone therapy
There is little information on hormonal treatment in patients with advanced liver disease as for many years this approach was considered to be contraindicated in these patients. However, transdermal estrogen treatment prevents bone loss or even increases BMD in patients with PBC or autoimmune cirrhosis with no adverse effects on liver disease. Short-term hormonal treatment with estradiol in postmenopausal women after liver transplantation was associated with an increase in lumbar and femoral neck BMD, together with a decrease in the serum levels of a marker of bone formation. In males with hemochromatosis and hypogonadism, treatment with testosterone and venesection is also effective [47]. One concern about restoring testosterone levels in cirrhotic patients is that this might increase the risk of hepatocellular carcinoma. Therefore, the potential risk/benefit must be discussed with each patient before starting replacement therapy.

Despite these results, hormone therapy is not considered to be the most appropriate treatment, as there are other efficacious non-hormonal agents with lesser side effects for the treatment of osteoporosis.

Other treatments
The effect of calcitonin as an anti-catabolic drug in patients with liver disease is not clear, although a study carried out in PBC reported that the combined administration of calcitonin, calcium and vitamin D over 12 months was associated with lower bone loss, and apparently the long-term effects were more favourable in patients with osteopenia [48]. Other studies have described negative results [49]. In transplant patients, the intramuscular administration of 40 IU/day of calcitonin over a period of one year was associated with a significant increase in BMD [50]. Nevertheless the effects of calcitonin on fracture rate were not apparent [51].

The safety and efficacy of raloxifene has been evaluated in nine postmenopausal women with PBC [52]. Lumbar BMD improved significantly after one year of therapy but not in matched controls. Favourable effects of sodium fluoride were also observed in PBC and transplanted patients, although with lesser capacity for improving bone mass than bisphosphonates.

To the best of our knowledge there are no studies assessing the effects of anabolic drugs or strontium ranelate in patients with osteoporosis and liver diseases. Only one study assessed intermittent administration of parathyroid hormone (hPTH 1-34) in bile duct-ligated rats, showing that PTH restores BMD as well as trabecular thickness. Therefore, PTH 1-34 can be a potential therapy for osteoporosis in patients with cholestasis [53].

Conclusion and future perspectives
Osteoporosis is a frequent complication in chronic liver disease, especially in the end-stages and in cases with chronic cholestasis, hemochromatosis and alcohol abuse. The problem is more critical in transplant patients when bone loss is accelerated during the period immediately after surgery. The pathogenesis of osteoporosis is mainly characterized by low bone formation, particularly related to the effect of retained substances of cholestasis, such as bilirubin and bile acids, or to the iron and alcohol on osteoblastic cells. Increased bone resorption has also been described, especially in cholestatic women with advanced disease.

For the prevention and treatment of osteoporosis good nutrition is recommended, as are the suppression of the risk factors for osteoporosis and the administration of supplements of calcium and vitamin D. There is no specific treatment for osteoporosis, although it has been demonstrated that bisphosphonates, especially weekly alendronate and monthly ibandronate, are effective in increasing bone mass in patients with chronic cholestasis. The efficacy of bisphosphonates in patients after liver transplantation remains to be confirmed, although weekly alendronate prevents bone loss and appealing effects of zoledronic acid have been reported. The outcome in reducing the incidence of fractures has not been adequately demonstrated essentially because of the low number of patients included in the therapeutic trials. The development of larger trials with bisphosphonates and the assessment of new drugs for osteoporosis may change the future.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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