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REVIEW

Osteoporosis and fractures in liver disease: Relevance, pathogenesis and therapeutic implications

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Abstract

It is being increasingly recognized that patients with liver disease develop bone loss that can be severe enough to lead to atraumatic fractures and thus markedly diminish life quality and expectancy. The estimated prevalence for liver-related osteoporosis is between 20-420/100000 of the general population, and fractures between 60-880/100000. It should be kept in mind that up to 40% of patients with chronic liver disease may experience a fracture. The pathogenic mediators include fibronectin, insulin like growth factor-Ⅰ, and various cytokines, but decreased vitamin D and/or treatment with corticosteroids contribute to worsening bone health. Despite the advances in bone biology that have shed some light on the pathogenesis of this bone loss, treatment options remain nonspecific and tightly linked to treatments of other forms of osteoporosis. Thus, treatment should include calcium and vitamin D supplementation in all patients with chronic liver disease. Therapy with bisphosphonates should be considered, especially in patients receiving corticosteroids. This review focuses on the prevalence of this entity as well as the evidence available with regard to the pathogenesis of bone loss in liver disease, the diagnostic steps required in all patients, and the therapeutic options available.

Key words: Osteoporosis; Liver disease; Fracture; Prevalence; Pathogenesis; Fibronectin; Insulin like growth factor-Ⅰ; Therapy; Vitamin D; Calcium

Core tip: Up to 40% of patients with chronic liver disease may experience a fracture. The pathogenic mediators include fibronectin, insulin like growth factor-Ⅰ, and various cytokines. Decreased vitamin D and/or treatment with corticosteroids contribute to worsening bone health. Treatment should include calcium and vitamin D supplementation in all patients with chronic liver disease. Therapy with bisphosphonates should be considered, especially in patients receiving corticosteroids.

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INTRODUCTION

Osteoporosis denotes a state in which the bones become porous resulting in increased risk for fractures[1]. The general population started first associating this condition with menopause and loss of estrogen, even though it was clear to members of the medical profession from the beginning that it is a condition associated with a great variety of diseases ranging from inadequate calcium intake or uptake to abnormalities in various bone-associated cell functions[2-4]. Because of the involvement of the liver in many metabolic effects it is not surprising that one of the secondary causes of osteoporosis is liver disease.

The bone represents the pool that allows for the tight

regulation of circulating calcium. Indeed, calcium is a most tightly controlled electrolyte in the blood stream[5]. This takes place at the level of the bone forming cells - the osteoblasts -, the bone resorbing cells, - the osteoclasts -, or the bone-embedded cells - the osteocytes. In this review we discuss the evidence on the role of these cells in the pathogenesis of osteoporosis associated with liver disease. Most of the bone consists of a collagen matrix[6], but a great number of proteins and growth factors such as insulin like growth factor- I (IGF- I) have also been found in this matrix and affect osteoblast function as they are produced or osteoclast function when bone is resorbed[7].

Since the liver produces various molecules that can act as growth factors or hormones it has been further postulated that a decrease in liver function will result in osteoporosis, through affecting the production of bone-active liver molecule. A selection of these various factors will be discussed.

Lastly, a diagnostic approach based on the pathogenesis of bone loss associated with liver disease will be followed by a discussion of the possible therapeutic options available and their merits.

CLINICAL RELEVANCE OF BONE LOSS ASSOCIATED WITH LIVER DISEASE

The definition of osteoporosis is based on a low bone mineral density (BMD) usually measured using dual energy X-ray densitometry (DXA) and prior fracture[8]. A BMD measurement 2.5 standard deviations below that of healthy young adults defines the presence of osteoporosis[8]. However, this value only reflects the decrease in mineral content in the bone matrix. While on a population scale this value seems to offer a good measure of the risk for fractures, this does not hold true for individuals. Recent attempts have been made to individualize risk assessment based on the development of the Fracture Risk Assessment Tool called FRAX, which take age and other measures in evaluating the risk for an individual of developing a fracture over the next 10 years[9] (Link for tool to calculate risk: http://www.shef.ac.uk/FRAX/). In validating this method roughly a doubling of the risk for development of an osteoporotic fracture was found in patients with liver disease (hazard ratio: HR for men 3.59 and 1.79 for women)[9]. Microarchitectural abnormalities are not directly taken into account using FRAX evaluations of fracture risk. However the FRAX algorithm takes into account the development of previous fractures, which independently reflects poor bone quality and can be associated with micro cracks.

A major consequence of the development of fracture is the associated disability that makes the patient dependent on others resulting in excess death within 1 year of 10/100 hip fractures/100000 persons/year (excess risk of death of 10% in patients with hip fractures)[10,11].

The prevalence of cirrhosis in Europe is 0.1%, non alcoholic liver disease in the population ranges between 2%-44%, chronic hepatitis B between 0.1-0.7, chronic hepatitis C ranges between 0.003% to 4.5%, and autoimmune liver diseases 0.03%[12]. In addition, despite the relatively small number of patients who receive liver transplants amounting to 5000 transplants per year in Europe this group is at an especially high risk for bone disease[12]. Thus the potential for bone loss associated with chronic liver diseases amounts in the most conservative calculations to 2.23% (This number was obtained by adding the numbers at the lower ranges of the prevalence of different types of liver disease: 0.1 + 2 + 0.1 + 0.003 + 0.03 = 2.233) and can reach up to half the population (this number was obtained by adding the numbers at the upper ranges of the prevalence of different types of liver disease: 0.1 + 44 + 0.7 + 4.5 + 0.03 = 49.33) (Table 1). Unfortunately, epidemiologic data are missing with regard to the real extent of osteoporosis in patients with chronic liver disease. However, a range of 1%-21% prevalence of osteoporosis and a risk of fracture between 3%-44% have been reported in the past[13,14]. Taken together, this suggests that per 100000 persons there are at least 2000 patients with chronic liver disease, of whom 20-420 have osteoporosis, and 60-880 experienced fractures. Of note is that a previous fracture increases the risk for later fractures further. Thus, the potential social and economic burden of the development of osteoporosis and the associated increased in fracture risk in patients with liver disease that tend to be younger than most osteoporotic patients is remarkable. A health problem of this size requires increased awareness for this problem, a better understanding of the underlying causes, and development of useful therapeutic concepts.

PATHOGENESIS OF OSTEOPOROSIS IN LIVER DISEASE

Normal physiology

In the adult skeleton a continuous remodeling takes place whereby the osteoclasts resorb bone and the osteoblasts form new bone[14]. The purpose is to repair the micro defects that accumulate in the skeleton and provide stable circulating calcium levels[5]. This remodeling is tightly controlled by a variety of molecules ranging from calcium-regulating hormones, to cytokines active in hematopoiesis and a variety of systemic proteins[14]. Whenever relatively more resorption or relatively less bone formation takes place, bone is lost. This results in the development of osteoporosis and the resulting increased risk of fractures. The osteocyte, which represents terminally differentiated osteoblasts embedded in the matrix and is the mediator of bone remodeling in response to mechanical strain has emerged as a major regulator of bone resorption by controlling the number of osteoclasts, as well as bone formation by modifying osteoblast-induced bone mineralization. Finally, they also control phosphate homeostasis[15].

Table 1 Epidemiology of bone abnormalities in liver disease

[1]Prevalence of liver diseases[12]	
Cirrhosis	0.10%
Non-alcoholic liver disease	2%-44%
Chronic hepatitis B between	0.1%-0.7%
Chronic hepatitis C	0.003%-4.5%
Autoimmune liver diseases	0.03%
Liver transplantations	5000/yr
Total	2.233%-49.36%
In patients with liver disease	
Prevalence of osteoporosis[13,14]	1%-21%
Estimated prevalence	20-420 osteoporotic patients/2000 patients with liver disease/100000 persons
Fractures[13,14]	3%-44%
Estimated risk	60-880 osteoporotic patients/2000 patients with liver disease/100000 persons

[1]The data on the prevalence of liver diseases are obtained from a study limited to Europe.

Reported changes in bone in various liver diseases

Chronic liver dysfunction can severely affect bone[13]. Early reports focussed on an increase in bone resorption, since in these studies patients were mostly either postmenopausal women or older men[16]. Later it became clear that mostly bone formation was affected resulting in a disease entity called hepatic osteodystrophy, which denotes bone loss associated with liver disease[17-22]. It is however important to realize that there are different liver disease entities that differ in their pathogenesis and hence may partially differ in the cause of the associated bone loss (Table 2). While hemochromatosis and Wilson disease are associated with increased iron and copper load and hence may affect bone disease[23-25], viral hepatitis is associated with an activated immune response and release of mostly resorption-activating cytokines[26-30]. Autoimmune diseases can be grouped in cholestatic diseases including primary biliary cirrhosis and primary sclerosing cholangitis and non-cholestatic autoimmune hepatitis[17,18,31-34]. Since cholestasis is associated with increased bilirubin levels the possibility of bone deterioration due to increased bilirubin should also be addressed[35]. Decreased liver function is associated with a number of abnormalities that will be discussed. Treatment of the various liver conditions is associated with the use of sometimes bone active substances, adding a further layer of complexity in understanding liver associated bone disease[36]. Finally, the worsening in liver function, which is common in all types of liver disease, is in of itself associated with changes that also can explain bone loss[27].

For a better understanding of bone loss in chronic liver disease examples will be provided for each disease entity:

Viral hepatitis: In this disease entity an inflammatory response dominates the pathophysiologic response to the infection with an association of increased cytokine release[27]. Twenty-one percentage of the patients had osteoporosis that could be attributed to an increase in osteoclast-mediated bone resorption. Of note is that the cohort was cirrhotic, vitamin D-25 deficient and partially hypogonadal, suggesting that the increase in resorption could be a reflection of the other problems including vitamin D deficiency or hypogonadism[7]. Further, in early stages of disease another picture at the bone cell level may ensue. In a group of kidney transplant recipients patients, none was vitamin D deficient and there were no differences between patients affected with chronic hepatitis C and those not infected in the incidence of osteoporosis, which was 18%[37]. Finally, in a cohort of liver transplant recipients, patients with chronic hepatitis B or C had lower BMD values compared to patients with NASH (and hence insulin resistance), but similar values as the alcoholic cirrhotic patients[38]. Whatever the changes in BMD however there is an increased risk for fractures: 2.69 events/1000 person-years *vs* 1.29 which is more than two fold[39].

Table 2 Predominant changes in bone cell activity in various liver diseases

Increased resorption	Viral hepatitis
	Transplantation
	Corticosteroid therapy
Decreased formation	Cholestatic liver disease
	Iron and copper overload

Cholestatic liver disease: The two cholestatic liver diseases, primary biliary cirrhosis and primary sclerosing cholangitis have been associated with an increased risk for osteoporosis and hence an increase in fracture risk[40]. Histomorphometric evaluations have shown that the most consistent associated abnormality is a decrease in bone formation[17]. This occurs in the absence of vitamin D deficiency or hypogonadism, and could possibly be attributed to the increase in bilirubin[17,41]. With regard to autoimmune hepatitis, it can be viewed as a condition between cholestatic immune liver disease and viral hepatitis.

Iron overload: Hemochromatosis is associated with iron accumulation and results in liver failure. The best evidence on the role of iron overload are studies in animals loaded with iron and resulting in a decrease in bone formation[23]. In a study from 2009 in patients with hemochromatosis, 25% had osteoporosis and 41% had osteopenia. Bone mineral density was lower in patients with higher iron loads and with lower markers of bone formation[42]. This confirms the findings on bone histomorphometry from older studies that show a decrease in bone formation in patients with higher tissue iron load[14,24].

Wilson disease: Copper accumulation in the liver is known as Wilson's disease. It is hereditary and tends to affect patients at a younger age compared to hemochromatosis. Accumulation of copper in bone is also detrimental for bone health, where osteoporosis was

documented in 41% of the adults and 68% of the children[43,44]. Most disturbing in this regard was the lack of improvement in the children 1 year after chelation therapy, even though, at least in adults, penicillamine does not seem to affect mineral metabolism[45]. This, taken together with the knowledge that penicillamine used for treatment in patients with Wilson's disease results in hypercalciuria and hyperphosphaturia, suggest the need for rigorous follow-up of mineral metabolism and appropriate replacement in these patients in the hope of restoring bone health[46].

Transplant recipients: Liver transplant effects on bone can be divided in two parts. First, the liver disease that resulted in the need for a transplant in of itself will result in decreased bone mineral density as discussed above. The second issue is that associated with the transplant itself, in particular the medications used. Thus, these patients tend to have extensive problems related to their bones[47-52]. The reported excellent response to bisphosphonates may suggest that the major pathogenic contributor is an increase in bone resorption due to treatment and immune suppression[48,52].

Non alcoholic fatty liver disease: There is only data on BMD but no evaluations of bone biopsies, which suggest a doubling of osteoporosis risk in men in the presence of fatty liver changes[53]. In women, the data are inconclusive[54,55].

ROLE OF THE LIVER IN BONE REMODELING

The liver controls many processes in the healthy individual. It produces a large number of proteins, some of which have been documented to affect bone health such as IGF-I [56] and fibronectin[57-59]. It can respond to bone-active hormones by producing cytokines such as PTH induction of liver interleukin-6 (IL-6)-production[60], and it can even metabolize various bone-active molecules therefore shortening their half life, affecting their circulating levels or activity such as osteocalcin[61].

EXAMPLES OF PROTEINS PRODUCED BY THE LIVER AND AFFECTING BONE THROUGH THE CIRCULATION

Factors implicated in inducing bone loss in liver disease are listed in Table 3 and discussed below.

Fibronectin

Fibronectin is a large molecule produced by almost all cell types in humans. The osteoblasts produce fibronectin at the same time that collagen is produced as they lay down the matrix during bone formation[57]. Once mineralized, this matrix represents the new bone. Fibronectin is also produced in large amounts by the liver; it moves from there into the blood stream and circulates at a concentration of 300 mg/L (1/100 of albumin)[62]. Its production by the liver is diminished in liver disease and in cases of poor nutritional status[63]. Similarly to studies on the IGF system, genetic manipulation in animals provided interesting insights. Indeed, it turns out that circulating fibronectin can infiltrate the bone matrix, where it contributes to enhancing matrix mineralization and strength thereby affecting the microarchitectural properties of bone[57]. A major limitation for looking at a relationship between circulating fibronectin levels and bone characteristics in patients, however, is the large variability in circulating levels in healthy adults and the association of decreased fibronectin levels with malnutrition, a condition that in of itself affects bone health[63]. Further, there are no known pharmacologic interventions that can affect circulating fibronectin independent of their effects on nutritional status.

Adding to the complexity of understanding the fibronectin role in bone is the fact that an isoform of fibronectin, called oncofetal fibronectin that is produced by the matrix-producing stellate cells in the liver, is increased in patients with cholestatic liver disease, chronic hepatitis C, as well as a variety of other liver diseases[58,63]. This isoform can directly inhibit osteoblast function and its administration results in a decrease in bone mineral density by almost 20% after two weeks in mice. This makes this molecule an important candidate to counteract in patients with chronic cholestatic liver disease. Unfortunately, there are currently no therapeutic interventions that are under study to counteract this effect.

Insulin-like growth factor family

IGF- I is produced by osteoblasts and by the liver[56,64]. It binds to IGF binding proteins, which consists of a set of 6 regulatory proteins that can enhance or diminish its functional effects. The third component is an acid labile subunit that binds to IGF- I and hence prolongs its half life in serum[7]. IGF-I is diminished with aging and in patients with liver disease[7]. These two populations have a higher incidence of osteoporosis making this system a candidate for mediating bone loss in patients with chronic liver diseases. Much insight was gained from studies in various genetic models affecting this system in mice. Most importantly, these studies unequivocally established a role for circulating IGF- I in affecting bone health[56,65]. While restoration of circulating IGF- I in the absence of IGF- I in osteoblasts normalized bone mechanical properties and morphology in adults, increasing circulating IGF- I by three fold in the presence of normal osteoblast IGF- I production resulted in improved mineral density by 18% in adulthood[65]. Further, studies using low dose IGF- I seem to suggest a beneficial effect on bone mineral density[66]. However, because of the complexity of the IGF system, its role in increasing bone resorption and its involvement in glucose metabolism it failed to become established as a therapeutic regimen[7]. This is unfortunate, because patients with osteoporosis associated with liver disease might have benefitted from the development of this therapeutic option.

Table 3 Factors implicated in inducing bone loss in liver disease

Fibronectin (plasma and oncofetal forms)
IGF- I
RANKL/OPG
IL-6
Sex hormones
Bilirubin
Vitamin D metabolism
Corticosteroid therapy

IGF- I : Insulin like growth factor- I ; IL: Interleukin; OPG: Osteoprotegerin; RANKL: Receptor-activator of nuclear factor kappa ligand.

Role of cytokines

The liver itself produces a variety of cytokines in response to bone active hormones, such as IL-6 production in response to PTH. However, the diseased liver can also produce a variety of cytokines, such as in chronic viral hepatitis infection. Most of these cytokines, if able to get to the bone can affect bone homeostasis. Two cytokine systems will be discussed.

Receptor-activator of nuclear factor kappa ligand/osteoprotegerin system: Parathyroid hormone is a key molecule regulating calcium homeostasis. At the level of the bone it is able to stimulate the osteoblasts to form bone and the osteoclasts to resorb bone. Since the osteoclast does not have a PTH receptor, the effect of PTH on the osteoclasts is mediated by other molecules produced in response to PTH on osteoblasts[67]. The best known cytokines are receptor-activator of nuclear factor kappa ligand (RANKL) and osteoprotegerin system (OPG). RANKL can directly activate the osteoclast leading to increased resorption, while osteoprotegerin acts as a decoy receptor that binds RANKL and hence prevents it from activating the osteoclast. An increase in RANKL or a decrease in osteoprotegerin enhance bone resorption and hence increase bone loss[68].

Patients with alcoholic and chronic liver disease have an increase in RANKL and normal OPG in early disease stages[69]. Thus, in non-cirrhotic patients the ratio of RANKL/OPG was higher than in controls supporting a role for increased resorption in these patients. In advanced stages however, RANKL was normal and OPG was increased, resulting in reversal of the relationship. This would suggest a decrease in bone resorption and possibly an increase in bone formation[68]. A unifying hypothesis would be that since RANKL is produced by osteoblasts in response to PTH, the decrease in RANKL reflects diminished osteoblast function. In addition, since OPG is normally taken up by the liver, a decrease in liver function might be associated with an increase in OPG that has not been cleared away yet[70]. Why OPG does not exert any substantial effects on bone mineral density in patients with liver disease is probably due to the lack of a molecule to inhibit in view of the lower than normal RANKL values. Taken together, these data suggest that a modification of this system is unlikely to provide any therapeutic benefits with regard to bone health in patients with liver disease.

IL-6 family of cytokines: This family includes among others, IL-6 and IL-11. IL-6 is produced by osteoblasts and can either directly activate the osteoclasts or stimulate the osteoblasts to produce RANKL and thus indirectly activate the osteoclasts[71]. Its effects seem to be counteracted by IL-11 at the bone[72]. In the osteoblasts its role is not clear, with some studies showing inhibition of differentiation *in vitro*[73] and others showing stimulation[74-76]. In the liver, IL-6 is upregulated after injury and results in the acute phase response and liver regeneration. Since any type of liver injury is also associated with the attempt at regeneration, IL-6 is essentially upregulated in all types of liver disease[77,78]. This increase will eventually result in activation of the osteoclasts and increased bone resorption. Indeed, inhibiting the IL-6 receptor in mice blocks osteoclast resorption[79]. A humanized antibody against IL-6 receptor has already been approved for the treatment of rheumatoid arthritis but has not been tested in liver disease[80].

Sex hormones

Normal sex-hormone levels are required for healthy bones. Despite the differential effects of estrogen and testosterone on bone architecture, it is established that hypogonadism or menopause are associated with accelerated bone loss due mostly to increased osteoclast activity[81,82]. The liver is responsible for metabolizing sex hormones and produces sex-hormone binding globulins. This is exemplified by the development of gynecomastia in men with liver cirrhosis in whom the change in sex-hormone binding proteins effects a relative increase in estrogens in relationship to androgens[83]. However chronic diseases are often associated with a change in the metabolism of estrogens with a decrease in degradation of weak estrogen metabolites[84]. Since these estrogens are weak they cannot overrule the estrogen deficiency associated with menopause in women or affect enough protection in men to overcome the liver disease-associated bone problems. In women, it has been established that estrogen replacement is not contraindicated due to chronic liver disease[85,86]. It should be noted however, that since orally administered estrogen is to a large degree affected by a first pass metabolism through the liver in healthy women, the use of similar doses in women with liver disease may result in higher circulating levels. For this reason a transdermal form of administration should be considered. In men, the low testosterone levels have been associated with a decrease in survival[87], presumably because of the association between hypogonadism and severity of chronic diseases. Nevertheless, testosterone replacement can be associated with liver toxicity and increased risk of hepatocellular carcinoma development. Because most of the toxicity is due to first pass metabolism it is also reasonable in men to use transdermal modes of delivery

instead of oral administration[88]. The possibility of development of hepatic carcinoma seems minimal at best, but nevertheless needs to be discussed with the patient[89].

Bilirubin

Liver diseases are often associated with increased bilirubin levels. *In vitro* data have shown that bilirubin can inhibit osteoblast proliferation[35]. There is some controversy on whether bilirubin elevations are associated with decreased BMD, because advanced liver disease can be associated with increased bilirubin levels, but also with many more abnormalities which themselves can cause a decrease in BMD[90,91]. In contrast, in patients with cholestatic autoimmune liver diseases there seem to be a relationship whereby increased bilirubin results in decreased BMD and increased fracture risk[40]. The attempt at bulking advanced liver diseases with cholestatic autoimmune liver diseases might have caused a problem in establishing such a relationship[41]. At any rate, it has been established in bone histomorphometry studies that chronic cholestatic liver disease leads to decreased bone formation[19] associated with significantly decreased blood levels of osteocalcin, a marker of bone formation[92,93].

Vitamin D metabolism

Vitamin D3 becomes hydroxylated in the liver to D 25 before the kidney forms the active metabolite vitamin D 1,25, which increases calcium resorption in the gastrointestinal tract, osteoclast-mediated bone resorption, and osteoblast-mediated mineralization[94]. A decrease in vitamin D 25 is a reflection of diminished liver function or malnutrition. However, liver disease has to be advanced in order for vitamin D metabolism to become compromised[95,96]. Another issue is that in liver disease bile production is hampered leading to a decrease in fat absorption and a resultant abnormal uptake of vitamin D[95]. Indeed, 92% of patients with liver disease have some degree of vitamin D deficiency[97]. This is reflected in decreased calcium resorption (which depends on adequate levels of vitamin D), and a resultant need to maintain calcium in the blood by activating bone resorption. The net result is bone loss[97]. It therefore should be kept in mind that normalization of mineral metabolism is the first step to improve bone health in patients with liver disease.

Side effects of treatments used in the therapy of various liver diseases

The most important one seems to be the use of corticosteroids, which itself inhibits the osteoblasts, diminishing bone formation, but also interferes with vitamin D metabolism and calcium absorption[98,99]. Therefore the need to supplement all patients receiving any amount of corticosteroids with 1000 mg of supplemental calcium and 800-1000 IU of supplemental vitamin D has been increasingly recognized[36]. Since this will only counteract some of the effects of corticosteroids on bone it has been proposed to add bisphosphonate therapy in patients at medium or high risk for the development of fractures and who will be treated for more than 4-12 wk with corticosteroids[36].

The use of penicillamine has been discussed above (under Wilson disease). The use of ursodeoxycholic acid improves cholestasis in patients with cholestatic liver disease, but neither improves nor worsens bone disease[95,100]. In the case of viral hepatitis[28] antiviral therapy increases BMD by 3%-4% over 2 years. This increase takes place in the responders, while BMD in non-responders remained stable.

Other players

A large number of modifiers exist, including malnutrition, muscle wasting, low body mass index, all of which are affected in sick patients and will result in lower bone density and increased risk for fractures as occurs in the general population[101-103]. Genetic factors have also been examined including polymorphisms of the vitamin D receptor (VDR)[104-107], collagen α1(I) (COL1A1)[107-110], IGF-I, IL-1 receptor antagonist (IL1RA), and estrogen receptor-α (ERα)[108]. Conflicting data exist for VDR and Col1A1, no association with IGF-1 or IL1RA, and increased risk for osteoporosis in the presence of polymorphisms in ERα. Another potential player is homocysteine, which is elevated in liver disease[111]. It is detected in bone, and mostly indirect evidence suggests effects on osteoblasts, osteoclasts and collagen crosslinking[112-114]. Some studies reported a relationship between increased homocysteine levels and increased fracture risk, while others reported only a relationship between increased circulating homocysteine levels and decreased bone mineral density[115,116]. Finally, abnormalities in cytokines include an increase in colony stimulating factor-1, which stimulates osteoclasts and bone resorption[117], tumor necrosis factor, which also stimulate bone resorption[118-121], and IL-17[122]. Leptin production is increased in fibrosing diseases of the liver[123] and in patients with chronic hepatitis C[124]. In cholestatic liver disease it is diminished, presumably because of the poor nutritional status[125,126].

TRANSLATING THE INFO INTO A DIAGNOSTIC REGIMEN

Based on the prevalence of osteoporosis in patients with liver disease and the increased risk for fractures it seems reasonable to exclude contributing factors to osteoporosis and measure BMD in all patients with liver disease. The following steps are cheap but can have a major impact on bone health in these patients (Table 4).

Vitamin D status

A measurement of Vitamin D 25 can be performed and should be used to determine whether vitamin D replacement is needed. In patients with liver cirrhosis, osteoporosis or those receiving corticosteroids moving to calcium and vitamin D supplementation even without testing seems reasonable.

Table 4 Diagnostic testing

Vitamin D (not needed if supplementation contemplated)
Calcium (to exclude endocrine problems)
Bone mineral density measurement (particularly if considering corticosteroid therapy)

Table 5 Therapy

All patients
Vitamin D supplementation
Calcium supplementation
Depending on the general condition and confounding problems
Consider Bisphosphonate therapy, especially in patients receiving corticosteroids)

Calcium level in the circulation

Normally the body maintains circulating calcium levels at the expense of bone calcium. The evaluation of calcium levels is therefore not mainly in order to detect hypocalcemia due to vitamin D deficiency, which should not be found in a patient receiving medical care for liver disease, but to detect cases of hypercalcemia due to primary hyperparathyroidism, which is more prevalent in older women at 2.1% *vs* 0.3% in the general population, and result in bone loss[127]. Treatment of hyperparathyroidism is then indicated.

Bone mineral density measurement

Due to the overall risk of osteoporosis and fractures in this patient population it seems reasonable to evaluate bone mineral density at least once in patients with chronic liver disease. Patients with density 2.5 standard deviation below peak bone mass should then be evaluated and treated based on the guidelines available for the normal population. Patients with liver disease and osteopenia [BMD 1-2.5 SD below peak bone mass] should be viewed as a high risk population and therapy should be more aggressively contemplated than in the normal population. Patients receiving corticosteroids should also undergo a BMD measurement, supplementation with calcium and vitamin D, and the option of therapy with a bisphosphonate should be discussed with them. Due to the increased risk of fractures that is independent of BMD measurement it might be worthwhile to consider evaluating the risk based on FRAX algorithms and then making a decision for therapy if the patient does not wish to perform a bone mineral density measurement.

SUMMARY OF THERAPEUTIC IMPLICATIONS

The evidence points to a decrease in bone formation and in some cases an increase in bone resorption. The therapeutic options have increased in recent years but compared to other disease entities remain limited (Table 5). In addition to calcium and vitamin D supplementation the current options are available:

Stimulation of osteoblast function

The best therapeutic intervention would be to improve liver function and hence diminish the inhibitory signals (oFN and bilirubin) and increase the stimulating signals (IGF- I) originating from the liver. Parathyroid hormone administered intermittently has been shown to stimulate bone formation to a larger degree than bone resorption[128]. Unfortunately no data exist on its efficacy in patients with liver disease. Another option would be the administration of GH or IGF- I . Because GH levels tend to be normal and a beneficial effect was only shown in GH-deficient states this is not a viable option[129]. The administration of IGF- I seems beneficial in rats, but no studies exist in humans on the use of IGF- I [130]. Strontium ranelate is also an option that has not been studied in patients with liver disease[131]. There are, however, reports of liver abnormalities that developed after treatment with strontium ranelate[132]. Since the Wnt-signaling pathway is activated in osteoblasts during bone formation, indirectly activating this pathway (by neutralizing the endogenous inhibitors) results in increased bone formation. One such molecule is an antibody to sclerostin, and is currently under investigation in humans, but data on patients with liver disease will not be available in the near future[130].

Inhibition of osteoclast resorption

The currently available inhibitors are bisphosphonates and RANKL antibody. There are some studies looking at the use of bisphosphonate in patients with liver disease but none on the use of RANKL antibody, despite the potential for its use. The benefit of these medications even in cases in which bone formation is inhibited and bone resorption is not increased was documented. This is because bisphosphonates decrease remodeling and hence diminish the normal bone loss associated with aging. This occurs at the expense of loss of the rejuvenating function of remodeling required for the repair of microfractures and matrix structural abnormalities that accumulate over the years. Nevertheless, despite this theoretical disadvantage, the few studies that looked at the use of bisphosphonate in cholestatic liver disease showed an improvement in BMD and a decrease in fracture rates[48,52,106,133,134]. Hormone replacement therapy could be considered in postmenopausal women. Raloxifene has been tested as well as calcitonin in small studies, but in view of currently available data on bisphosphonates, it seems reasonable to consider these as a second line therapy[135-137].

CONCLUSION

Liver diseases are associated with bone loss that is due to decreased bone formation or increased bone resorption depending on the etiology of liver disease. This is associated with increased fracture risk. Factors related to the role of liver in bone health are also involved in mediating

the bone loss. Bone loss in liver disease is an important yet neglected disease entity that should be addressed in all patients with chronic liver disease. A minimum of vitamin D and calcium supplementation should be complemented by evaluation of bone density and treatment based on the guidelines set for patients at moderate to high risk in the general population.

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