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REVIEW

Osteoporosis across chronic liver disease

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Abstract Osteoporosis is a complication of chronic liver disease, with impact on morbidity, quality of life, and survival. The progress of medicine and the new therapies stretched the disease's natural history and improved the survival of patients with liver disease. So, it is fundamental to make better the quality of life and to prevent complications. Metabolic bone disorders are common complications of chronic liver disease (CLD). Patients with CLD have an increased risk of bone fractures, with significant impact on morbidity, quality of life, and even on survival. Bone diseases, including osteomalacia, osteoporosis, and osteopenia, are frequently observed in many types of liver disease. The pathogenesis of damage and the mechanisms of bone loss are different in relation to the specific liver disease. The relevance of these conditions induced many authors to create a new nosographic entity known as "hepatic osteodystrophy", although this term is rarely used anymore and it is now commonly referred to as osteopenia or osteoporosis associated with chronic liver disease. This review is based on the personal experiences of the authors and upon research done of the available literature on this subject matter. The authors searched the PubMed database for publications containing the term "liver disease" in combination with "bone disease", "hepatic osteodistrophy", "osteoporosis", "osteopenia", "osteomalacia", and "fractures". They selected publications from the past 10 years but did not exclude older seminal publications, especially for colestatic liver diseases. This review of literature shows that osteoporosis crosses all CLD. It is important to underline that the progress of medicine and the new therapies stretched the disease's natural history and improved the survival of patients with CLD. It is fundamental to make better the quality of life and it is mandatory to prevent complications and in particular the osteoporotic ones, especially fractures.

Keywords Fractures · Liver disease · Osteoporosis

Abbreviations

CLD	Chronic liver disease
PBC	Primary biliary cirrhosis
BMD	Bone mineral density
DeXA	Dual X-ray absorptiometry
RANK	Receptor activator of nuclear factor kB
RANKL	Receptor activator of nuclear factor kB ligand
OPG	Osteoprotegerin
PTH	Parathyroid hormone
IGF-1 and IGF-2	Insulin-like growth factor-1 and 2
PSC	Primary sclerosing cholangitis
IBD	Inflammatory bowel disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
MS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
LT	Liver transplantation
HRT	Hormone replacement therapy
HH	Hereditary hemochromatosis
HREs	Hormone response elements
ERK	Extracellular-signal-regulated kinases

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Introduction

Metabolic bone disorders are common complications of chronic liver disease (CLD). Patients with CLD have an increased risk of bone fractures, with significant impact on morbidity, the quality of life, and even on survival. Bone diseases, including osteomalacia, osteoporosis, and osteopenia, are frequently observed in many types of liver disease [1]. The pathogenesis of damage and the mechanisms of bone loss are different in relation to the specific liver disease. The relevance of these conditions induced many authors to create a new nosographic entity known as "hepatic osteodystrophy" [2], although this term is rarely used anymore and it is now commonly referred to as osteopenia or osteoporosis associated with chronic liver disease.

This review summarizes current understanding of bone disease associated with liver pathologies and the new advances made in this field. The different mechanisms by which cholestatic and parenchymal liver disease can lead to reduced bone mass, the prevalence of osteopenia and osteoporosis in patients with early and advanced liver disease, and the influence of osteoporotic fractures on patient survival will be the topics of discussion included in this paper.

Search strategy and selection criteria

This review is based on the personal experiences of the authors and upon research done of the available literature on this subject matter. The authors searched the PubMed database for publications containing the term "liver disease" in combination with "bone disease", "hepatic osteodistrophy", "osteoporosis", "osteopenia", "osteomalacia", and "fractures". They selected publications from the past 10 years but did not exclude older seminal publications, especially for colestatic liver diseases. They reviewed the list of publications found by this search strategy and selected those they judged relevant. Point estimates of prevalence and mean bone density were extracted and combined. Although not a formal meta-analysis, results can be taken to reflect general trends in the published data and should be useful for assessing the overall magnitude of the impact of various liver disorders on bone metabolism.

Definitions

Osteomalacia

Osteomalacia is a disorder of the bone characterized by defective bone mineralization following the cessation of bone growth. In contrast to rickets, which affects mineralization of growing bones, osteomalacia does not affect the growth plates; although, hypomineralization of trabecular and cortical bone occurs. Osteomalacia is traditionally associated with vitamin D deficiency, albeit the mere presence of vitamin D deficiency is not sufficient to cause osteomalacia. Bone biopsy is the gold standard for diagnosing osteomalacia even if hepatic osteomalacia, as defined by strict histomorphometric criteria, is rare [3].

However, osteomalacia is quite uncommon in patients with liver diseases, and it has been reported only in isolated patients with advanced primary biliary cirrhosis (PBC) and severe intestinal malabsorption in geographical areas with limited sunlight exposure. Osteomalacia, although historically reported in up to 64 % of individuals with primary biliary cirrhosis in the 1970s, is now rarely seen in adult patients with chronic liver disease [3]. The change in prevalence probably reflects differences in diagnostic criteria, selection bias, and possibly improved nutrition, or there is the possibility that we conduct studies on less serious liver diseases than in the past. Although two thirds of patients with cirrhosis (from any cause) and 96 % of patients awaiting liver transplantation have documented low vitamin D levels, they nevertheless do not have osteomalacia using histomophometric criteria.

The classical biochemical changes are hypocalcaemia, hypophosphataemia, increased parathyroid hormone, and elevated bone alkaline phosphatase although serum calcium and phosphate are often normal, as not all patients with lower serum vitamin D levels will have osteomalacia.

Osteoporosis

It is now widely accepted that, although the potential for osteomalacia exists, osteoporosis is the primary metabolic bone disease found in association with CLD, with vitamin D playing a minor role [4–6]. Metabolism of vitamin D is normal in hepatic osteodystrophy, but malabsorption of both calcium and vitamin D may occur, which contributes to skeletal effects [7].

Osteoporosis is defined by the WHO as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and with subsequent increased risk of susceptibility to fracture. The clinical relevance resides in the fact that the fractures, as well as their attendant morbidity and mortality, arise as a consequence of the condition of osteoporosis [8].

Osteoporosis is further defined by the WHO criteria as a reduction of bone mineral density (BMD) to less than 2.5 standard deviations below normal adult peak bone mass. This equates to a T-score of less than or equal to −2.5 as assessed by dual X-ray absorptiometry (DeXA). It is to be noted that risk of fracture increases dramatically with decreasing BMD. Osteoporosis is clinically important as, unlike osteomalacia, it is frequently identified in patients with cirrhosis, leading to spinal fractures that often go undetected clinically, but nonetheless lead to significant patient morbidity [9].

Osteopenia

Osteopenia represents a milder degree of bone loss and it is diagnosed when the T-score is between −1.0 and −2.5 [10].

Physiology and pathogenesis of bone metabolism in chronic liver diseases

The pathogenesis of bone loss in patients with chronic liver disease is multifactorial, differs among the various liver etiologies and probably varies according to the progression of liver disease, having also different risk factors: low sunlight exposure, reduced physical activity, increased body mass index, vitamin D deficiency, hypogonadism, alcohol abuse, or nutritional deficiencies [11].

The bone is implicated in structural support, protection of organs, calcium homeostasis and environment for the marrow. It is composed of support cells (osteoblasts and osteocytes), remodeling cells (osteoclasts), matrix of collagen and non-collagenous proteins (osteoid), and anorganic mineral salts. Once the skeleton reaches maturity, regeneration continues in the form of periodic replacement of old bones tissue with new ones, and the temporal structural unit responsible for this is called basic multicellular unit. The balance between bone resorption and bone deposition is determined by the activities of two principle cell types, osteoclasts and osteoblasts, which are from two different origins. Osteoblasts derive from an undifferentiated mesenchymal cell under the influence of specific stimulating factors. Osteoclasts are large multinuclear cells, derived from the hematopoietic series, with the function of bone resorption [12].

The equilibrium between bone formation and bone resorption is under the control of multiple systemic and local factors such as: sex hormones, parathyroid hormone, growth hormone, and pro-inflammatory cytokines [13].

The molecular mechanism that controls osteoclastogenesis has been clearly established with the discovery of receptor activator of nuclear factor kB (RANK) and its ligand (RANKL), which is as a key factor for osteoclast differentiation and activation [13]. RANKL, expressed on the surface of preosteoblasts, binds to RANK on the osteoclastic precursor cells and this is critical for the differentiation, activation, and survival of osteoclastic cells. Osteoprotegerin (OPG) is a potent inhibitor to osteoclastogenesis due to its ability to act like a RANKL and to bind RANK. OPG is synthesized in the liver and it is considered to have a major role in the development of osteoporosis in patients with CLD [13].

Bone metabolism and hormones in CLD

The liver and its pleotropic functions play a fundamental role in regulating metabolism, and it is also an inevitable target of multiple metabolic disorders. The numerous and constant relationships and feedback mechanisms between the liver and all endocrine organs are reflected by the fact that an alteration of one oftentimes results in the malfunction of the other [14] (Table 1).

The relationship between the adrenal gland and the liver is complex, and the dysfunction of one of these organs tends to cause functional abnormalities in the other organ as well. Both excess and insufficiency of adrenal function may result in altered liver function, and adrenocortical dysfunction may be present in patients with cirrhosis, especially during episodes of decompensation. Again an important player which affects both the endocrine system and the liver, alcohol may be associated with pseudo-Cushing syndrome. Sex hormones, both intrinsic as well as extrinsically administered, have an important impact on liver function. While estrogens are related to cholestatic liver damage, androgens are the culprit of adenomas and hepatocellular carcinoma, among others [15]. Chronic liver disease, on the other hand, has profound repercussions on sex hormone metabolism, inducing feminization in men and infertility and amenorrhea in women [15].

Beside a direct effect on bone cells, hormones have an indirect effect on bone metabolism through the RANK-RANKL-OPG system. Parathyroid hormone (PTH), 1, $25(OH)_2$ vitamin D_3, glucocorticoids increase RANKL levels and decrease OPG levels, while estrogens have no effect on RANKL levels but increases the OPG level [13].

The parathyroid hormone is responsible for maintaining extracellular calcium level and releasing calcium from the bone deposits in response to hypocalcaemia. It also increases renal tubular calcium re-absorption and renal calcitriol production [16]. PTH acts through its specific receptor that also possesses an endogenous ligand (PTH-rP). PTH has a negative feedback with vitamin D_3 in the homeostasis of calcium [17].

Vitamin D_3 is synthesized in the skin or absorbed through the gut. It is hydroxylated first in the liver by the enzyme 25-alpha-hydroxylase then in the kidney by the 1-alpha-hydroxylase, and results in the formation of the active metabolite 1, $25(OH)_2$ vitamin D_3 (calcitriol) [18]. Low serum concentrations of 25-hydroxyvitamin D have been associated with

Table 1 Factors involved in osteoporosis in patients with liver diseases

Factors involved in osteoporosis in liver diseases
RANKL-OPG system
Fibronectin
IGF-1 and IGF-2
Corticosteroid and other medications
Steroids (especially estrogens)
Vitamin D-PTH axis
Leptin
Inflammatory cytokines

many non-skeletal disorders. However, whether low 25(OH)D is the cause or result of ill health is not known. Investigators of most prospective studies reported moderate to strong inverse associations between vitamin D concentrations and cardiovascular diseases, serum lipid concentrations, inflammation, glucose metabolism disorders, weight gain, infectious diseases, multiple sclerosis, mood disorders, declining cognitive function, impaired physical functioning, and all-cause mortality. High vitamin D concentrations were not associated with a lower risk of cancer, except colorectal cancer [19].

Several studies have supported the notion that vitamin D, in addition to its classical action of maintaining systemic calcium homoeostasis and bone mineralisation, has non-classical extraskeletal actions including a potential capacity to inhibit fibrosis in various tissues [20]. Moreover, vitamin D reduced the collagen expression and other key profibrotic factors and increased the expression of antifibrotic factors, such as BMP7 and matrix metalloproteinase 8, in those cells [21]. It is well known that liver fibrosis is a reversible wound-healing response caused by the hepatic stellate cell (HSC)-mediated excessive accumulation of extracellular matrix proteins, which leads to the destruction of liver architecture and liver cell dysfunction [22]. Noteworthy, in a recent study published by Beilfuss et al., basically incontrovertibly demonstrated the antifibrotic effect of vitamin D in liver fibrosis providing additional support to previous pilotal studies [23]. The main contribution of the study by Beilfuss is represented by the powerful antifibrotic effects of vitamin D on human primary TGF-β stimulated HSCs, as well as on HSCs isolated from morbidly obese patients with non-alcoholic fatty liver disease (NAFLD) whose underwent bariatric surgery [23].

The growth hormone, together with insulin-like growth factor-1 and 2 (IGF-1 and IGF-2), plays an important role in maintaining BMD. More than 90 % of IGF-1 is synthesized in the liver and declines in the early stages of cirrhosis even before other liver function test (albumin, bilirubin, prothrombin) [24].

Corticosteroid therapy is widely used in some hepatic diseases. Glucocorticoids stimulate both bone resorption and bone formation. Steroids promote mature osteoblast synthesis, but also have, as explained below, an inhibitory effect on their activity, in addition also increase osteolysis and augment osteoclast recruitment [25]. It is presumed that the effects of steroids, especially estrogens, are mediated by two types of receptors on the surface of osteoblasts and osteoclasts. The first one, located only on the surface of osteoblasts, carries the hormone into the nucleus and activates different genes (hormone response elements, HREs) (nuclear way). The second one, found on the surface of osteoblasts, osteoclasts, and osteocytes, is connected to cytoplasmatic triggers like SRC, extracellular-signal-regulated kinases (ERK) and through ERK-1 indirectly influences the transcription (cytoplasmatic way). Estrogens have an anti-apoptotic effect on the osteoblasts and a pro-apoptocic effect on the osteoclasts. In addition, estrogens suppress the production of IL-6, a pro-osteoclastogenic cytokine. This mechanism seems of particular relevance in all diseases associated with hypogonadism, like liver cirrhosis. Alcohol use also affects the levels of estrogen, testosterone, and their bioavailability in a dose-dependent manner, even in the absence of cirrhosis [25].

Steroid-induced osteoporosis is the best known form of drug-induced osteoporosis, but it is important to remember that many other medications are potentially cause of osteoporosis, like immunosuppressive drugs, thyroid hormone, hypogonadism-inducing agents, thiazolidinediones, antidepressants, anticonvulsants, antiretroviral therapy, heparin, loop diuretics, or proton pump inhibitors [26].

Patients with cholestatic liver disease show malabsorption of vitamin K, an important agent in carboxylation of bone proteins. In healthy populations, a low vitamin K level is associated with osteoporosis and a high risk of fractures [26].

Osteocalcin, a protein secreted by osteoblast cells in bone, has recently emerged as an important metabolic regulator with insulin-sensitizing properties. In humans, osteocalcin levels are inversely associated with liver disease. Moreover, osteocalcin robustly reduced expression of pro-inflammatory and profibrotic genes (Cd68, Mcp1, Spp1, and Col1a2) in liver and suppressed inflammatory gene expression in white adipose tissue [27].

Leptin, mainly produced by adipocytes, has a role not only in regulating hunger and satiety but also in maintaining BMD by central and peripheral mechanisms. Hypothalamic neurons involved in leptin antiosteogenic central functions are distinct from the neurons responsible for the regulation of energy metabolism [28]. Peripheral leptin increases osteoblast proliferation, suppresses RANKL production and stimulates the synthesis of bone matrix. As a consequence, all these actions increase BMD. From the molecular point of view, leptin has an immunomodulatory effect, stimulating in turn the synthesis of other cytokines such as IL-1 and TNF-alpha [29]. Leptin production is increased in activated stellate cells, in patients with chronic hepatitis C, and its level correlates with liver fibrosis scores [28]. On the contrary, in patients with cholestatic liver disease, the leptin level is decreased compared to healthy controls [28].

Bone metabolism and inflammation

Activation of inflammatory cells in patients with CLD induces the production of pro-inflammatory cytokines such as TNF, IL-1, IL-13, IL-6, IL-7, IL-11, IL-15, and IL-17. These cytokines can increase bone loss either by the direct activation of osteoclast precursors, or by inducing the production of RANKL by osteoblasts [29].

Inflammatory cytokines influence BMD in both physiological and pathological conditions. CLD is characterized by an inflammatory status. Interleukina-6 (IL-6), synthesized in osteoblasts, osteoclasts, and stromal cells, is a potent activator of osteoclasts and bone resorption, but also promotes osteoblast generation in conditions of high bone turnover. Similarly, other cytokines, like IL-1, IL-11, and TNF-alpha influence ostoclast function. IL-8, besides its pro-inflammatory role, causes an increase in PTH levels. Prostaglandins, especially PGE2, stimulate both bone formation (in response to mechanical stress) and bone resorption. Cyclooxygenase 2 (COX2) is needed for PGE2 synthesis, and also non-steroidal anti-inflammatory drugs that inhibit COX-2, decrease osteosynthesis [29].

Ethanol seems to stimulate IL-6 production. Also, serum levels of TNF are elevated in patients with alcoholic or viral liver disease, and serum levels of the TNF receptor, TNF-R1, correlate with the severity of liver disease.

In vitro studies, it has been demonstrated that fibronectin, an adhesive protein that transmits information between matrix and cells, is necessary for the osteoblast functions. Plasma fibronectin is produced by the liver and patients with liver disease exhibit altered fibronectin production, represented by a large number of variant isoforms [30]. Circulating fibronectin isoforms produced by activated stellate cells represent a viable marker for the presence, or lack thereof, of significant fibrosis in patients with chronic hepatitis C [30].

Cholestatic liver diseases

Cholestatic patients are at a higher risk of osteoporosis (prevalence 51.5 %) than chronic viral hepatitis patients (prevalence 38.7 %) and healthy controls (prevalence 19.6 %) [31].

The prevalence of osteoporosis in patients with primary biliary cirrhosis (PBC) ranges from 20 to 45 % [32–35] (Table 2). The prevalence of fractures has been analyzed in few studies. In particular, in patients with PBC, the prevalence of vertebral (through X-rays of the spine), non-vertebral, and overall fractures is reported about 11, 12, and 20 %, respectively [36]. It has been shown that patients with cholestatic liver diseases have increased prevalence of osteoporosis compared to other chronic liver diseases. On the other hand, most studies comparing cholestatic and non-cholestatic CLD have not been able to demonstrate the role of cholestasis in the pathogenesis of bone disease [31]. In patients with PBC female gender, low weight and height, but not BMI, correlated strongly with low BMD. Vitamin D levels, even in advanced stages of disease, are normal. The risk of osteoporosis in PBC has been shown to correlate with age, female gender, disease stage, lower BMI, and history of fractures [33, 37].

Table 2 Prevalence of osteoporosis in liver diseases

Liver diseases	Prevalence of osteoporosis
Primary biliary cirrhosis	20–45 %
Primary sclerosing cholangitis	15 %
Hemochromatosis	25–34 %
Chronic viral hepatitis	20–53 %
Cirrhosis	12–55 %

In patients with primary sclerosing cholangitis (PSC) [38], the prevalence of established osteoporosis was found about 15 %, a lower percentage level than the prevalence of 20 to 45 % reported in patients with PBC [36, 39, 40]. On the other hand, osteoporosis occurs commonly in patients with PSC and inflammatory bowel disease (IBD). In particular, longer duration of IBD contributes significantly to the severity and rate of progression of bone disease, and this effect seems to be independent of other risk factors identified previously in the cholestatic population, even if literature lacks of a rate of prevalence [38].

However, both clinical and experimental evidence to indicate whether vitamin D-administration can be utilized to modulate chronic cholestatic liver disease is limited to date. For this reason, Reiter et al., tried to address this question [41] with an in vivo study based on the ATP-binding cassette transporter b4 (Abcb4/Mdr2) knockout-mouse lacking the canalicular phospholipid export pump, that is an established model for biliary liver fibrosis, developing a phenotype mimicking features of human PSC. They showed that in Abcb4$^{-/-}$-mice, administration of calcitriol ameliorates inflammatory liver damage but has no effect on biliary fibrosis after 4 weeks of treatment [41].

Hemochromatosis

In patients with hereditary hemochromatosis (HH) the prevalence of osteoporosis ranges from 25 to 34 % [42] (Table 2). The prevalence of osteopenia is about 41 % [43]. BMD measurements fell with rising hepatic iron content. After iron depletion by phlebotomy, a melioration of lumbar spine BMD was observed [43]. High iron levels rather than the presence of cirrhosis most closely predicted osteoporosis. Serum-free testosterone, lack of HLA-A3, and low BMI are additive risk factors for osteoporosis [42].

Autoimmune hepatitis

Current literature does not show studies that have evaluated the risk and prevalence of osteoporosis in patients with autoimmune hepatitis.

Viral hepatitis

In patients with chronic viral hepatitis who are cirrhotic, the prevalence of osteoporosis ranges between 20 and 53 % [31] (Table 2), while the prevalence of fracture was estimated of 6.7 % [44]. In 2005, Schiefke et al. demonstrated that patients with chronic hepatitis B virus (HBV), or hepatitis C virus (HCV) infection without cirrhosis, already had significantly reduced BMD and the reduction correlated with the degree of liver fibrosis [44]. Studies in patients with viral and toxic hepatic disease proved that vitamin D levels could be considered as a marker of liver function insufficiency and bone health [45, 46]. Fisher et al. evaluated vitamin D levels in 100 patients with liver disease (hepatitis and cirrhosis). The prevalence of vitamin D deficiency was significantly higher in cirrhotic than in non-cirrhotic subjects, and vitamin D levels were significantly decreased in patients with Child C class compared to those with Child A class [47].

Recently, Petta et al., found a correlation between lower 25(OH)D levels and the severity of liver fibrosis in genotype 1 chronic hepatitis C patients [48, 49].

Controversial data are available in literature about the relation between vitamin D levels and SVR. Villar et al. demonstrated that vitamin D supplementation is statistically associated to increased sustained virological response rate in chronic hepatitis C [50]. On the contrary, Kitson et al. shows that vitamin D is not a predictor of SVR in univariate and multivariate analysis [51], while Esmat et al. concludes that, despite its role in other genotypes, vitamin D supplementation has no significant impact on SVR in HCV genotype 4 patients [52].

More recent data indicate that vitamin D supplementation is a relatively inexpensive therapeutic option to reduce live fibrosis and improve SVR [53]. Interestingly, two potentially modifiable factors, CD4+ nadir and serum vitamin D levels, were both independent modulators of liver fibrosis progression and determinants of portal pressure [53, 54].

Alcoholic liver disease

Alcohol is an independent risk factor for osteoporosis; alcoholism being associated with an approximate 2.5-fold increase in the risk of hip fractures [55]. In men, excess alcohol, irrespective of cirrhosis or low testosterone levels, is a risk factor for osteoporotic fractures [56]. Alcoholic cirrhosis will be treated in the cirrhosis paragraph. A recent meta-analysis showed a significant association between bone fractures and alcoholic liver disease, independent of BMD or the presence of osteoporosis [55]. In terms of the main mechanism, it is inferred that alcohol causes an imbalance in bone remodeling with a predominant decrease in bone formation. Alcohol is known to cause direct effects on the numbers and activity of osteoblasts and osteoclasts. In addition, many indirect effects have also been reported. These indirect effects are mainly linked to impaired nutrition, which leads to weight loss, decreased fat and lean body mass, and hormone alterations, which may change in bone cell activity [57].

Metabolic liver diseases

Low BMD has been recognized as a potential health problem in both men and women suffering from metabolic syndrome (MS) [58–62], the hepatic manifestation representation of which is NAFLD.

A lot of studies focus on the rapidly expanding body of evidence that supports a strong association between NAFLD and the risk of decreased BMD, expression of low bone mass (osteoporosis), or reduced mineralization (osteomalacia) [63, 64]. Although the mechanisms behind the reduced BMD in NAFLD are still not completely understood, several factors that may influence bone health and mineralization in NAFLD can be discussed. These include the chronic low-grade inflammation itself, which causes the release of cytokines from the inflamed liver (pro-inflammatory, pro-coagulant, and pro-fibrogenic mediators), insulin resistance, vitamin D deficiency, and limited physical activity [59]. Circulating markers of bone metabolism, including osteopontin, OPG, osteocalcin, and fetuin-A, have been found to be altered in patients with NAFLD [58].

Recently, Moon and coworkers [65] have examined the association between BMD and NAFLD in 381 pre and postmenopausal women. The results indicated that the mean lumbar BMD was lower in subjects with NAFLD than those without NAFLD in postmenopausal women, even after adjusting for the presence of MS. The authors considered BMD as related to NAFLD per se (i.e., independently of MS) in postmenopausal females, and suggested that postmenopausal women with NAFLD may have a greater risk of osteoporosis than those without.

In a recent study by Beilfuss et al., is reported the powerful antifibrotic effects of vitamin D on human primary TGF-β stimulated HSCs, as well as on HSCs isolated from morbidly obese patients with non-alcoholic fatty liver disease (NAFLD) whose underwent bariatric surgery [23]. However, as recently highlighted by Skoien et al., multiple mechanisms may explain fibrogenesis associated with different aetiologies and consequently influence the antifibrotic response to vitamin D supplementation [66]. In this picture, the treatment with vitamin D could exert its beneficial effects better at the early stage of fibrogenesis than in advanced disease. This hypothesis makes vitamin D an antifibrotic agent that could be used soon before it is too late, therefore potentially effective particularly in pediatric NAFLD in which liver fibrosis is not predominantly severe [66]. Accordingly, Nobili et al. reported a statistically significant inverse correlation between vitamin D levels and histological liver damage in children with NAFLD, independently of age, gender, body mass index, and other potential confounders [67].

Cirrhosis

Osteoporosis and fractures are more common in cirrhotic patients than in the normal population, in the absence of confounding risk factors such as female sex, cholestasis, and excess alcohol intake. The prevalence of osteoporosis is related to the severity of cirrhosis (Child-Pugh score) [68]. On the other hand, until now there are no studies that assess the prevalence of osteoporosis in relation to the severity of cirrhosis.

Cirrhosis increases the risk of fracture by about twofold, regardless of the etiology of the liver disease.

Bone turnover laboratory parameters widely confirmed these results. In particular, a significantly reduced levels of IGF-1, PTH, and vitamin D, which are associated with a reduced bone formation and, in parallel, increased levels of alkaline phosphatase and urinary-free deoxypyridinoline/creatinine suggesting an increased bone turnover [69].

The prevalence of osteoporosis is variously reported between 12 and 55 % [70] (Table 2). The rather wide variability of reported prevalence rates of osteoporosis and fractures is probably due to differences in the ages of the patients studied and the severity of their liver disease [70]. In view of this high prevalence, screening for metabolic bone disease and vitamin D status on diagnosis of cirrhosis, irrespective of underlying etiology or disease severity, is recommended [70].

Ascites and gastroesophageal varices appear to be clinical markers for lower BMD. Coexisting gastrointestinal diseases (such as IBD in PSC) may be an additional risk factor. Recently, Trépo et al., affirmed that severe vitamin D deficiency is directly associated with cirrhosis severity, with early mortality in alcoholic patients. So, it was suggested that vitamin D may well represent both a biomarker of the severity and the prognosis in alcoholic patients [71].

Liver transplantation

The abnormalities in bone metabolism are very similar regardless of organ transplanted type, of pre-existent bone disease and of previous treatment. Frequently, bone loss occurs in the first year after the organ transplant, due the adverse effects of immunosuppressive drugs and due to the long period of immobilization. However, it is important to note that low bone mass and fractures may antedate transplantation, which could be related to effects on the skeleton of chronic disease and the presence of concomitant risk factors for osteoporosis.

A rate from 12 to 55 % of patients may have osteoporosis before liver transplantation (LT) as a result of their underlying chronic liver disease. It has been demonstrated that the bone health before transplantation maybe a predictive factor of bone loss and fracture after the liver is transplanted [72].

In a recent study, Loria et al. [73] confirmed that patients with advanced liver disease awaiting LT show a high prevalence of bone alterations. They examined a population of mixed etiology. The majority of patients were either post-alcoholic or affected by viral cirrhosis. None of their patients complained of clinical symptoms or reported a history of bone fractures. Osteodystrophy was found in 40 % of patients; moreover, among patients undergoing LT, there was further deterioration in BMD in the short term (3 months). Likewise, Galtieri et al., in their study, confirmed that osteodystrophy affects more than half of patients awaiting LT and that an adequate evaluation and treatment of bone disorders may allow for stabilization or even reduction of the rate of this complication after LT [74].

Between LT and 4 month post-transplant, the incidence of osteoporosis and osteopenia increased abruptly in all patient groups, due to 5 % average bone loss; a very high rate of bone loss rarely seen in other clinical situations. Males and females were equally affected. The rate of bone loss did not change with time, despite changes in immunosuppressive regimens. Following liver transplantation, the fracture risk is further increased due to the use of high steroid doses and prolonged immobility, particularly when post surgery complications arise [75].

After LT, the increase in bone turnover may result from resolution of cholestasis or hypogonadism, increased PTH secretion, or cyclosporine A or tacrolimus or everolimus administration. Significant increase in osteoprotegerin and RANK-L levels demonstrated during the first 2 weeks after liver transplantation provide further evidence of high bone turnover state. Osteoporosis remains a potential complication of liver transplantation, although its incidence may be significantly reduced by the use of lower doses of GCs [76]. According to a unifying hypothesis for cardiac, lung, and liver transplantation, there seem to be two main phases in post-transplant bone disease: the early and the late post-transplantation periods. Before LT, there is a low bone turnover state, supported by biochemical and especially histomorphometric analysis of bone biopsies. In the first 3 months after LT, there is a significant and quantitatively large increase in bone turnover, substantiated by histomorphometric data and early increase in the biochemical markers of bone resorption that exceeds bone formation markers [68]. The second phase, which generally appears 6 months after transplantation, is characterized by an increase in both the histologic parameters as well as the biochemical markers of bone formation. At this time, bone loss at the lumbar spine has stopped and BMD has begun to increase spontaneously. The factors involved in bone turnover in this second phase after transplantation are the normalization of liver function and the gradual reduction in glucocorticoids [77].

The fractures occur mainly in the 6–12 months following the transplantation, with rates ranging from 24 to 65 %; the ribs and vertebrae are the most common sites [68, 76–79]. Treatment with bisphosphonate along with

calcium and vitamin D before the transplant has been demonstrated to prevent the bone loss and the high rates of fractures following LT [80].

Hepatocellular carcinoma

There are no studies in current literature that have evaluated the risk and prevalence of osteoporosis in patients with hepatocellular carcinoma.

Prevention and supportive care

Prevention and supportive care for osteoporosis in patients with liver disease are the same as those for the general population.

The prevention of osteoporosis through modification of risk factors and supportive measures for bone health, represent the first line of approach. The factors contributing to bone loss should be reduced to a minimum; basically by stopping alcohol intake and smoking [81]. As much physical activity as possible is recommended, as are exercises aimed at improving spine mechanics. Moreover, physical exercise is considered to strengthen the bones through gravitational forces or muscle pull producing strains within the skeleton [82]. For this reason, physical activity is currently considered as a cornerstone for the prevention of both osteoporosis and NAFLD, although the mechanisms remain poorly understood [83, 84]. Therefore, lifestyle modifications with weight loss and physical exercise are regarded as first line treatments in patients with osteoporosis. Whenever possible, a balanced diet should be prescribed [81, 85, 86]. The dose of glucocorticoids should be adjusted to the minimum requirement, particularly in transplant patients who also take immunosuppressive drugs [87, 88].

Vitamin D and calcium

The effectiveness of vitamin D and calcium supplementation in preventing fractures or osteoporosis in patients with liver diseases is unclear. In 34 intervention studies including 2805 individuals with mean vitamin D concentration lower than 50 nmol/L at baseline supplementation with 50 μg per day or more did not show better results. Supplementation in elderly people (mainly women) with 20 μg vitamin D per day seemed to slightly reduce all-cause mortality. The discrepancy between observational and intervention studies suggests that low vitamin D is a marker of ill health. Inflammatory processes involved in disease occurrence and clinical course would reduce vitamin D, which would explain why low vitamin D status is reported in a wide range of disorders. In elderly people, restoration of vitamin D deficits due to aging and lifestyle changes induced by ill health could explain why low-dose supplementation leads to slight gains in survival [89].

The beneficial skeletal effects of vitamin D preparations in patients with hepatic osteodystrophy presumably result from correction of vitamin D deficiency [20]. Particular attention should be given to patients who are on cholestyramine treatment, because it may block the absorption of vitamin D. In the absence of more extensive studies on the effect of vitamin D supplementation on BMD in liver patients, it seems reasonable to recommend correction of vitamin D insufficiency with a daily oral dose of calcium (1000—1500 mg) and vitamin D (400—800 IU or 260 μg every 2 weeks) or any dose required to maintain normal levels [90].

Bisphosphonates

Bisphosphonates are anti-catabolic drugs which increase bone mass and reduce the incidence of fractures in postmenopausal osteoporosis [91]. These drugs are usually given in association with calcium and vitamin D. The bisphosphonates have been extensively studied in treating osteoporosis in patients with chronic liver disease. For the most part, these drugs have been studied in PBC patients. In a study of Guanabens et al., etidronate has been shown to prevent bone loss after 2 years of treatment and alendronate has been shown to increase bone mass in PBC patients [91]. Another study demonstrated that alendronate, 70 mg/week, increased bone mass in PBC patients after 1 year of treatment [92]. As might be expected, adherence to monthly ibandronate was better than adherence to weekly alendronate, without differences in the improvement of BMD or hepatotoxicity. Despite these promising results, there are no long-term studies of bisphosphonates in preventing fractures in patients with chronic liver disease.

Bisphosphonates have also been studied in LT setting. In a Spanish trial, 90 mg of intravenous pamidronate, given in the first 2 weeks, and at 3 months after LT, preserved lumbar spine BMD and was well tolerated, but the fracture incidence was not affected [93]. Alendronate, 70 mg/week, along with daily calcium and calcitriol increased BMD during the first 2 years after LT when compared to calcium and calcitriol alone, with no effect on the fracture rate [94]. Recently, Shane et al. demonstrated that one 5 mg infusion of zoledronate or 70 mg weekly alendronate prevent bone loss at the hip and, in liver transplant patients, increase spine BMD [95].

Hormone replacement therapy

Estrogen plays a fundamental role in skeletal growth and bone homeostasis in both men and women [96]. Although the term estrogen actually refers to a large number of steroidal and non-steroidal molecules capable of inducing ovulation, in the context

of this article, estrogen refers to a pharmacological agent in hormone replacement therapy (HRT) to prevent postmenopausal bone loss in older women. Taking estrogen orally in various formulations or as an adhesive skin patch increases circulating levels of this hormone and compensates for its loss after menopause, thus relieving the symptoms of menopause. It slows down the loss of bone minerals and increases estrogen deficiency can also affect young women, and oral estrogen is prescribed to young women with hormonal imbalances thickness [97].

HRT of osteoporosis has become a second-line therapy in considering the risks of thrombosis and gynecological malignancy [98]. Moreover, HRT should be given, when possible, via the transdermal route, as physiological blood estrogen levels can be achieved without exposing the liver to high levels of conjugated estrogens. Transdermal estradiol should be used at a dose of 50 μg/day, equivalent to 2 mg daily of oral estradiol [99].

Osteoporosis monitoring in CLD

Osteoporosis monitoring in patients with CLD is similar to the standard one. There are some particular conditions that require specific approaches.

When attendant, it is useful to consider hypogonadism correction and then to repeat DEXA in 2–3 years.

In case of long-term corticosteroids treatment, the target will be to minimize the dose and repeat DEXA in 1 year.

In presence of simple osteopenia, to the basic preventive measures, it is important to add the repetition of DEXA in 2–3 years.

In patients with osteoporosis is desirable to begin a therapy with bisphosphonates and/or vitamin D and repeat DEXA in 1 year. Moreover, it is necessary to forward a screening for other low BMD causes (i.e., laboratory screen: complete blood count, serum creatinine, serum calcium, serum phosphate, alkaline phosphatase, protein electrophoresis, 25-OHD, PTH, thyroid function tests, estradiol, FSH, LH, and testosterone [in men]).

Conclusions

In conclusion, the review of literature shows that osteoporosis crosses all CLD. It is important to underline that the progress of medicine and the new therapies stretched the disease's natural history and improved the survival of patients with CLD. For these reasons, it is fundamental to make better the quality of life and it is mandatory to prevent complications and in particular the osteoporotic ones, especially fractures.

Compliance with ethical standards

Conflicts of interest None.

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