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HEPATIC OSTEODYSTROPHY: A GLOBAL (RE)VIEW OF THE PROBLEM

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SUMMARY – Hepatic osteodystrophy is a common and frequently untreated complication, manifested as osteoporosis or osteopenia, encountered in the evolution of chronic liver diseases. This article provides a narrative review of hepatic osteodystrophy. The aim is to revise the prevalence, pathophysiology, diagnosis and management of hepatic osteodystrophy. We searched medical literature *via* PubMed, Google Scholar, Wiley, Science Direct, and Springer Link using respective keywords to obtain data on low bone mineral density connected to chronic liver diseases. Many studies have reported an increased prevalence of osteoporosis/osteopenia in patients with chronic liver diseases. The pathogenesis is multifactorial, involving genetic factors, vitamin deficiencies, proinflammatory cytokines, hypogonadism, hyperbilirubinemia, antiviral therapy, corticosteroid drugs, and lifestyle factors. The management of patients should include individualized assessment for fracture risk factors and bone mineral density. Vitamin D and calcium supplementation should be recommended in all patients with chronic liver diseases and osteoporosis. Bisphosphonates are the most efficient drugs used in the treatment of hepatic osteodystrophy. In the future, it is necessary to define better the management and specific treatment of hepatic osteodystrophy for prevention of fragility fractures and to improve the patient quality of life.

Key words: *Bone diseases, metabolic – diagnosis; Bone diseases, metabolic – physiopathology; Osteoporosis; Liver diseases; Prevalence; Bone density; Risk factors; Fractures, bone; Antiviral agents; Bisphosphonates*

Introduction

Alterations of bone metabolism in patients with chronic liver diseases (CLD) represent an important complication that has been in the researchers' focus in recent years. This pathology is represented by osteoporosis or osteopenia, and seldom by osteomalacia, that may lead to morbidity (bone pain, skeletal deformities, immobilization, and fragility fractures)[1]. All alterations of bone metabolism that appear in the evolution of CLD are defined as hepatic osteodystrophy (HO)[2]. HO is a common complication of CLD and it involves impairment of bone mineral density (BMD). Therefore, assessment should be made in patients with CLD in order to preserve their quality of life and predict long-term prognosis[3]. There are many factors that are involved in the etiology of HO but the pathogenesis of this form of secondary osteoporosis is still incompletely understood[2]. Bone disorders may be found in viral, autoimmune or alcoholic CLD, but more frequently in CLD associated with cholestasis such as primary biliary cirrhosis and primary sclerosing cholangitis[4,5]. This article provides an overview of this topic.

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Material and Methods

For our narrative review, we searched medical literature using the following databases: PubMed,

Google Scholar, Wiley, Science Direct, and Springer Link, and we collected English language articles from 1990 till 2015. We used the following keywords: "hepatic osteodystrophy", "cirrhosis", "hepatitis", "osteoporosis", "osteopenia", "bone density", "pathogenesis", "fracture", "antiviral therapy" and "bisphosphonates". We sorted out 148 papers (original articles and reviews) and we included in our review 100 papers which were more suitable and which met our review aim. All these articles included data on patients (older than 18 years) with CLD as: low BMD, pathogenesis and risk factors for low BMD, diagnosis, management, and treatment of HO.

Prevalence of Hepatic Osteodystrophy

Physiologically, peak bone density is achieved at around 30 years and then bone is lost at a rate of 0.5%-1% *per* year. In women, bone loss is accelerated in menopause, especially for 3-5 years of menopause onset. BMD also decreases with age, so the risk of fractures increases dramatically, mainly after the age of 60. Thus, osteoporotic fractures are known to impair the quality of life and daily activities, cause chronic pain and social isolation, increase the usage of pain killers and increase mortality[6].

The prevalence of osteoporosis in patients with CLD ranges from 3% to 48%[7-18], whereas the prevalence of osteopenia varies between 20% and 68%, depending on the etiology, pathogenesis and size of patient samples[8-10,13-18]. The prevalence of fractures in patients with HO is between 5.3% in patients with chronic viral hepatitis or primary biliary cirrhosis and 23.7% in patients before orthotopic liver transplantation (Table 1)[8,13]. Most of these studies used dual energy x-ray absorptiometry (DXA) to assess BMD (at lumbar spine and femoral neck) and to diagnose osteopenia and osteoporosis (except for the first study in Table 1, where spinal quantitative computed tomography and single photon absorptiometry were used). The etiology of HO in these studies varied from viral hepatitis and viral cirrhosis to primary biliary cirrhosis and end stage liver disease.

Pathogenesis of Hepatic Osteodystrophy

In pathologic conditions, BMD is reduced as a result of imbalance between bone formation and bone resorption. Some studies focused on bone resorption, especially in postmenopausal women, whereas other studies have reported decreased bone formation[19,20].

The risk of fractures in patients with CLD is determined by BMD, trabecular architecture and geometry, bone turnover, and risk factors[2]. Many risk factors for HO have been reported such as genetic factors, vitamin D deficiency and calcium disorders, vitamin K deficiency, insulin-like growth factor 1 (IGF-1) deficiency, hyperbilirubinemia, hypogonadism, inadequate activity of the system of receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG), medication, fibronectin, hiperhomocysteinemia, leptin, and lifestyle (Table 2)[2].

Genetic factors

Genetic polymorphisms of vitamin D receptor and genetic polymorphisms of proteins that are implicated in vitamin D synthesis have been reported to play a role in CLD bone disorders, especially in primary biliary cirrhosis[21]. Other genetic factors have also been reported to be involved in bone loss in patients with primary biliary cirrhosis, such as polymorphisms of collagen α 1 (I) gene, IGF-1, interleukin 1 (IL-1) receptor antagonist (IL1RA), and estrogen receptor α (ERα)[21,22]. Data on vitamin D receptor and collagen α 1 (I) gene are discordant and no correlation has been found with an increased risk of osteoporosis for IL1RA or IGF-1 in the presence of ERα polymorphisms[23]. Additionally, other known factors for osteoporosis may increase the risk of HO development. Female gender is a common risk factor for osteoporosis, including CLD osteoporosis. There has been reported that 21% of women aged 50-84 have osteoporosis (more than 12 million women from countries such as Germany, France, Italy, Spain and United Kingdom)[24]. White and Asian races are those with lower BMD than other ethnic groups[25]. Family risk of hip fracture has also been reported to be associated with the occurrence of osteoporosis and osteoporotic fractures in women, according to the study by Pinheiro *et al.*[26].

Vitamin D deficiency and calcium disorders

Previtamin D_3 (the first form of vitamin D which comes from the cholesterol metabolite 7-dehydrocholesterol under the effect of ultraviolet-B radiation) is transformed into vitamin D_3 in the skin. Only a very

Table 1. Prevalence (%) of osteoporosis, osteopenia and fractures in chronic liver diseases

Author, year	Osteoporosis prevalence	Osteopenia prevalence	Fracture prevalence	Factors associated with low BMD	CLD etiology	Demographic data
Diamond *et al.*, 1990[7]	30%-48%	-	12%-18%	Hypogonadism	Mixed etiology	N=115 M/F: 72/43 Mean age 49.8 (range 20-74) yrs
Carey *et al.*, 2003[8]	13.8%-28.1%	36.8%-41.5%	23.7% (before OLT) 17% (first year after OLT)	Increased bilirubin levels, CTP, MELD score	OLT (alcoholic, viral – HCV)	N=207 M/F: 131/76 Mean age 51 (range 32-68) yrs
Schiefke *et al.*, 2005[9]	26%	51%		Increased PTH, BALP levels	Hepatitis B, C	N=43 M/F: 12/31 Mean age 49 (range 26-77) yrs
George *et al.*, 2009[10]	-	68%	-	Hypogonadism, vitamin D deficiency, decreased IGF-1 levels	Cirrhosis (alcoholic, viral)	N=72 Ethnicity: Indian M/F: 63/9 Mean age 45 (range 22-50) yrs
Gonzalez--Calvin *et al.*, 2009[11]	30.8%-46%	-	-	Increased sTNFr, estradiol and OPG levels	Viral cirrhosis, postmeno-pausal women	N=84 Ethnicity: Caucasian M/F: 0/84 Mean age 65.1 (range 55-80) yrs
Goral *et al.*, 2010[12]	37%	-	-	Increased TNFα, IL-6, IL-1 levels	Mixed etiology	N=55 M/F: 38/17 Mean age 44.8 yrs
Wariaghli *et al.*, 2009[13]	45.3%	39.1%-50%	5.3%	Cholestasis, female sex, lower weight and height	PBC, Hepatitis B, C	N=64 M/F: 16/48 Mean age 51.6 (range 26-76) yrs
Mitchell *et al.*, 2011[14]	21.4%	47%	-	Decreased IGF-1 levels	ESLD	N=117 M/F: 74/43 Mean age 50.4 (range 18-73) yrs
Soylu *et al.*, 2012[15]	1.9% -13%	20%	-	Increased IL-2, IL-6 serum levels	Cirrhosis (alcoholic, viral)	N=44 M/F: 44/0 Mean age 50.8 yrs
Orsini *et al.*, 2013[16]	3%-36%	32%	-	-	Chronic hepatitis C	N=60 M/F: 60/0 Mean age 41.5 yrs
Abdel-kader *et al.*, 2014[17]	6.7%-10%	36.7% -43.3%	-	Decreased testosterone levels	Chronic C hepatitis and cirrhosis	N=60 M/F: 52/8 Mean age 39.3 (range 22-55) yrs
Barbu *et al.*, 2015[18]	11.6%	46.6%	-	Smoking, low BMI, liver fibrosis	Chronic B, C hepatitis	N=60 Ethnicity: Caucasian M/F: 40/20 Mean age 44.9 (range 20-70) yrs

BALP = bone specific alkaline phosphatase; BMD = bone mineral density; BMI = body mass index; CLD = chronic liver diseases; CTP = Child-Turcotte-Pugh; ESLD = end stage liver disease; F = female; HCV = hepatitis C virus; IGF-1 = insulin-like growth factor 1; IL-1 = interleukin 1; IL-2 = interleukin 2; IL-6 = interleukin 6; M = male; MELD = Model for End Stage Liver Disease; N = number; OLT = orthotopic liver transplantation; OPG = osteoprotegerin; PBC = primary biliary cirrhosis; PTH = parathyroid hormone; sTNFr = soluble tumor necrosis factor receptor; TNFα = tumor necrosis factor α; yrs = years

Table 2. Factors involved in bone loss in chronic liver diseases

Genetic factors: Vitamin D receptor (VDR) polymorphisms Collagen α1 (I) gene polymorphisms IL-1 receptor agonist (IL1RA) polymorphisms Estrogen receptor α (ERα) polymorphisms IGF-1 polymorphisms
Vitamin deficiencies: Vitamin D deficiency and calcium disorders Vitamin K deficiency
IGF-1 deficiency
Hyperbilirubinemia
Sex hormone deficiency
RANKL/OPG system
Drugs: Glucocorticoids Antiviral therapies (IFNα plus RBV, nucleos(t)ide analogs)
Other factors: TNF-α Leptin C-reactive protein Fibronectin Homocysteine
Lifestyle factors: Alcohol Cigarette smoking Malnutrition Low BMI Sedentary lifestyle

BMI = body mass index; IFNα = interferon α; IGF-1 = insulin-like growth factor 1; RANKL/OPG system = receptor activator of nuclear factor kappa B ligand/osteoprotegerin system; RBV = ribavirin; TNFα = tumor necrosis factor α

small part of vitamin D comes from diet. Vitamin D_3 becomes hydroxylated to vitamin D 25 in the liver and then the second hydroxylation process occurs in the kidney, which leads to vitamin D 1,25 (active metabolite). The role of this active form is to increase calcium resorption in the gastrointestinal tract, osteoclast activity (bone resorption) and osteoblast activity (bone mineralization)[27]. In the study by Arteh *et al.*, vitamin D deficiency has been reported in most patients with CLD (92%), and one-third of patients presented severe vitamin D deficiency[28]. Vitamin D deficiency in CLD is caused by malnutrition, limited sun exposure, intestinal malabsorption, and decreasing skin synthesis (especially in patients with jaundice)[2]. Nevertheless, the relationship between vitamin D and CLD remains unclear. A strong relationship has been reported in patients having undergone liver transplantation. Low serum vitamin D 25 levels have been correlated with osteoporosis post liver transplantation[29]. However, after the first four months post liver transplantation, bone mass increased and higher serum vitamin D 25 levels were found[30]. Vitamin D deficiency has recently been associated with high activity grade and stage of liver fibrosis in patients with chronic viral hepatitis C; in addition, vitamin D deficiency seems to be a risk factor in patients with no sustained virologic response when treated with peginterferon and ribavirin[31]. In the study by Duarte *et al.*, serum calcium was lower in patients with cirrhosis than non-cirrhotic ones; there was no proven connection between vitamin D deficiency and bone loss in chronic viral hepatitis[32]. Verma *et al.* found that patients with primary biliary cirrhosis presented low spinal and femoral neck BMD and reduced fractional calcium absorption. However, additional studies are necessary to confirm that an increase in fractional calcium absorption may result in increased bone strength in patients with primary biliary cirrhosis[33].

Vitamin K deficiency

Vitamin K has an important role in the production of the bone matrix protein osteocalcin (a protein produced by osteoblast cells). Data have shown that in primary biliary cirrhosis, bone disorders were caused by vitamin K deficiency and that supplementation of vitamin K may prevent bone loss[34].

Insulin-like 1 growth factor deficiency

Osteoblasts and liver produce IGF-1, which is lower in the elderly and CLD patients. There are studies suggesting that low levels of IGF-1 may cause bone disorders, especially in CLD with cholestasis[4,12].

Hyperbilirubinemia

High bilirubin levels are often found in CLD, although the sequels of chronic cholestasis on bone tissue have not yet been established. Ruiz-Gaspa *et al.* studied the effects of bilirubin and serum from patients with jaundice on bone cells. They have reported that

unconjugated bilirubin and serum from these patients affect osteoblast function and cause decreased bone formation, thus possibly contributing to the pathogenesis of HO[35].

Sex hormone deficiency

Normal bone metabolism requires normal sex hormone balance. In cirrhotic postmenopausal women, low levels of luteinizing hormone, follicle-stimulating hormone and estradiol, but normal testosterone levels were found[36]. Deficiency of testosterone is a common factor for bone disorders in men with CLD, especially when liver disease is severe (end stage liver disease) and it is an independent predictor of mortality[37,38].

Receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) system

Inadequate activity of the RANKL/OPG system has been reported. This system includes cytokines that modulate osteoclast activity, since parathyroid hormone (PTH) does not have receptors on this type of cells. Usually, this system works as activating osteoclasts by RANKL (increasing bone resorption) and inhibiting osteoclast activity by osteoprotegerin; osteoprotegerin binds RANKL so that its activating power is stopped (decreasing bone resorption). Thus, any imbalance of this system such as increasing RANKL activity or decreasing osteoprotegerin activity leads to bone disorders (loss of bone mass)[39]. This hypothesis is not yet clearly defined. In their study, Gaudio *et al*. did not confirm the fact that RANKL/OPG system could have a role in HO pathogenesis and they suggest that the increasing levels of osteoprotegerin may represent not only compensation for bone resorption but also a result of the inflammatory process in CLD[38]. Interleukin-6, a cytokine synthesized by osteoblasts, is an osteoclast activating factor. It may also stimulate osteoblasts to produce RANKL and thus promote bone resorption[40]. There are studies which suggest that blockade of IL-6 receptor may lead to inhibition of the osteoclasts both *in vitro* and *in vivo*[5].

Drugs

Glucocorticoid therapy may lead to drug-induced osteoporosis. The usage of glucocorticoids in CLD treatment (autoimmune and chronic cholestatic liver diseases) may accelerate development of osteoporosis. Glucocorticoids alter the balance between osteoclast and osteoblast activity in mineral bone metabolism (induce osteoblast apoptosis and prolong the lifespan of osteoclasts)[41,42].

Other drugs have been reported to interfere with calcium absorption, e.g., diuretics, antibiotics, and non-steroidal anti-inflammatory drugs[43]. The use of benzodiazepine drugs has been found to correlate with fragility fractures in women[26]. Cholestyramine is also a drug that may interfere with bone metabolism because of the adverse effect on the intestinal vitamin D absorption[4].

Regarding antiviral therapy little is known about the effect of the combination of ribavirin plus interferon (IFN) on BMD in patients with chronic hepatitis C, but back pain and bone fractures have been reported[44]. Hofmann *et al*. have reported that BMD increased in patients administered pegylated interferon α and ribavirin, especially in those having achieved sustained virologic response[45]. In their study, Solis-Herruzo *et al*. concluded that in patients with chronic hepatitis C the IFN-α and ribavirin therapy for 12 months could induce bone loss in almost all patients[46]. Redondo-Cerezo *et al*. have reported recently that bone mass improved in hepatitis C patients who responded to antiviral therapy with ribavirin and pegylated IFN-α[47]. The reduction of BMD in hepatitis B patients who received nucleoside (telbivudine, entecavir) and nucleotide (adefovir, tenofovir) analogs has also been studied but there are controversies. In a study of 319 chronic hepatitis B patients, the parameters such as age, gender, and nucleoside and nucleotide analog therapy correlated independently with bone loss[48]. Buti *et al*. have recently shown data on long-term tenofovir disoproxil fumarate treatment in chronic hepatitis B infection, and no significant change in BMD was noticed in 7 years of the study[49]. In another study, the prevalence of bone loss in chronic hepatitis B was similar in patients that were not treated with tenofovir and in those having received tenofovir for 12 months[50]. Still, evaluation of BMD should be performed in patients receiving prolonged tenofovir treatment[51]. Data are also limited about adefovir dipivoxil but lately many cases of osteomalacia due to adefovir treatment have been reported. Tanaka *et al*. have published a case of a patient who received adefovir depivoxil as treatment of lamivudine-resistant hepati-

tis B infection for 5 years and underwent total hip arthroplasty for osteomalacia and pathological hip fracture probably due to this treatment[52]. Reduced BMD may be partially caused by CLD *per se*; also, low BMD may have existed prior to the introduction of antiviral therapy.

Other factors

Tumor necrosis factor (TNF) stimulates bone resorption and may cause bone disorders in patients with CLD[53]. Elevated levels of soluble TNF receptor (sTNFR-55) may also have a role in the pathogenesis of HO[47]. Another factor involved in the pathophysiology of osteoporosis in CLD is leptin, a cytokine produced by adipocytes. Leptin plays a role both in hunger/satiety mechanisms and in bone metabolism. There is a hypothalamic central mechanism of leptin with anti-osteoporotic activity and also a peripheral leptin mechanism of increasing osteoblast proliferation, stimulating bone matrix synthesis and inhibiting RANKL activity[54,55]. Data suggest that leptin levels are associated with BMD loss, especially in patients with primary biliary cirrhosis[56]. Piche *et al*. have reported that high leptin levels are found in patients with chronic hepatitis C and these are correlated with the severity of liver fibrosis[57]. In addition, it has been reported that there is an inverse association between serum leptin levels and BMD in patients with advanced liver disease[58]. Pacifico *et al*. investigated the relationship between BMD and serum adipokines and high sensitivity C reactive protein levels in patients with nonalcoholic fatty liver disease, and found that low grade of systemic inflammation may decrease BMD (high sensitivity protein C was an independent factor associated with bone loss and low Z scores at lumbar spine)[59]. Fibronectin is also a factor involved in bone metabolism. Fibronectin is a protein produced by a variety of cell types including cells of bone and liver. Fibronectin produced by liver goes to blood stream and its concentration is low in malnutrition and severe liver disease. The circulating isoform of fibronectin provided by the liver infiltrates the matrix of bone and increases matrix mineralization without affecting bone function and number of bone cells[60]. An isoform of fibronectin named oncofetal fibronectin has been found in high levels in patients with primary biliary cirrhosis and it mediates bone loss by inhibiting bone formation[61]. Homocysteine is also a player implicated in bone remodeling by increasing osteoclast activity, decreasing osteoblast activity, and it also has a direct effect on the bone matrix[62]. Hyperhomocysteinemia has been reported to be associated with low BMD as an independent risk factor for osteoporosis and osteoporotic fractures[63]. High levels of homocysteine have been found in patients with viral hepatitis C and can be reduced to normal range by standard antiviral therapy with IFN-α and ribavirin[64].

Lifestyle factors

In the pathogenesis of bone disorders due to CLD, behavioral factors such as alcoholism, cigarette smoking, malnutrition, low body mass index (BMI) and sedentary lifestyle have also been studied. Alcohol is an independent risk factor for osteoporosis; the hip fracture risk is 2.8 times higher than normal in alcoholic individuals[1]. Kim *et al*. have reported that chronic alcohol consumption leads to low BMD in the femur Ward's triangle and trochanter[65]. Cigarette smoking is also a risk factor that may be associated with osteoporosis in CLD[16,18,20,66]. In postmenopausal women who have never smoked, passive smoking has been correlated with osteoporosis; also, the severity of lumbar and femoral neck osteoporosis has been positively associated with the number of cigarettes smoked by cohabitant smokers[67]. Low BMI and malnutrition encountered in alcoholics are associated with bone loss, especially in those that have irregular feeding habits[68]. Low BMI has been found to be associated with low BMD in patients with CLD[16,18,66]. In the study by Pinheiro *et al*., 2420 individuals were investigated and sedentary lifestyle was found in women as a risk factor, along with age, family history of hip fracture, early menopause, poor quality of life, diabetes mellitus, use of benzodiazepine drugs, and recurrent falls. In the same study, the risk factors for osteoporosis in men were sedentary lifestyle, current smoking, poor quality of life, and diabetes mellitus[26].

Diagnosis of Hepatic Osteodystrophy

Osteoporosis is a systemic bone disease consisting of low bone mass and micro architectural disorders of bone tissue which leads to bone fragility and bone fractures (fragility fractures)[69]. The gold standard in the diagnosis of HO is assessment of BMD by using DXA at lumbar vertebrae and femoral neck[70]. According to

the World Health Organization (WHO), osteoporosis is defined as T-score less than -2.5 (BMD less than 2.5 standard deviations compared to normal average score of young adults); osteopenia is defined as T-score between -1 and -2.5[70]. In individuals less than 50 years of age, the Z-score is used, which represents BMD of patient compared to mean BMD of age-, race- and sex-matched controls[71]. These ranges refer only to BMD decrease, but there are many individual factors that should be assessed. Because of the individual risk, WHO has developed the Fracture Risk Assessment Tool (FRAX®), an instrument which takes into consideration many individual factors such as clinical factors and BMD at femoral neck. FRAX calculates the probability of hip fracture in ten years and the probability of major osteoporotic fracture (vertebral fractures, hip, humerus, forearm) in ten years[72,73].

In 2002, Collier *et al*. published guidelines for osteoporosis management in patients with CLD[1]. Strong risk factors for osteoporosis require systematic BMD measurements and optimal treatment for prevention of fragility fractures, both in the absence and presence of CLD (associated with one or more risk factors) in every patient (Table 3)[1,6]. Additionally, fragility fractures indicate severe osteoporosis and patients need immediate treatment without BMD scan[1].

In 2003, the American Gastroenterological Association (AGA) published guidelines for osteoporosis in liver and gastrointestinal disease[74]. AGA recommends that vitamin D levels and BMD be assessed in all cirrhotic patients. Patients who have a history of personal fragility fracture, postmenopausal women and patients with long-term glucocorticoid therapy (>3 months) should have BMD evaluation. BMD measurement should also be performed in patients with primary biliary cirrhosis, cirrhosis, and patients undergoing liver transplantation. Patients who have risk factors and normal initial BMD test should be assessed after 2-3 years in order to exclude significant bone loss. A shorter interval for reevaluation of BMD (1 year) is recommended for patients on glucocorticoid therapy initiated recently and in high doses. In patients diagnosed with osteoporosis who have both elevated γ-glutamyltransferase and serum alkaline phosphatase levels, screening for anti-mitochondrial antibodies should be performed because of the underlying cholestatic liver disease (which may have osteoporosis as the first clinical manifestation).

Table 3. Risk factors strongly associated with osteoporosis in the presence or absence of liver disease[1,6]

History of premature maternal hip fracture (<60 years)
Hypogonadism (primary hypogonadism, early menopause (age <45 years), secondary amenorrhea >6 months)
5 mg prednisolone (or equivalent)/day (≥3 months)
Osteopenia evidenced by x-ray scan
Height loss >4 cm
Low body mass index (<19 kg/m^2)

Table 4. Diagnosis of hepatic osteodystrophy

Blood vitamin D level
Blood calcium level
Assessment of risk factors for osteoporosis FRAX calculation – estimates risk fracture in ten years
T-score, Z-score and BMD assessment using DXA

BMD = bone mineral density; DXA=dual energy x-ray absorptiometry; FRAX = WHO Fracture Risk Assessment Tool (FRAX®), http://www.shef.ac.uk/FRAX/?lang=en[73]

The 2003 World Gastroenterology Organization (WGO) Practice Guidelines for osteoporosis in gastrointestinal diseases recommend that repeated DXA scans should be performed at 12- to 18-month intervals[6]. In addition, WGO recommends that fracture risk be assessed individually and decision should be made 'patient-by-patient'. If DXA scan is not available, patients at a high risk may be treated empirically[6].

Considering the high prevalence of HO, every patient with CLD should have complete evaluation of bone mass by detecting vitamin D and blood calcium levels, measuring BMD by DXA, besides using FRAX. The thyroid and gonadal functions should also be evaluated in patients to exclude other forms of osteoporosis (Table 4).

Vitamin D blood level should be determined in HO patients, especially those with possible low levels, for example, those receiving glucocorticoids.

Blood calcium level should be determined in patients with HO in order to exclude other causes of secondary endocrine osteoporosis. Evaluating the risk of osteoporosis at least once in the evolution of CLD should be considered[23]. Patients with T-score less than -2.5 need immediate anti-osteoporotic treatment. De-

tection of T-score values between -1 and -2.5 indicates osteopenia and supplementation of calcium and vitamin D intake is required. In cirrhotic patients with ascites, paracentesis should be performed first, followed by BMD measurements because it has been demonstrated that fluid may erroneously reduce BMD values at lumbar spine during DXA scan[23,75,76].

In patients with bone disorders, bone turnover markers may also be detected; they are products of the bone remodeling process found in the blood and urine of these patients. The most widely used osteogenesis markers are osteocalcin, alkaline phosphatase (bone isoenzyme), procollagen type 1 carboxyterminal propeptide, and procollagen type 1 aminoterminal propeptide. Resorption markers are urinary pyridinoline, deoxypyridinoline, type 1 collagen amino-terminal telopeptide, and hidroxyprolinuria. All these markers are expressed related to urinary creatinine. There is little information in studies about bone turnover markers. In the study by Yenice *et al.*, higher levels of urinary telopeptide were reported in postmenopausal women with chronic hepatitis B than in other groups[77]. Schiefke *et al.* found elevated levels of alkaline phosphatase (bone isoenzyme) to be associated with histologically proven advanced viral chronic hepatitis[9]. So far, there is no consensus regarding their use in clinical practice in CLD patients[1,2,13,77].

Management of Hepatic Osteodystrophy

Data on the management of patients with HO are insufficient and the best algorithm for diagnosis and treatment of patients with HO is individual management of every patient with CLD[1,74]. According to the AGA, the management of osteoporosis in liver disease refers to three categories of patients who need BMD measurements using DXA: patients with CLD plus any of risk factors; patients with CLD undergoing liver transplantation; and patients with CLD and vertebral compression fractures in whom DXA scan is optional at baseline but treatment is mandatory[74].

- For patients with normal T-score (T-score >-1), general prevention measures are recommended; for patients receiving long-term corticosteroid treatment and having normal T-score on DXA scan, both general measures and BMD reevaluation by DXA in one year are necessary.
- For osteopenia (T-score between -1 and -2.5), patients should follow general prevention measures and repeat DXA scan in two years; in patients with long-term glucocorticoid therapy and osteopenia, bisphosphonates should be considered and DXA scan performed in one year.
- Finally, for osteoporotic patients (T-score <-2.5), the recommendations are: general prevention measures, screening for other causes of osteoporosis and considering bisphosphonate therapy, otherwise they should be referred to a bone specialist.

Treatment of Hepatic Osteodystrophy

Treatment of HO patients includes general prevention measures and specific anti-osteoporotic therapy.

General prevention measures

Lifestyle measures involve reducing alcohol consumption, stopping smoking, having regular moderate physical exercise, and avoid falls[1,2]. It is also recommended to limit the use of drugs such as diuretics, glucocorticoids and cholestyramine[78]. Dietary measures refer to appropriate nutrition to avoid malnutrition and low BMI as risk factors for osteoporosis; dietary supplementation of calcium and vitamin D is recommended. The National Osteoporosis Foundation has established that adequate calcium intake is 1200 mg/day or more and vitamin D intake 800 -1000 IU/day; the optimal blood level of 25-hydroxyvitamin D is approximately 30-60 ng/mL[79]. Serum level of 20-30 ng/mL of vitamin D indicates vitamin D insufficiency[80,81].

In their review of vitamin D and CLD, Kitson and Roberts have recommended that vitamin D status be investigated in all patients with CLD; if vitamin D is deficient, supplementation with vitamin D3 in a dose of 1000-1400 IU/day is recommended[82]. In the study by Yurci *et al.*, patients with chronic viral hepatitis and cirrhosis who had reduced T-scores at DXA were treated for one year with different therapeutic regimens; one group of patients was treated only with 400 IU of vitamin D and their T-scores improved in the femoral neck region[83]. So far, the role of calcium and vitamin D supplementation in preventing HO has not been established and clinical trials focused on this issue are required[1,2,74]. However, data are discordant

about optimal doses of vitamin D and calcium and their benefit; it is generally considered that patients with cirrhosis and low BMD should receive calcium and vitamin D supplementation. It is preferable to use parenteral high dose of vitamin D rather than oral low dose of vitamin D, but further research is needed to investigate this approach[84].

Specific anti-osteoporotic therapy

The agents used in osteoporosis treatment so far are hormone replacement therapy (HRT), selective estrogen receptor modulators, bisphosphonates, calcitonin, parathyroid hormone, and a combination of different therapies. The WGO recommends that if these drugs are not available for any reason, then vitamin D intake and sun exposure should be increased; the possibility to add vitamins in the food has also been discussed[6].

Currently, using HRT in HO treatment remains controversial. HRT with estrogens and progesterone is indicated as sequential or continuous combination therapy in women with liver disease and it can be administered orally or transdermally[1,85]. This treatment should be used with caution because of its potential long-term risk to develop breast, gallbladder, endometrium or bladder cancers; however, HRT may have a protective effect against colorectal and liver cancers[6,86]. HRT with testosterone in men without liver disease increased BMD[87]. There are reports on the safety of these drugs in patients with liver disease[85]. These drugs increased BMD by 5% and reduced the risk of fracture by 50%[6]. The impact of HRT on BMD and fracture rate in postmenopausal or hypogonadal women with CLD was investigated in small studies[1]. In patients with primary biliary cirrhosis, HRT improved lumbar spine BMD without impairing cholestasis[88].

Selective estrogen receptor modulators have beneficial effects on BMD at lumbar spine and femoral neck, and decrease vertebral fracture risk in postmenopausal women[2]. Raloxifene improved BMD in osteopenic women with primary biliary cirrhosis[89]. Also, raloxifene proved to be an adjuvant in standard treatment with pegylated IFNα2a and ribavirin in postmenopausal women with chronic hepatitis C[90].

Bisphosphonates are the most widely used drugs in postmenopausal osteoporosis reducing the rate of vertebral/hip fractures and height loss. They are antiresorptive agents that inhibit osteoclast activity and thus stop bone loss[91]. They are also used in preventing glucocorticoid induced osteoporosis. In the study by Yurci *et al.*, patients with chronic viral hepatitis and cirrhosis who had reduced DXA T-scores were treated for one year with different therapeutic regimens; three groups of patients were treated with alendronate 10 mg, alendronate 70 mg and risendronate 5 mg, respectively. T-scores improved significantly in all regions with alendronate 70 mg, and at lumbar spine and distal radius regions with alendronate 10 mg and risendronate 5 mg[83]. Wolfhagen *et al.* have reported that cyclic etidronate seems to prevent osteoporosis induced by prednisone treatment in patients with primary biliary cirrhosis[92]. Cyclic etidronate has also been reported to reduce the incidence of bone fractures in postmenopausal women with chronic hepatitis B and C[93]. Pennisi *et al.* have suggested that pamidronate treatment decreases bone turnover and prevents bone loss after liver transplantation but the effect on bone at 12-month follow-up is limited to trabecular bone and not to cortical bone of the femur[94]. In patients with primary biliary cirrhosis, alendronate has better antiresorptive effect than etidronate[95]. Oral administration of alendronate should be avoided because of the risk of ulceration in esophageal mucosa (especially in cirrhosis patients with esophageal varices in whom variceal hemorrhage may appear). In contrast, risendronate has not been reported to have adverse effect on esophageal mucosa[1,96]. Additionally, in another study, there were no adverse effects, including variceal hemorrhage[83]. Zolendronic acid, another bisphosphonate, has been investigated in the last years and was found to prevent bone loss and reduce bone turnover and fractures in the first year after liver transplantation[97,98].

Currently, bisphosphonates are the most frequently used drugs for the treatment of HO, however, there is little information about their usage in liver diseases[74,78]. They have been labeled as safe and most efficient ones, not only in preventing cortical bone loss but also in preventing trabecular bone loss, especially in chronic viral liver disease[83].

Calcitonin decreases bone loss and vertebral fracture rate in osteoporosis of postmenopausal women[1]. Data on the efficacy of calcitonin in patients with CLD are discordant. Calcitonin and bisphosphonates have been reported to improve vertebral BMD after 12 months of treatment in patients having undergone liver transplantation[99]. In the study by Yurci *et al.*, pa-

tients with chronic viral hepatitis and cirrhosis who had reduced T-scores at DXA were treated with different therapeutic regimens; one patient group was treated with calcitonin 200 IU and their T-scores improved significantly in the lumbar spine region after one-year treatment[83]. In patients with primary biliary cirrhosis, parenteral calcitonin administration had no effective results on bone loss when administered for 6 months[100]. Additionally, 6-month calcitonin therapy had no effect on preventing or reducing bone loss or fractures occurring in the first year of liver transplantation in patients with primary biliary cirrhosis and primary sclerosing cholangitis[101]. So far, this drug has been tested in a small number of studies and it remains as second line therapy after bisphosphonates.

Parathyroid hormone as a human recombinant form may be used to treat osteoporosis. It is administered subcutaneously and has been approved for the treatment of postmenopausal osteoporosis[74]. PTH administration is very expensive and it is used in severe cases of osteoporosis (T-score < -3.5)[6]. Recently, Leder *et al*. studied a novel synthetic peptide analog of PTH related protein named abaloparatide in postmenopausal women with osteoporosis. They concluded that abaloparatide increased BMD at lumbar spine, femoral neck and total hip in a dose dependent manner[102]. There is little information about using PTH in osteoporosis due to liver disease. Recently, Anagnostis *et al*. have published a case of a liver transplant patient with severe osteoporosis who developed *de novo* autoimmune hepatitis after administration of PTH (1-34) and PTH (1-84)[103].

Conclusions

Hepatic osteodystrophy is a common complication in patients with CLD, which has attracted attention of many researchers from this field in the last years. This pathology involves osteoporosis or osteopenia, and sometimes osteomalacia, and may lead to morbidity (bone pain, skeletal deformities, immobilization, and fragility fractures) which affects the quality of life and survival. There are many factors that have been reported in the etiology of HO but the pathogenesis of this type of osteoporosis is still incompletely understood. Bone loss should be assessed in all patients with CLD. The management of bone disorders in CLD has not yet been established because of the lack of large therapeutic interventional trials in this field. Therefore, it is mandatory that the researchers keep their focus on HO in order to define better the pathogenesis, management of fracture risk, and treatment of this complication of CLD.

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Sažetak

JETRENA OSTEODISTROFIJA: GLOBALNI PRE(PO)GLED PROBLEMA

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Jetrena osteodistrofija je česta i nerijetko neliječena komplikacija koja se manifestira kao osteoporoza ili osteopenija, a susreće se u bolesnika s kroničnim bolestima jetre. Ovaj narativni pregled jetrene osteodistrofije preispituje učestalost, patofiziologiju, dijagnostiku i liječenje jetrene osteodistrofije. Proveli smo pretragu medicinske literature u bazama podataka PubMed, Google Scholar, Wiley, Science Direct i Springer Link pomoću prikladnih ključnih riječi kako bismo dobili podatke o niskoj mineralnoj gustoći kosti povezanoj s kroničnim bolestima jetre. Mnoga istraživanja izvještavaju o povećanoj učestalosti osteoporoze/osteopenije u bolesnika s kroničnim jetrenim bolestima. Patogeneza je multifaktorijalna i uključuje genetske čimbenike, pomanjkanje raznih vitamina, proupalne citokine, hipogonadizam, hiperbilirubinemiju, protuvirusnu terapiju, kortikosteroidne lijekove te čimbenike povezane s načinom života. Liječenje ovih bolesnika treba obuhvatiti individualiziranu procjenu čimbenika rizika za prijelome te mineralnu gustoću kosti. Svim bolesnicima s kroničnim bolestima jetre i osteoporozom treba preporučiti uzimanje dodataka vitamina C i kalcija. Bisfosfonati su najučinkovitiji lijekovi za liječenje jetrene osteodistrofije. Potrebno je bolje definirati zbrinjavanje i specifično liječenje jetrene osteodistrofije kako bi se spriječili prijelomi zbog krhkih kosti te poboljšala kvaliteta života ovih bolesnika.

Ključne riječi: *Koštane bolesti, metaboličke – dijagnostika; Koštane bolesti, metaboličke – patofiziologija; Osteoporoza, jetrene bolesti; Učestalost, kost, gustoća; Rizični čimbenici; Prijelomi kosti; Protuvirusna sredstva; Bisfosfonati*