OSTEODYSTROPHY IN CHRONIC LIVER DISEASES

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[L'osteodistrofia nelle malattie croniche di fegato]

SUMMARY

Osteoporosis and osteomalacy are, to date, among the most common metabolic disease in the world.

Recently, association between metabolic bone diseases and chronic liver diseases has been increasingly reported, inducing many authors to create a new nosographic entity known as "hepatic osteodystrophy".

The importance of such a condition is, moreover, further increased by morbidity of these two diseases, which greatly reduce patients quality of life because of frequent fractures, especially vertebral and femoral neck ones. For this, early identification of high-risk patients should be routinely performed by measuring Bone Mass Density.

The explanation for the association between bone diseases and chronic liver disease is still uncertain, and involves many factors: from hypogonadism to use of corticosteroid drugs, from genetic factors to interferon therapy. To date, few studies have been conducted, and all with a small number of patients, in order to establish definitive conclusions about the possible treatment, but some evidences are beginning to emerge about the safety and efficacy of bisphosphonates.

Key words: Osteoporosis, osteomalacy, chronic liver diseases, bisphosphonates

RIASSUNTO

L'osteoporosi e l'osteomalacia sono, ad oggi, fra le malattie metaboliche dell'osso più diffuse al mondo.

Di recente, l'associazione fra malattie metaboliche dell'osso ed epatopatie croniche si è sempre più consolidata, spingendo molti autori a creare una vera e propria nuova entità nosografica, nota come "osteodistrofia epatica".

L'importanza di una simile condizione è, poi, ulteriormente accresciuta dalla morbilità di queste due malattie, che riducono notevolmente la qualità di vita dei pazienti, per le frequenti fratture, specialmente quelle vertebrali e del collo femorale. Per tale motivo, la precoce identificazione dei soggetti a più alto rischio dovrebbe essere eseguita routinariamente, tramite misurazione della densità minerale ossea.

La spiegazione dell'associazione fra malattie metaboliche dell'osso ed epatopatie croniche è ad oggi ancora incerta, e coinvolge molteplici fattori patogenetici: dall'ipogonadismo all'uso dei farmaci corticosteroidi, dai fattori genetici alla terapia con interferoni. Fino ad ora sono stati condotti pochi studi, e tutti con un ridotto numero di pazienti, al fine di trarre conclusioni definitive circa una possibile terapia della malattia, ed alcune evidenze si sono già iniziate a registrare circa la sicurezza e l'efficacia dell'uso dei bisfosfonati.

Parole chiave: *Osteoporosi, osteomalacia, epatopatie croniche, bisfosfonati*

Introduction

Metabolic bone diseases, i.e. osteoporosis and osteomalacy, are frequent complications of patients affected with chronic liver disease, to the point that some authors have coined the term "hepatic osteodystrophy" to mean the complex of structural and metabolic changes of the bone in patients with both cirrhotic and not cirrhotic chronic liver disease[1].

Among these, osteoporosis is particularly important because more frequent than osteomalacy, and often responsible of fractures, which, although most often asymptomatic, contribute, in any case, to morbidity and reduction of patients quality of life.

Unlike vertebral fractures, femoral neck and extremities ones, symptomatic by definition, are less frequent in these patients, because, even in subjects not suffering from chronic liver disease, they occur about 10 years after the former, that is beyond life expectancy of many patients with chronic liver disease[2].

Osteomalacy and chronic liver diseases

Osteomalacy is a metabolic osteopathy characterized by reduced amount of bone mineral content due to lack of mineralization. This osteopathy, which potentially can be found in several pathological conditions, is usually caused by reduced availability or abnormal metabolism of vitamin D[3]. Osteomalacy, although, in the past, has been reported in more than 60% of patients with primary biliary cirrhosis, is currently demonstrated in only a small percentage of patients with chronic liver disease, especially in cholestatic ones[4]. The changes in prevalence of this disease, occurring in recent decades, reflect, probably, the use of different diagnostic criteria, errors in selection of patients included in trials, and nutritional improvements. However, the gold standard for osteomalacy diagnosis is bone biopsy, because not all patients with low serum levels of vitamin D suffer from this metabolic disease[5].

As a matter of fact, vitamin D includes a group of fat-soluble prohormones. The group includes two compounds with very similar biological activity: the cholecalciferol (D3), derived from cholesterol and synthesized in animals, and the ergocalciferol (D2), of vegetable origin. In humans, vitamin D3 is produced by ultraviolet irradiation of the skin from a precursor, 7-dehydrocholesterol, which is in subcorneal layer. Adequate exposure to sunlight grants endogenous production of cholecalciferol able to satisfy the needs of whole organism, so dietary supplement is not necessary. The digestive tract absorption of vitamin D from food sources, animal (D3) or vegetable (D2) follows similar processes employed by other fat-soluble vitamins. As a matter of fact, it is incorporated into the micelles, formed by interaction between hydrolyzed lipids and bile, cross the intestinal epithelium, and finally it is incorporated in chylomicrons, which, in turn, enter the lymphatic circulation.

In various tissues, especially in the liver, hydroxylation of cholecalciferol produce 25-hydroxycholecalciferol (25-OHD), which then passes into general circulation, and interacts with a specific transport protein (vitamin D binding protein, DBP), synthesized by the liver. In the kidney, the 25-OHD may undergo to two different hydroxylation reactions, caused by different hydroxylase, 1-hydroxylase and 24-hydroxylase, generating, respectively, 1,25-dihydroxycholecalciferol (1,25-OHD), the active form of D-vitamin, and 24,25-dihydroxycholecalciferol (24,25-OHD), the inactive form[6]. As liver is involved in production of bile, vitamin D3 absorption (fat-soluble vitamin) and blood transport, through the DBP synthesis, and 25-hydroxylation, which produces 25-OHD, it would be easy to assume a high prevalence of osteomalacy in patients suffering from chronic liver disease, not confirmed, as mentioned above, in late years[7].

In fact, adults obtain most of their vitamin D3 from cutaneous photoconversion of 7-dehydrocholesterol, and patients with cholestasis seem to have normal skin photoconversion processes. In addition, intestinal vitamin D3 absorption is altered only in presence of a severe cholestasis. The succeeding 25-hepatic vitamin D3 hydroxylation has so far been little studied in human, but in experimental animals, with severe cholestasis, does not seem impaired. In any case, about 2/3 of patients with liver cirrhosis and 96% of terminal cirrhotic patients waiting for liver transplant present with low serum levels of vitamin D3, without, however, demonstrated osteomalacy[8].

Osteoporosis and chronic liver diseases

Osteoporosis, as known, is defined as a value of Bone Mineral Density (BMD), measured by Dual-Energy X-ray absorptiometry (DEXA), less than 2.5 standard deviations below the average of a young adult population control bone mass peak (corresponding to the normal bone mass peak) (T score -2.5). Although the risk of fractures increases gradually with BMD decreasing, other clinical risk factors for fractures have been identified, all independent from BMD, such as advanced age, menopause, Body Mass Index (BMI) <19 kg/m2 (expression of malnutrition or poor nutrition), alcohol intake >3 units/day (1 unit = 8g alcohol), an oral corticosteroid therapy >5 mg/day for at least 3 months, previous fragility fractures, and a maternal history of hip fracture. Most important of these independent risk factors is represented by previous fragility fractures. Once a vertebral fracture occurred, the risk of further vertebral fracture increased by 10 times, while risk of a subsequent hip fracture increase of 2.3 times[9].

In patients affected with chronic liver disease it's possible to find out many of these risk factors, including hypogonadism, malnutrition, excessive alcohol intake and use corticosteroid drugs (e.g. treatment of autoimmune liver diseases, as primary biliary cirrhosis and primary sclerosing cholangi-

tis), and, in addition, many patients with primary biliary cirrhosis are, by definition, postmenopausal women. Contrariwise, it is still questionable if liver cirrhosis and cholestasis are, themselves, independent risk factors for osteoporosis, since this topic has been yet no completely studied[10].

As testosterone is metabolized to estrogen, long duration hypogonadism, in men, is associated with a reduction of circulating estrogens and consequent reduced bone turnover, with decreased osteosinthesis, nevertheless reversible, with adequate hormone replacement therapy.

Hypogonadism, measured via free serum testosterone levels dosage, was described in almost 3/4 of patients with cirrhosis awaiting liver transplant, but did not appear related to the aetiology of cirrhosis (see below)[11]. Excessive alcohol intake, as well, is an independent risk factor for osteoporosis. Alcohol intake seems to inversely correlate with BMD. Alcoholism, a characteristic of many patients with chronic liver disease, in turn, is associated with reduced testosterone serum levels, which may contribute, by hypogonadism, to determine osteoporosis in these patients, and with low vitamin D3 serum levels[12].

The role of hypogonadism in liver cirrhosis

Among osteodystrophy pathogenic mechanisms in chronic liver disease, a particularly important role has certainly hypogonadism. Absolute testosterone low levels and estrogens relative increase point out hypogonadism in men with liver cirrhosis. Advanced liver disease is characterized by this anomaly, as evidenced by a study that showed levels of circulating free testosterone lower in men with liver cirrhosis, than in non-cirrhotic controls (0.11+0.02 vs. 0.22+0.03 nmol/L)[13].

Frequency with which low free testosterone levels is observed appears to be extremely high, up to 100% of patients studied[14]. Reduction of testosterone levels depends on a lower gonadal production, which is dependent, at least in part, by alteration of sensitivity of the hypothalamic-pituitary-gonadal axis. Several other factors contribute to abnormalities of estrogens/testosterone ratio in cirrhotic patients. Among them, alteration of testosterone production circadian rhythm[15] and reduced hepatic uptake of sex hormones, which normally "covers" 20-50% of their physiological clearance. Finally, a role is played by alteration of hypothalamic regulation: as a matter of fact, patients affected with liver cirrhosis show LH and FSH levels only slightly increased, but certainly not high as expect because of severe lack of circulating sex hormones[16]. Since endocrine alterations described above play heavy clinical role in male, it is clear that most of studies on this aspect have been conducted in cirrhotic males. However, limited data, obtained in female patients with cirrhosis, show that levels of testosterone, LH and FSH were significantly reduced[17]. In young women with liver cirrhosis, these hormonal changes can lead to secondary amenorrhea[18], emphasizing the link between osteoporosis and liver disease.

Measurement of BMD in patients with chronic liver disease: who and when?

Despite some differences, most of guidelines and recommendations agree about timing of DEXA determinations in chronic liver disease patients: in every menopause patient or, if male, in subject with more than 50 years of age, and/or if suffering from hypogonadism, and/or if treated with corticosteroids for long term period, and/or if reports history of fragility fractures. In all these cases, if an osteoporosis framework is diagnosed, a medical treatment should be immediately started[19,20].

BMD should be measured in patients with liver cirrhosis too, both in biliary and in non-biliary one, before hepatic transplant. Indications to BMD measurement are less clear in patients with cholestatic liver disease, not waiting for transplant. For example, the guidelines of the American Gastroenterological Association suggests that BMD should be measured in all patients with primary biliary cirrhosis at diagnosis time, while others recommendations suggests BMD measurement only in cholestatic patients with bilirubin greater than 3 times the upper limit of normal range[19,20].

Frequency of BMD measurements is still debated. In absence of osteoporosis, but in presence of risk factors for the disease, there is probably no need to repeat BMD measurement more often than once every 2-3 years. Contrariwise, patients who received or receive high corticosteroids doses might be re-evaluated once a year. Considering, then, that osteoporosis may also be first clinical manifestations of an underlying cholestatic liver disease, it is advisable to screen for anti-mitochondrial antibodies all osteoporotic patients with low BMD and high cholestasis markers (gamma-glytamyl transpeptidase, γ-GT and alkaline phosphatase).

Finally, it seems there are no indication to routine measurements of serum and urinary markers of bone turnover neither to stratify fractures risk, nor to assess deterioration of bone health during follow-up[19,20].

Pathophysiology of osteoporosis in chronic liver diseases

As above mentioned, sex hormone changes probably account for a mainly role in pathophysiology of osteoporosis in cirrhosis. In general, however, biological mechanisms underlying osteoporosis of patients with chronic liver diseases are complex and nowadays slightly understood, and include, perhaps, also genetic and acquired factors. Among the former, it must be consider collagen 1α1, vitamin D receptor, estrogen receptor and LRP5 (low density lipoprotein receptor-binding protein 5) genes, but their polymorphism has not yet been associated with an increased, specific, fractures risk, even in patients without chronic liver disease[21]. Bone loss, subsequent to bone mass peak overtaking, can be explained looking at a possible, acquired, dissociation between bone formation and resorption. Increase in osteoclasts activity, resulting in enhanced bone resorption, is mediated by osteoclastogenic pro-inflammatory cytokine, such as IL-1 and TNF, often involved both in hepatic inflammation and fibrosis.

Lately, receptor activator of NF-kβ (RANK) protein and RANK ligand (RANKL), in addition to osteoprotegerin (OPG), have been involved in osteoclastic bone resorption mechanisms in patients with no hepatic osteoporosis, while assessment of their involvement, in chronic liver disease patients, has, so far, produced contradictory results[22].

Contrariwise, reduction of bone formation, observed in patients with chronic liver disease, was associated with low serum levels of insulin-like growth factor-1 (IGF-1), a protein known to be involved in bone remodelling and maintenance of bone mass[23].

A clear association between IGF-1 serum levels and osteoporosis, in chronic liver disease in human, has not been, however, still clearly demonstrated[24]. Vitamin K is also involved in bone metabolism, by carboxylation of glutamic acid residues of bone proteins, such as osteocalcin, but there are, still, no literature data about vitamin K deficiency role in osteoporosis pathogenesis in hepatic diseases[25].

Finally, although indirect (unconjugated) bilirubin inhibits the activity of osteoblasts and their function, both in vitro and in animal models, in vivo studies, conducted in patients with chronic liver disease, showed no correlation between total, direct and indirect bilirubin levels and BMD[26].

Prevalence of osteoporosis in chronic liver diseases

Cirrhosis

Several studies conducted over the past two decades demonstrated that prevalence of osteoporosis in patients with liver cirrhosis, albeit with wide variability among the studies, is around 33%. These differences in prevalence reflect, probably, differences in age, etiology and severity of liver disease, nutritional status (expressed as BMI), and in hypogonadism status of studied patients. In all cases, liver cirrhosis seems to increase the risk of fractures by about 2 times[27].

Biliary Diseases

The etiologic relationship between primary biliary cirrhosis and osteoporosis have been, especially in the past, very controversial, because patients suffering from this disease are classically menopausal women, themselves, therefore, at high risk of osteoporosis. However, more recent studies confirmed a substantially increased osteoporosis and fractures risk in this particular group of patients compared with age-matched healthy controls, with a prevalence of 43% for osteoporosis and 22% for fractures[28].

In primary sclerosing cholangitis prevalence of osteoporosis stands at 20.3%, with wide variability among the studies, while risk of fracture, approximately 15%, correlates with increasing age, more advanced biliary disease and duration of a coexisting and associated inflammatory bowel disease[29].

Other liver chronic diseases

There are some reports of increased prevalence of osteoporosis and fractures in patients with no cirrhosis or biliary liver chronic diseases, such as chronic hepatitis, and those undergoing liver transplant.

Viral hepatitis

In a recent study, BMD was low in patients with chronic non-cirrhotic h¬epatopathy, suffering from chronic viral infection by hepatitis C virus. The study, however, did not describe any control

group and there were no details about alcoholic intake of patients[30].

A possible negative effect of ribavirin and interferon therapy, used in the treatment of patients with HCV-related chronic active hepatitis, on BMD of these subjects, initially showed in some studies, it was not lately confirmed. Interferon reduces markers of bone turnover and appears to inhibit formation of osteoblasts, while ribavirin osteoporizing mechanisms are totally unknown[31].

Liver transplant

Patients who underwent liver transplant, showed post-transplant high prevalence of osteoporosis and fractures. As long-time survival of these patients is known to be considerably increased in recent years, osteoporosis has become a major cause of their co-morbidity[32]. Etiology of this metabolic disorder is multifactorial, and risk factors contributing to it are both pre-transplant and post-transplant ones. Among pre-transplant risk factors, pre-transplant fragility fracture is more predictive for post-transplant recurrent fractures compared to the simple values of BMD. However, BMD measurement, of course, is also crucial in these patients, cause low BMD values, before and after transplant, was, however, associated with a higher frequency of fractures. Furthermore, there is large consensus about effects of age (>45 for women, >65 for men), gender (female, although some studies showed an increased susceptibility to osteoporosis and fractures of male patients), menopausal status (postmenopausal), type of pre-transplant liver disease (increased risk for alcohol-related and/or cholestatic disorders?), and exposure to corticosteroids in the pre-transplant phase, on osteoporosis and fractures risk in post-transplant patients. Other pre-transplant factors, for which there is no unanimous consensus, in regard themselves as risk factors for post-transplant osteoporosis and fractures, are 25-OHD, PTH serum levels, bone turnover markers, and biochemical parameters of liver function (with reference also to the Child-Pugh class of membership, with class C at greater risk of osteoporosis than class A) and kidney[33,34].

Among post-transplant factors, however, the most important is represented by acute osteopenia that occurs immediately after transplant, with a significant decrease of BMD in the first 3 months, and a return to pre-transplant values only after about 2 years. Therefore, it was reported a frequency of fragility fractures, from minor trauma or apparently non-traumatic ones, both vertebral, symptomatic or not, and non-vertebral, femoral and/or of extremities, of about 21%, most of which within first 2 years after transplant.

Unlike pre-transplant fracture, most of post-transplant ones seem to be symptomatic, and, most commonly, vertebral ones, followed by rib ones, with a minor prevalence of hip and extremities ones, probably because predominantly cortical bone sites are, in fact, less susceptible to osteoporotic fractures compared with trabecular ones[35,36]. Use of high doses of corticosteroids and other immunosuppressive agents, such as cyclosporine A and tacrolimus, immobility and poor nutrition, probably, all contribute to cause rapid bone loss of immediate post-operative period of these patients[36].

Cumulative steroid doses, administered in early post-transplant, and, in this delicate phase, at particularly high dosage, has been repeatedly implicated in pathogenesis of acute bone loss observed in these patients, while current use of lower steroids doses after transplant, as shorter time of hospitalization and immobilization, explain, probably, the sharp reduction of osteoporosis and fractures frequency in post-transplant observed in the last decade and reported in several studies[37].

In contrast, effects of calcineurin inhibitors (e.g. tacrolimus), administered after liver transplant as anti-rejection drugs, on bone turnover are still controversy, as it is difficult to separate possible bone loss effects of these drugs than those of corticosteroids drugs, associated, generally, in anti-rejection treatment regimens. However, it seems that patients treated with tacrolimus had an earlier recovery of mineral content and trabecular bone structure compared to patients taking cyclosporine A, but effects of both on bone loss in early post-transplant remain unclear. Both, however, seem to increase turnover and bone resorption, cyclosporine, perhaps, more than tacrolimus[38]. However, post-transplant variables that do not seem to have any effect on prevalence of fractures after intervention are: waiting time before the procedure, hospitalization length, immunosuppressive doses used, both daily and cumulative, and episodes of organ rejection[39].

Treatment of osteoporosis in chronic liver diseases

Current recommendations suggest starting osteoporosis treatment in all patients affected with

liver chronic disease, especially if aged >65 years, and/or if 7.5 mg or more of steroid drugs are required daily for more than three months, although it is probable an increased osteoporotic risk for lower steroid doses too. In younger patients, suffering from chronic liver disease, treatment is indicated if BMD shows T-score values of -2.5[19,20].

Although serum and urine markers of bone turnover have been used in the assessment and treatment monitoring of patients affected with postmenopausal osteoporosis, there are few studies about their use in osteoporotic patients with chronic liver diseases, and, actually, they should not be routinely indicated in this patients subgroup[40]. Treatment of osteoporosis in patients with chronic liver diseases is based, essentially, on results of large trials conducted in women with postmenopausal osteoporosis.

Contrariwise, there are, to date, only few, small studies specifically conducted in patients with chronic liver diseases, particularly affected with primary biliary cirrhosis, that, moreover, considered, as primary outcome, the BMD increase rather than frequency reduction of fragility fractures[41].

Vitamin D and calcium

Vitamin D and calcium supplementation has been shown to be efficient in reducing fractures in elderly patients housed in protected residences. Consequently, all patients included in evaluation trials of other kinds of treatment of osteoporosis are regularly treated with vitamin D and calcium too, usually 400-800IU of vitamin D and 1000-1200mg of elemental calcium per day. However, there are very few studies on effectiveness of supplementation with vitamin D and calcium and their optimal dose and formulation in patients with chronic liver diseases but, in any case, vitamin D deficiency should be corrected to obtain a 25-OHD serum values of at least 25-30 ng/mL. In patients with documented associated malabsorption, will be used vitamin D higher doses (42).

Bisphosphonates

Bisphosphonates (alendronate, etidronate, ibandronate, and risidronate), drugs acting via inhibition of bone resorption, were all used in treatment of post-menopausal osteoporosis, most often in combination with vitamin D and calcium[43]. There are, however, very few studies about their use in patients with cirrhosis, especially with primary biliary cirrhosis, and, due to this reason, data about their safety and effectiveness are still inadequate. In patients with primary biliary cirrhosis, alendronate, more than etidronate, seems to increase bone mass and BMD and improve markers of bone turnover, while it seems to show no reduction in fractures incidence[44]. Complications from esophageal daily administration of alendronate were never observed, although other studies, also conducted in patients with primary biliary cirrhosis, suggest that alendronate is better tolerated when administered once a week, rather than daily[45]. In patients affected with non-biliary cirrhosis, bisphosphonates seem, overall, well tolerated in weekly administration, although they must be used with care in patients with a recent history of bleeding and/or with esophageal sclerotherapy, but these studies were carried out on too small series to make judgments about their effectiveness in this different context[46].

Bisphosphonates have also been used in some small studies in patients undergoing liver transplant, to reduce incidence of fractures after surgery. Most of them used intravenous pamidronate, obtaining variable results, from a fractures reduction to a BMD rising without change in the incidence of fractures, to neither fracture reduction nor BMD rising. Failure in detection of protective effect of this drug against fracture, found in some of these studies, may reflect, however, only the size of evaluated sample, whereas overall decrease of fractures was observed in post-transplant during the last 20 years[10]. In this context, it is important to take care of a particular side effect of bisphosphonate therapy, which is osteonecrosis of the jaw. Most of reported cases involved oncologic patients treated with intravenous pamidronate or zoledronic acid, but it has been reported even in patients without cancer in oral treatment. About 2/3 of cases occurred after tooth extraction. It is not absolutely known relevance and prevalence of this adverse reaction in patients with chronic liver disease[47].

Other treatments

Hormone replacement therapy

Hormone replacement therapy (HRT) is actually a second-line choice therapy for osteoporosis treatment, due to evidence of an increased risk of thromboembolic and gynecologic malignant neoplasm. However, it may be administered with safety in patients with chronic liver diseases, especially in pre-menopausal women with documented hypogonadism or in early menopause (before 45 years),

usually transdermal in order to increase BMD (48). Therefore, there are only few little studies about the effect of HRT on osteoporosis, especially due to uneasy recruiting of women in trials of this kind, highlighted, also, by high drop-out rate from treatment, and it was not, then, possible to select a sufficiently high number of patients to evidence a positive effect of treatment on osteoporosis, including fractures[49].

Raloxifene

Raloxifene is an estrogen receptor modulator, which has been shown to reduce frequency of vertebral fractures in women with postmenopausal osteoporosis. Contrariwise, it does not seem to affect the frequency of femoral fractures. Currently, there are few data on its safety and efficacy in osteoporotic patients with chronic liver diseases[50].

Testosterone

Hypogonadic male patients suffering from chronic liver diseases may be treated with transdermal testosterone, as treatment normalizes hormone values, without rapid increase of its serum levels, as caused, instead, after oral or controlled release administration. Currently, there are few data about its safety and efficacy in osteoporotic patients affected with chronic liver diseases. By the way, a limit to this kind of treatment it could be the increased risk to develop an hepatocellular carcinoma.

Strontium ranelate

Strontium ranelate is a reducing non-vertebral and vertebral fractures drug successfully used in patients with post-menopausal osteoporosis. Its mechanism of action is not well-known, and, to date, there are no studies on its efficacy and safety in patients with chronic liver disease, especially in intolerant to bisphosphonates ones[52].

Recombinant PTH

Recombinant PTH was used for secondary prevention of fragility fractures in women with post-menopausal osteoporosis, intolerant to bisphosphonate. It works rising bone synthesis. To date, there are no studies on its safety and efficacy in patients with chronic liver diseases[53].

Conclusions

Osteoporosis is the most important form of liver osteodystrophy, often clinically evident and, therefore, underdiagnosed. Despite a decline of osteoporosis incidence in last 20 years in patients with end stage chronic liver disease, a large rate of patients waiting for liver transplant is affected with osteoporosis, and many of them have already had fractures. It is important to identify these individuals, cause pre-transplant fractures increase risk of post-transplant ones, while fracture, whenever occurred, are associated to a great morbidity, even in non-transplanted cirrhotic patients. Identification of patients with chronic liver disease at high risk of osteoporosis and fractures contemplate BMD measurement, although it should be carefully considered other clinical risk factors. Evidence of beneficial effect of osteoporosis treatment in these particular patients, however, is still, mainly, based on extensive studies conducted in women with postmenopausal osteoporosis, being, to date, just few and with no appropriate number of subjects studies on patients with chronic liver diseases.

In particular, bisphosphonates appear to improve BMD and to be well tolerated, but studies in this regard are too small to show a real beneficial effect, even on the fractures frequency.

References

1) Rouillard S, Lane NE. *Hepatic osteodystrophy*. Hepatology 2001; 33: *301-7*.
2) Sanchez AJ, Aranda-Michel J. *Liver disease and osteoporosis*. Nutr Clin Pract. 2006; 21: *273-8*.
3) Pappa HM, Bern E, Kamin D, Grand RJ. *Vitamin D status in gastrointestinal and liver disease*. Curr Opin Gastroenterol 2008; 24: *176-83*.
4) Guichelaar MM, Malinchoc M, Sibonga J, Clarke BL, Hay JE. *Immunosuppressive and postoperative effects of orthotopic liver transplant on bone metabolism*. Liver Transpl 2004; 10: *638-47*.
5) Jones G, Horst R, Carter G, Makin HLj. *Contemporary diagnosis and treatment of vitamin D-related disorders*. J Bone Miner Res 2007; 22(Suppl 2): V11-5.
6) Christakos S, Dhawan P, Liu Y, Peng X, Porta A. *New insights into the mechanisms of vitamin D action*. J Cell Biochem 2003; 88: *695-705*.
7) Wills MR, Savory J. *Vitamin D metabolism and chronic liver disease*. Ann Clin Lab Sci 1984; 14: *189-97*.
8) Cabré E, Gassull MA. *Nutritional and metabolic issues in cirrhosis and liver transplant*. Curr Opin Clin Nutr Metab Care 2000; 3: *345-54*.
9) Dontas IA, Yiannakopoulos CK. *Risk factors and prevention of osteoporosis-related fractures*. J Musculoskelet Neuronal Interact 2007; 7: *268-72*.
10) Collier J. *Bone disorders in chronic liver disease*. Hepatology 2007; 46: *1271-8*.
11) Zietz B, Lock G, Plach B, Drobnik W, Grossmann J, Schölmerich J, Straub RH. *Dysfunction of the hypotha-*

lamic-pituitary-glandular axes and relation to Child-Pugh classification in male patients with alcoholic and virus-related cirrhosis. Eur J Gastroenterol Hepatol 2003; 15: *495-501*.

12) Santori C, Ceccanti M, Diacinti D, Attilia ML, Toppo L, D'Erasmo E, Romagnoli E, Mascia ML, Cipriani C, Prastaro A, Carnevale V, Minisola S. *Skeletal turnover, bone mineral density, and fractures in male chronic abusers of alcohol*. J Endocrinol Invest 2008; 31: *321-6*.

13) Cavanaugh J, Niewoehner CB, Nuttall FQ. *Gynecomastia and cirrhosis of the liver*. Arch Intern Med 1990; 150: *563-5*.

14) Madersbacher S, Ludvik G, Stulnig T, Grünberger T, Maier U. *The impact of liver transplant on endocrine status in men*. Clin Endocrinol 1996; 44: *461-6*.

15) Martínez-Riera A, Santolaria-Fernández F, González Reimers E, Milena A, Gómez-Sirvent JL, Rodríguez-Moreno F, González-Martín I, Rodríguez-Rodríguez E. *Alcoholic hypogonadism: hormonal response to clomiphene*. Alcohol 1995; 12: *581-7*.

16) Handelsman DJ, Strasser S, McDonald JA, Conway AJ, McCaughan GW. *Hypothalamic-pituitary-testicular function in end-stage non-alcoholic liver disease before and after liver transplant*. Clin Endocrinol 1995; 43: *331-7*.

17) Gavaler JS, Van Thiel DH. *Hormonal status of postmenopausal women with alcohol-induced cirrhosis: further findings and a review of the literature*. Hepatology 1992; 16: *312-9*.

18) Bell H, Raknerud N, Falch JA, Haug E. *Inappropriately low levels of gonadotrophins in amenorrhoeic women with alcoholic and non alcoholic cirrhosis*. Eur J Endocrinol. 1995;132: *444-9*.

19) Collier JD, Ninkovic M, Compston JE. *Guidelines on the management of osteoporosis associated with chronic liver disease*. Gut 2002; 50(Suppl 1): i1-9.

20) Leslie WD, Bernstein CN, Leboff MS; American Gastroenterological Association Clinical Practice Commitee. *AGA technical review on osteoporosis in hepatic disorders*. Gastroenterology 2003; 125: *941-66*.

21) Williams FM, Spector TD. *The genetics of osteoporosis*. Acta Reumatol Port 2007; 32: *231-40*.

22) Moschen AR, Kaser A, Stadlmann S, Millonig G, Kaser S, Mühllechner P, Habior A, Graziadei I, Vogel W, Tilg H. *The RANKL/OPG system and bone mineral density in patients with chronic liver disease*. J Hepatol 2005; 43: *973-83*.

23) Gallego-Rojo FJ, Gonzalez-Calvin JL, Muñoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. *Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis*. Hepatology 1998; 28: *695-9*.

24) Cemborain A, Castilla-Cortázar I, García M, Quiroga J, Muguerza B, Picardi A, Santidrián S, Prieto J. *Osteopenia in rats with liver cirrhosis: beneficial effects of IGF-1 treatment*. J Hepatol 1998; 28: *122-31*.

25) Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. *Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials*. Arch Intern Med 2006; 166: *1256-61*.

26) Smith DL, Shire NJ, Watts NB, Schmitter T, Szabo G, Zucker SD. *Hyperbilirubinemia is not a major contributing factor to altered bone mineral density in patients with chronic liver disease*. J Clin Densitom 2006; 9: *105-13*.

27) Ninkovic M, Skingle SJ, Bearcroft PW, Bishop N, Alexander GJ, Compston JE. *Incidence of vertebral fractures in the first three months after orthotopic liver transplant*. Eur J Gastroenterol Hepatol 2000; 12: *931-5*.

28) Solaymani-Dodaran M, Card TR, Aithal GP, West J. *Fracture risk in people with primary biliary cirrhosis: a population-based cohort study*. Gastroenterology 2006; 131: *1752-7*.

29) Angulo P, Therneau TM, Jorgensen A, DeSotel CK, Egan KS, Dickson ER, Hay JE, Lindor KD. *Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression*. J Hepatol 1998; 29: *729-35*.

30) Schiefke I, Fach A, Wiedmann M, Aretin AV, Schenker E, Borte G, Wiese M, Moessner J. *Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic chronic hepatitis B or C infection*. World J Gastroenterol 2005; 11: *1843-7*.

31) Solís-Herruzo JA, Castellano G, Fernández I, Muñoz R, Hawkins F. *Decreased bone mineral density after therapy with alpha interferon in combination with ribavirin for chronic hepatitis C*. J Hepatol 2000; 33: *812-7*.

32) Meys E, Fontanges E, Fourcade N, Thomasson A, Pouyet M, Del-mas PD. *Bone loss after orthotopic liver transplant*. Am J Med 1994; 97: *445-50*.

33) Guichelaar MM, Kendall R, Malinchoc M, Hay JE. *Bone mineral density before and after OLT: long-term follow-up and predictive factors*. Liver Transpl 2006; 12: *1390-402*.

34) Segal E, Baruch Y, Kramsky R, Raz B, Tamir A, Ish-Shalom S. *Predominant factors associated with bone loss in liver transplant patients - after prolonged post-transplant period*. Clin Transplant 2003; 17: *13-9*.

35) Monegal A, Navasa M, Guañabens N, Peris P, Pons F, Martinez de Osaba MJ, Rimola A, Rodés J, Muñoz-Gómez J. *Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplant*. Calcif Tissue Int 1997; 60: *148-54*.

36) Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. *Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors*. Hepatology 2007; 46: *1198-207*.

37) Adachi JD. *Corticosteroid-induced osteoporosis*. Int J Fertil Womens Med 2001; 46: *190-205*.

38) Encke J, Uhl W, Stremmel W, Sauer P. Immunosuppression and modulation in liver transplant. Nephrol Dial Transplant 2004; 19 (Suppl 4): iv22-5.

39) Leidig-Bruckner G, Hosch S, Dodidou P, Ritschel D, Conradt C, Klose C, Otto G, Lange R, Theilmann L, Zimmerman R, Pritsch M, Ziegler R. *Frequency and predictors of osteoporotic fractures after cardiac or liver transplant: a follow-up study.* Lancet 2001; 357: *342-7*.

40) Uretmen S, Gol M, Cimrin D, Irmak E. *Effects of chronic liver disease on bone mineral density and bone metabolism markers in postmenopausal women*. Eur J Obstet Gynecol Reprod Biol 2005; 123: 67-71.

41) Grey A. *Emerging pharmacologic therapies for osteoporosis*. Expert Opin Emerg Drugs 2007; 12: *493-508*.

42) Crawford BA, Labio ED, Strasser SI, McCaughan GW. *Vitamin D replacement for cirrhosis-related bone*

*disea*se. Nat Clin Pract Gastroenterol Hepatol 2006; 3: *689-99*.

43) Lambrinoudaki I, Christodoulakos G, Botsis D. *Bisphosphonates*. Ann N Y Acad Sci 2006; 1092: *397-402*.

44) Guañabens N, Parés A, Ros I, Alvarez L, Pons F, Caballería L, Monegal A, Martínez de Osaba MJ, Roca M, Peris P, Rodés J. *Alendronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis*. Am J Gastroenterol 2003; 98: *2268-74*.

45) Zein CO, Jorgensen RA, Clarke B, Wenger DE, Keach JC, Angulo P, Lindor KD. *Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial*. Hepatology 2005; 42: *762-71*.

46) Owens G, Jackson R, Lewiecki EM. *An integrated approach: bisphosphonate management for the treatment of osteoporosis*. Am J Manag Care 2007; 13(Suppl 11): S290-*308*.

47) Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. *A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics*. Clin Ther 2007; 29: *1548-58*.

48) Pereira SP, O'Donohue J, Moniz C, Phillips MG, Abraha H, Buxton-Thomas M, Williams R. *Transdermal hormone replacement therapy improves vertebral bone density in primary biliary cirrhosis: results of a 1-year controlled trial*. Aliment Pharmacol Ther 2004 19: *563-70*.

49) Boone RH, Cheung AM, Girlan LM, Heathcote EJ. *Osteoporosis in primary biliary cirrhosis: a randomized trial of the efficacy and feasibility of estrogen/progestin*. Dig Dis Sci 2006; 51: *1103-12*.

50) Levy C, Harnois DM, Angulo P, Jorgensen R, Lindor KD. *Raloxifene improves bone mass in osteopenic women with primary biliary cirrhosis: results of a pilot study*. Liver Int 2005; 25: *117-21*.

51) Tracz MJ, Sideras K, Boloña ER, Haddad RM, Kennedy CC, Uraga MV, Caples SM, Erwin PJ, Montori VM. *Testosterone use in men and its effects on bone health. A systematic review and metaanalysis of randomized placebo-controlled trials*. J Clin Endocrinol Metab 2006; 91: *2011-6*.

52) Blake GM, Fogelman I. *Strontium ranelate: a novel treatment for postmenopausal osteoporosis: a review of safety and efficacy*. Clin Interv Aging 2006; 1: *367-75*.

53) Girotra M, Rubin MR, Bilezikian JP. *The use of parathyroid hormone in the treatment of osteoporosis*. Rev Endocr Metab Disord 2006; 7: *113-21*.

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