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Case Report

# Multiple vertebral fractures in a liver transplant recipient with HCV cirrhosis: A case report

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**Abstract**

Cirrhosis is a known major risk factor for osteoporosis. The already compromised bone health of cirrhotic patients tends to deteriorate further after liver transplantation, mainly as a result of immunosuppressive treatment. This case report describes a 63-year-old man who presented with multiple vertebral fractures and severe osteoporosis, one year after orthotopic liver transplantation (OLT) because of end-stage HCV cirrhosis. At his initial consultation, the patient was taking everolimus and mycophenolate, while previously the immunosuppressive regimen included corticosteroids. We present follow-up data of the patient after anti-osteoporotic treatment, including consecutive measurements of bone mineral density, vertebral morphometry, biomarkers of bone turnover and related hormones. Two years after OLT, during which he followed treatment with calcium, vitamin D supplements and zolendronic acid (intravenous infusion of 5mg once a year), the patient showed remarkable improvement in bone densitometry, hormones and biomarkers of bone metabolism, with the exception of persistent secondary hyperparathyroidism. As the survival rates of liver transplant recipients improve, osteoporosis constitutes an important long-term complication among these patients. Consequently, prompt diagnosis and treatment of osteoporosis in cirrhotic and liver transplanted patients is crucial, with biphosphonates, and in particular zolendronic acid, a potent possible first-line therapeutical option.

**Keywords:** HCV cirrhosis, Orthotopic liver transplantation, Osteoporosis, Multiple vertebral fractures, Zolendronic acid

## Introduction

Osteoporosis is a common, under-diagnosed and poorly treated complication of liver cirrhosis. The prevalence of osteoporosis in patients awaiting liver transplantation ranges from 12 to 55% and the prevalence of fractures is up to 22%[1], depending on the etiology of cirrhosis, the degree of liver insufficiency and the presence of additional predisposing factors, such as chronic cholestasis or use of corticoids. Overall, the fracture risk is estimated as double in cirrhotic patients compared to healthy individuals[1]. In patients that undergo orthotopic liver transplantation (OLT), the pre-existing osteoporosis aggravates, mainly due to the immunosuppressive treatment with glucocorticoids and calcineurin inhibitors. The prevalence of bone disease after liver transplantations reaches 25% , and 15-30% of liver transplant recipients develop fractures shortly after the OLT, mainly vertebral ones[1,2]. Improved survival rates of transplanted patients and the increased number of transplantations performed nowadays, have turned osteoporosis and its complications into an important cause of morbidity and mortality among this population.

## Case report

A 63-year-old liver transplant recipient, with a background of end-stage HCV related cirrhosis, presented

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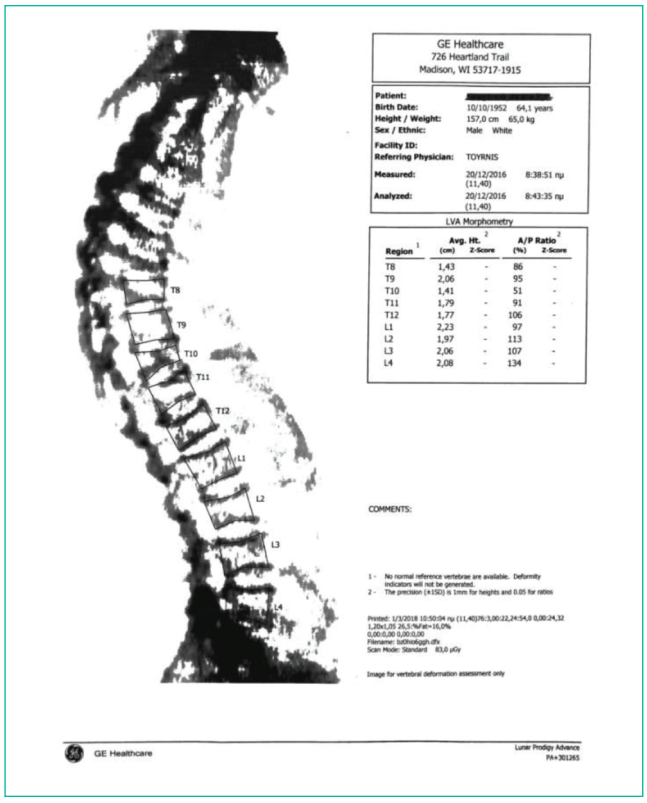


**Figure 1.** LVA Morphometry, 14 months post-transplantation.

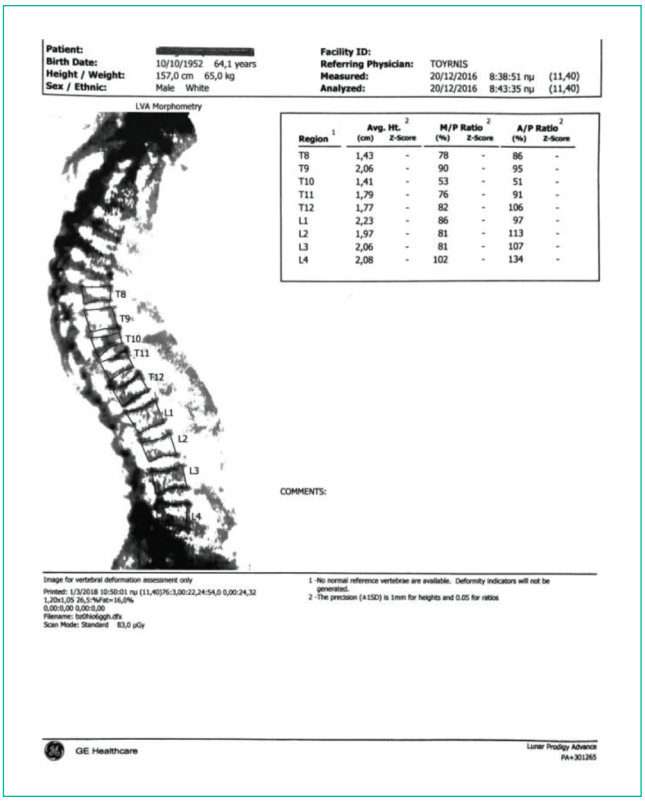


**Figure 2.** LVA Morphometry, 14 months post-transplantation.

one year after the transplantation with multiple vertebral fractures. The fractures were clinical and manifested with lumbar pain that appeared shortly after the OLT. Following the OLT, the patient received a short course of intravenous corticoids (methylprednisolone 1000 mg during surgery and then methylprednisolone 200 mg intravenously decreasing to 16 mg over a period of 7 days) continuing with 16 mg of oral methylprednisolone once a day with tapering to withdrawal over nine months. Afterwards, he remained under immunosupression with everolimus and mycophenolate mofetil. In the last year, he had an episode of cholangitis and underwent an anastomosis of the biliary tract. He also suffered from diabetes mellitus type 2 treated with insulin, and arterial hypertension.

Initially, a vertebral morphometry was performed (Figures 1 and 2). Using the Genant's vertebral fracture semi-quantitive assesment method, fractures of the T8 (grade 2), T10 (grade 3), T11 (grade 2), T12 (grade 1) and L2 (grade 1), L3 (grade 1) vertebrae were identified.

Bone mineral density (BMD) measurement of the lumbar spine (Table 1) and femur (Table 2) was performed at the first visit of the patient, one year after the OLT, following the detection of multiple vertebral fractures in simple radiographs, and repeated 8 and 14 months later, after the initiation of anti-osteoporotic treatment. The initial DXA revealed severe osteoporosis, a T-score of -4.5 at both the lumbar spine and hip. Unfortunately, no basal BMD measurement had been performed before the transplantation.

The patient presented at first consultation with vitamin D deficiency (8,54 ng/ml), secondary hyperparathyroidism, as well as high values of biomarkers of bone formation (bone alkaline phosphatase, osteocalcin, amino-terminal propeptide of type 1 collagen - PINP) and bone resorption (c-terminal telopeptide of type 1 collagen - CTX).

The patient was treated with calcium supplements (1500 mg per day), alpha-calcidol (0,5 μg a day), high doses of vitamin D3 (4000 IU per day during the first 3 months and then 2000 IU daily) and 5 mg of intravenous zolendronic acid once yearly (1/2016 and 1/2017).

Following the above mentioned anti-osteoporotic treatment, the lumbar BMD gradually increased by about 18% after six months and by over 40% after one year of treatment respectively, and two years after OLT overall (Figure 3). As for the femur, the BMD measurement also improved by 28% after a year of treatment (two years after the OLT). Comparing the BMD values from the Tables 1 and 2, it becomes evident that osteoporosis subsided more at the lumbar spine than at the femur, but one should bear in mind that lumbar fractures of this patient tend to falsely overestimate the BMD measurements of the lumbar spine.

| Date | L1 | L2 | L3 | L4 | L1-4 BMD(g/cm²)/T-score |
|---|---|---|---|---|---|
| 10/15 | 0.741 | 0.656 | 0.700 | 0.617 | 0.677/-4.5 |
| 6/16 | 0.810 | 0.731 | 0.853 | 0.793 | 0.797/-3.5 |
| 12/16 | 0.937 | 0.841 | 1.006 | 1.019 | 0.95/-2.2 |

**Table 1.** Lumbar spine densitometry.

| Date | FN | TROC | TOTAL (g/cm²)/ T-score |
|---|---|---|---|
| 10/15 | 0.516/-4.3 | 0.409/-4.7 | 0.508/-4.5 |
| 6/16 | 0.652/-3.2 | 0.500/-3.9 | 0.62/-3.6 |
| 12/16 | 0.583/-3.7 | 0.536/-3.6 | 0.652/-3.4 |

**Table 2.** Femoral densitometry.

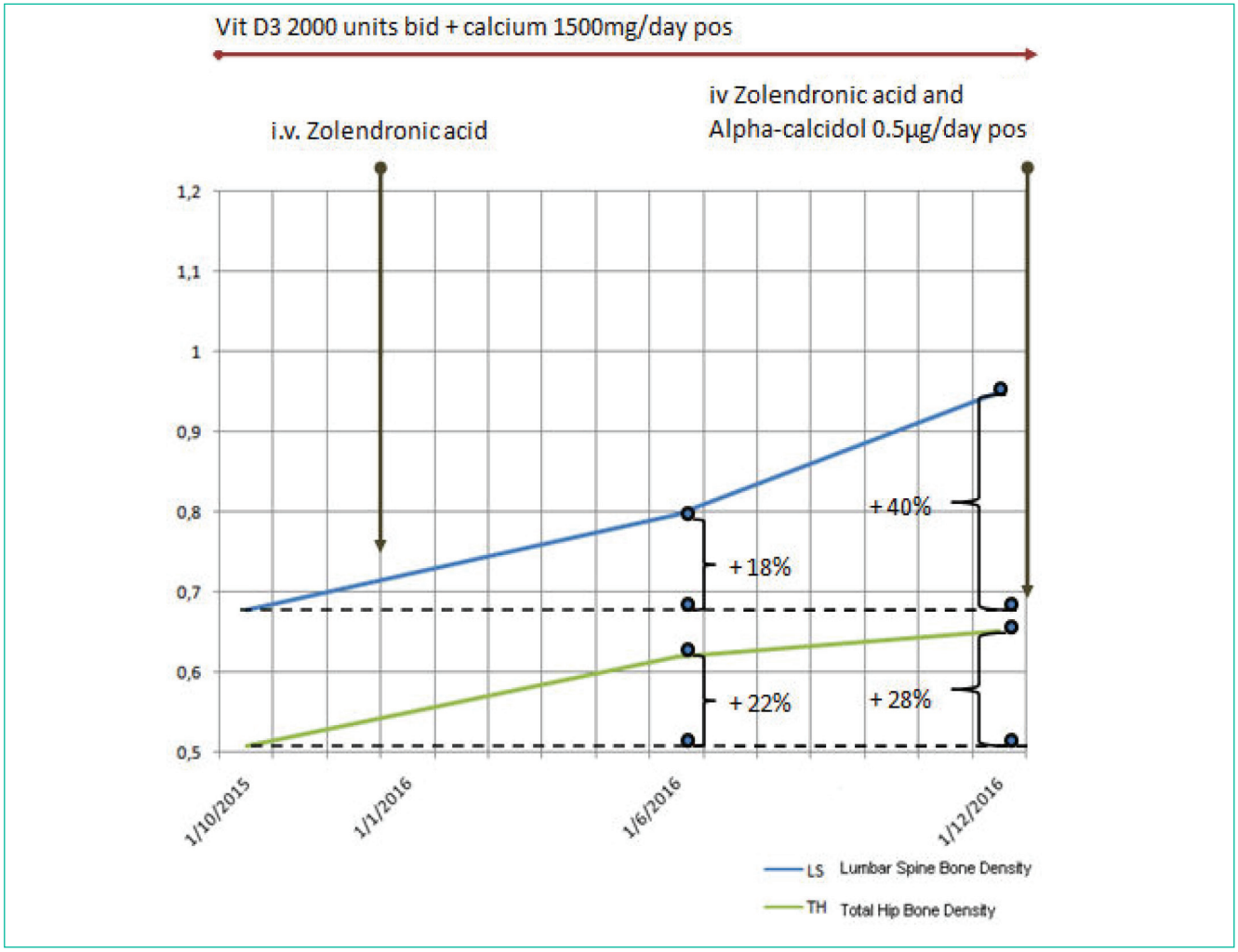


**Figure 3.** BMD changes in association with anti-osteoporotic treatment. (Anamnesis: 9/2014: transplantation of the patient (OLT), 10/2015: first visit of the patient).

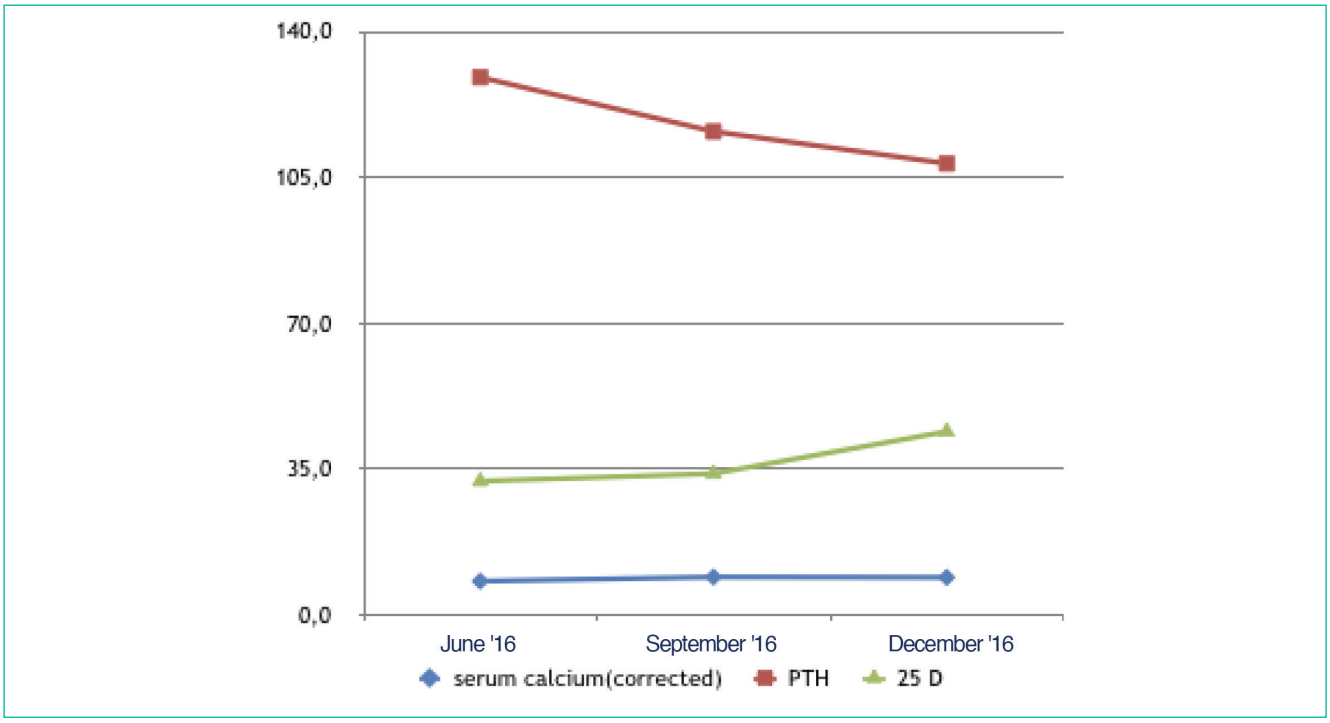


**Figure 4.** Serum calcium (mg/dl), 25-hydroxyvitamin D (25D, ng/ml) and parathormone (PTH, pg/ml)after initiation of anticatabolic treatment.

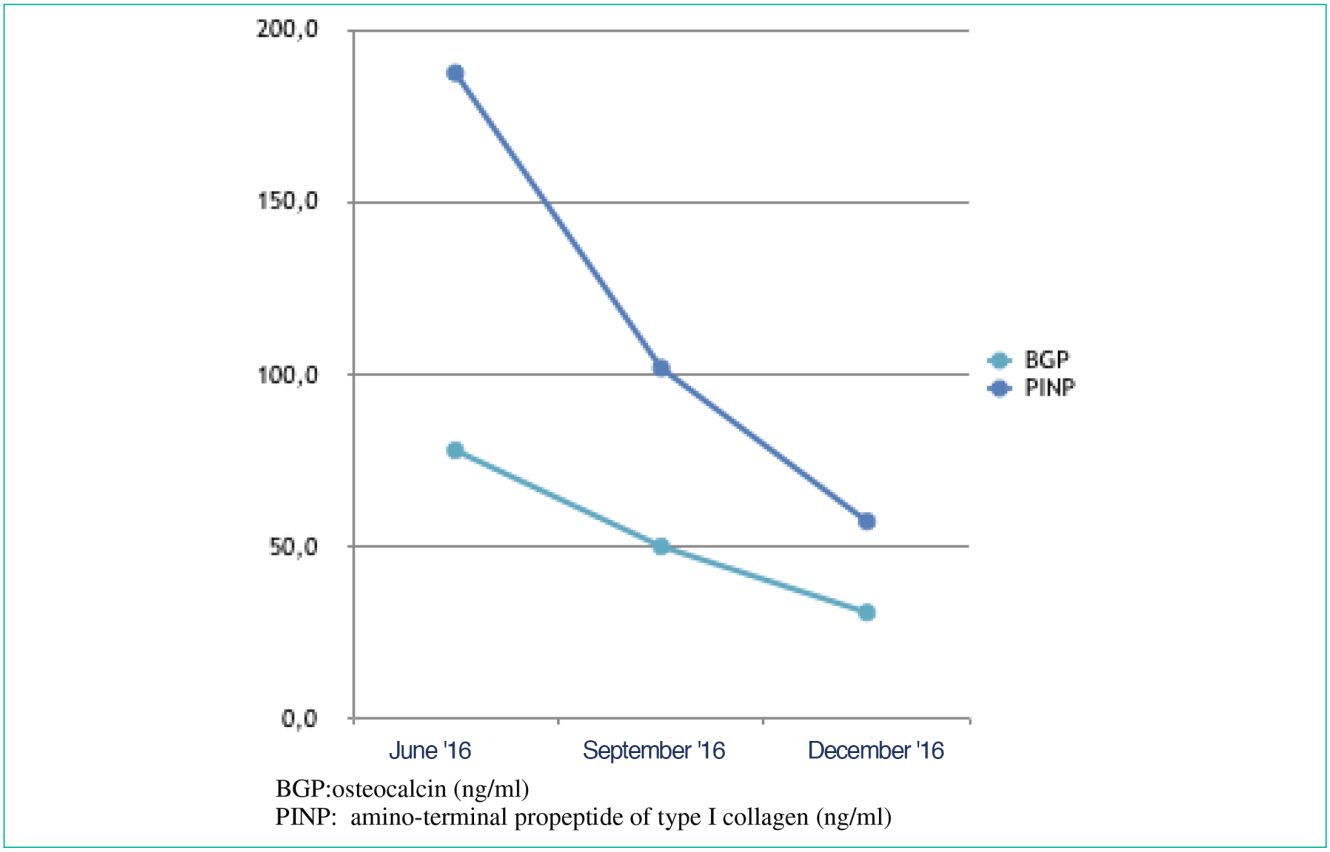


**Figure 5.** Biomarkers of bone formation after initiation of anticatabolic treatment.

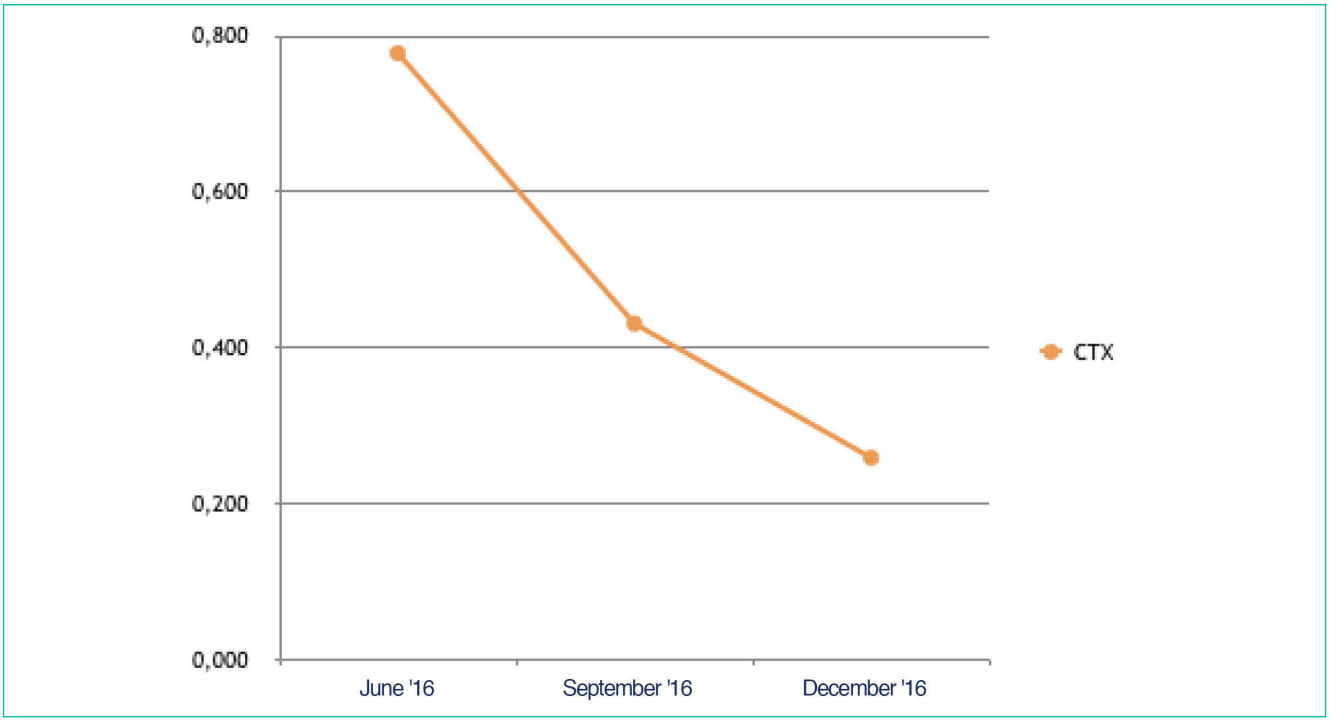


**Figure 6.** Biomarker of bone catabolism, c-terminal telopeptide of type 1 collagen (CTX, ng/ml) after initiation of anticatabolic treatment.

The gradual rise of vitamin D levels to the value of 44 ng/ml with substitution therapy, did not lead to normalization of the parathormone level, that remained remarkably high (108 pg/ml), even two years after the liver transplantation and despite the correction of calcium and vitamin D levels, and normal levels of serum creatinine (Figure 4).

Regarding the rest of biomarkers of bone turnover, there was a significant decline of all measured biomarkers, as a result of the anticatabolic treatment (Figures 5 and 6). From the clinical point of view, the patient did not suffer any new symptomatic or morphometric fractures during the 14-month period of treatment and follow-up.

## Discussion

Osteoporosis and osteopenia are a common complication among cirrhotic patients. Up to 11% of patients with viral or alcoholic compensated Child-Pugh A cirrhosis suffer from osteoporosis at the lumbar spine[3]. As the degree of liver failure and decompensation rises from Child-Pugh A to C, so does the risk of osteoporosis[2,4]. Cholestatic chronic liver disease (autoimmune hepatitis, primary sclerosing cholangiitis, and especially primary biliary cirrhosis), is related to a higher risk of osteoporosis than cirrhosis due to alcoholic or viral etiology, which is mainly attributed to the cholestasis itself and the concomitant use of corticoids in the above – mentioned diseases. BMD values are lower at more advanced cholestatic disease stages and the rate of bone loss correlates with bilirubin[5]. In studies in patients awaiting, or after OLT, the BMD at the lumbar spine in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) is generally lower than in patients with viral or any other cause of hepatic failure[5,6].

The relatively high prevalence of osteoporosis in cirrhotic patients presents a high morbidity and mortality due to complications, with an estimated frequency of fractures from 5 to 20% of all cirrhotic patients, mostly affecting the trabecular bone, vertebrae and ribs. Vertebral fractures occur in 7-35% of cirrhotic patients, while non vertebral ones have a prevalence of about 10%.

Higher prevalences of fractures are recorded in cholestatic liver disease and according to the severity of liver failure[7]. Moreover, osteoporotic fractures among patients awaiting liver transplantation remain noticeably prevalent (25%) over the last two decades, but fortunately there is a tendency to higher BMD scores and lower rates of fracturing[8,9].

Major risk factors of bone disease in patients with cirrhosis include all risk factors of osteoporosis in the general population. Thus, female gender, advanced age, previous fragility fracture, poor nutritional status, limited physical activity, oral glucocorticoid therapy, low body mass index (<19), high alcohol intake, maternal history of hip fracture, smoking and malnutrition render particularly probable the diagnosis of osteoporosis in a cirrhotic patient[10-13].

Furthermore, chronic cholestasis, low calcium,

vitamin D deficiency, secondary hyperparathyroidism and hypogonadism are risk factors of osteoporosis of great relevance among cirrhotic patients[12,14].

After orthotopic liver transplantation (OLT), osteoporosis is the result of two parameters: preexisting osteopenia at OLT and rapid decline in bone mass in the post-transplantation period. In the immediate period after the transplantation, especially the first six months, the patient suffers a rapid fall in BMD, as a result of preexisting bone disease, immobilisation, and corticosteroid and other immunosuppressive agents. Consequently, osteoporotic fractures occur, especially in the first three to six months after OLT. Data from many studies estimate that 24-65% of the patients after OLT develop fractures, especially vertebral ones, predominantly during the first 6-12 months after transplantation[15,16].

Predictive factors of post-transplantation fractures are fractures prior to transplantation, pre-transplantation low BMD, the cumulative dose of corticoids, advanced age and frailty (lack of coordination, inactivity, low muscle mass) and menopausal status[1,8,16]. On the contrary, the rate of bone loss and subsequent bone gain after OLT does not seem to correlate with post-transplant fracture rate[8]. The bone loss is more intense in liver, cardiac and lung and less eminent in kidney transplantation[5,6,17].

The data around the long-term evolution of this group of patients as regards bone densitometry, hormonal, bone biomarkers and histomorphometry are limited. The available data suggest an uncoupling of the bone formation and resorption processes, with a high bone turnover shortly after the OLT. At about 6 months afterwards, histomorphometric studies of bone biopsies suggest an increase in bone formation. Indeed, bone mineral density rises again spontaneously 6-12 months after OLT, even if no anti-osteoporotic therapy is given, especially at the lumbar spine. The bone mass recovery at the hip is a slower process- it lasts about 3 years after the transplantation- and partial, in comparison with the recovery of the lumbar spine BMD, which approaches pre-transplantation values at two years after OLT[5,16]. As regards the mineral metabolism parameters, it appears that vitamin D deficiency is very common among patients awaiting OLT, and closely related with Model for End-Stage Liver Disease (MELD) score[18,19] and serum albumin[20]. Nevertheless, calcium and vitamin D supplementation is insufficient in the majority of these patients[9]. Liver transplantation leads to an important rise in total 25(OH)D concentrations, that are accompanied and predicted by increases in serum albumin and vitamin D binding protein concentrations[20]. It also appears that the increase of 25-OH-vit D levels observed months after the OLT correlate with theBMD recovery[16].

It has been described in various series an increase of PTH after OLT, not related to creatinine levels and not well understood, that remains for 2 years and subsequently falls again. Moreover, this PTH elevation is inversely related to the femoral BMD recovery[16].

Clinicians who treat transplanted patients use immunosuppresive drugs that contribute to osteopenia. Shortly after OLT, corticosteroids indisputably account for the main part of changes in the bone mass and quality, with a dose-dependent deleterious effect especially on the trabecular bone. Corticosteroids interfere in several ways with the bone metabolism causing decreased formation, increased bone resorption, calcium malabsorption and inducing renal calcium loss. Bone loss after steroid treatment for OLT is difficult to estimate as it varies from one patient to another, even if they receive the same steroid treatment[5]. There is an effort to withdraw corticoids early after OLT or at least reduce as much as possible the steroid dose substituting glucocorticoids with other immunosuppressive agents, such as mycophenolate mofetil. It appears that such regimens can ensure both the patient safety and graft survival with less osteopenia and the rest of steroid adverse effects[21].

Nevertheless, whenever a use of corticosteroids for more than 3 months is expected, it is advisable to follow the American College of Rheumatology Guidelines (2010) and the Joint IOF-ECTS GIO Guidelines Working Group (2012) and evaluate the need for anti-osteoporotic prophylaxis or therapy. In patients under corticosteroids with high fracture risk, anti-osteoporotic treatment should be initiated as soon as glucocorticoid treatment begins[22].

Among the rest of immunosuppressive agents, everolimus and tacrolimus were less linked to osteoporosis in comparison to cyclosporine or corticosteroids[6,13,23]. Liver transplant recipients on cyclosporine present more fractures than patients on tacrolimus, which is explained mainly by the higher mean steroid dose used in the regimens with cyclosporine 8. Mycophenolate mofetil appears to be neutral to the bone density[6,13].

As far as patients with OLT are concerned, recommendations proposed by the American Association for the Study of Liver Diseases and the American Society of Transplantation (2012), include risk factors' detection and frequent evaluation of BMD, calcium, vitamin D, gonadal, thyroid function, thoracolumbar radiographies. Calcium and vitamin D supplements, biphosphonates and weight-bearing exercise are all recommended treatment for this group of patients. General non pharmaceutical measures are highly advised: smoking and alcohol cessation, a well-balanced diet with sufficient calories, calcium and vitamin D intake, reduction of fall risk at home and home safety assessment, correction of visual problems, avoidance of central nervous system depressants, use of antidiabetic agents that do not cause hypoglycemia, avoidance of orthostatic hypotension and aggressive antihypertensive treatments. The dosage of corticosteroids and immunosuppressive drugs should be as low as possible to achieve the transplantation success, as the osteoporotic effect of such therapies is dose-dependent[24]. It has been proposed and it seems quite rational to perform a bone densitometry evaluation in all patients awaiting liver transplantation[10].

Anticatabolic therapy, especially biphosphonates,

seem to be a safe and effective treatment option in cirrhotic and transplanted patients. Alendronate, Etidronate, Risedronate, Zolendronic acid together with sufficient uptake of calcium (1200-1500 mg/day) and vitamin D (800-1000 IU/day or more in case of insufficiency) are all first-line treatments, extrapolating the important results of those therapies in postmenopausal women to the setting of cirrhotic and transplanted patients. Zolendronic acid in particular, has shown that, when administered to liver transplant patients, it improves bone matrix mineralization parameters, reduces bone turnover, increases spine BMD and prevents bone loss at the hip, and decreases the fracture risk after OLT[18,19].

Initial concerns for possible ulceration of esophageal varices in cirrhotic patients subsided after several encouraging results from studies, and this risk seems to be lower than previously estimated[7]. Usually the regimen with oral biphosphonate once a week is well tolerated. In cases of esophageal varices and high bleeding risk the parenteral form may be preferred to prevent ulceration, gastroesophageal reflux and bleeding that oral biphosphonates can cause. In patients under parenteral biphosphonate we should always bear in mind the possibility of jaw osteonecrosis, but there is no evidence that this complication occurs more often in patients who take both biphosphonates and corticosteroids. Nonetheless, those patients are advised to maintain a very good oral hygiene.

Hormonal replacement treatments are generally considered second-line therapy, given the adverse effects on the cardiovascular risk and various types of cancer such as hepatocellular carcinoma. Nonetheless, studies have shown benefit of hormonal therapy on the BMD[7,12].

Teriparatide (PTH 1-34) has a protective effect on skeleton, augmenting the number of osteoblasts and slowing down the apoptosis of osteoblasts and osteocytes. It cannot be used in patients with primary or secondary hyperparathyroidism. It is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women with high risk for fracture.

Other treatments such as calcitonine, sodium fluoride and raloxifene, have not shown consistent and conclusive results in studies and are thus not recommended. Denosumab still remains to be tested in this group of patients[7,12,22,24].

## Conclusions

It is crucial to initiate the diagnosis, prevention and treatment of osteoporosis in the cirrhotic patients early in the course of their disease, before the occurrence of fractures which entails serious disability, morbidity and mortality rates. The diagnosis of osteoporosis not only requires a BMD measurement, radiological methods and biochemical bone metabolism markers, but also an estimation of the overall fracture risk. Clinicians should focus on high-risk patients treated with glucocorticoids or immunosupressive drugs. The transplantation process requires pre-transplantation screening for osteoporosis and close follow-up of the patient after the transplantation, for the early detection of rapid declines in bone mineral density and prompt initiation of antiosteoporotic therapy when indicated. Conventional treatment with biphosphonates, calcium and vitamin D supplements, together with weaning from corticosteroids when possible, are the keys to the effective treatment of the transplanted cirrhotic patient with osteoporosis. Given the improved survival rates of transplanted patients over the last decades, there is a need for better management of osteoporosis, in order to reduce fractures and, as a result, the morbidity and mortality and ensure the quality of life of these patients.

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