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ORIGINAL RESEARCH

Bone Disease in Patients Awaiting Liver Transplantation. Has the Situation Improved in the Last Two Decades?

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Abstract In recent years, there has been speculation about the possibility of a reduction in the incidence of fractures after liver transplantation (LT) because of changes in the characteristics of candidates and the use of different immunosuppressive therapies. We analyzed the characteristics of LT candidates (CTC) and compared them with historical data from a group of LT candidate patients (HTC). Data from 60 CTC patients consecutively included in a screening program of metabolic bone disease were compared with data from 60 HTC patients prospectively evaluated between 1992 and 1993. In all patients, we analyzed the clinical and laboratory characteristics, bone mineral density (BMD) dual-energy X-ray absorptiometry, and skeletal fractures. Patients in the CTC group were older than patients in the HTC group. The CTC group had lower femoral neck *T* scores. No differences were observed between groups in the proportion of patients with osteoporosis (22 vs. 30 %, p = ns) or fractures (36 vs. 33 %, p = ns). The percentage of patients with normal BMD decreased from 38 to 20 %. 25(OH)D values were low in both groups. Only 7.5 % of the CTC patients received calcium and/or vitamin D supplementation. The prevalence of fractures among CTC patients was similar to that seen two decades ago. At present, candidates for LT are older and have lower femoral bone mass. Vitamin D deficiency remains frequent; however, calcium and/or vitamin D supplementation is uncommon.

Keywords Liver · Transplantation · Osteoporosis · Fracture · Vitamin D

Introduction

Since the onset of liver transplant programs, it has become evident that patients have significant disorders in bone and mineral metabolism, including the development of skeletal fractures [1–7]. Indeed, bone disease after liver transplantation (LT) may cause a high incidence of skeletal fractures (ranging 24–65 %, depending on the series), especially in the first year after transplantation [1–7]. Therefore, major efforts have been made to assess the characteristics and factors involved in the development of posttransplant bone disease [5, 8].

In the development of fractures after LT multiple risk factors have been identified. Thus, advanced age, type and severity of liver disease, history of previous fractures, and low bone mass have been considered the most important pretransplant factors related to the development of bone fractures after transplantation [9–12]. In the posttransplant period, immunosuppressive drugs, especially glucocorticoids, and immobilization are the main factors associated with bone disease.

In recent years, a lower incidence of fractures and less bone loss have been reported in these patients [13].

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However, whether this decrease in the incidence of fractures after LT is related to better metabolic bone mineral conditions previous to transplant or to a lower bone loss in the posttransplant period has not been clarified. Thus, whereas Premaor et al. [13] indicated an improvement in the pretransplant bone health of these patients, other studies linked the decreased incidence of fractures in the posttransplant period to the introduction of new immunosuppressive drugs and new treatment regimens with reduced doses of glucocorticoids. Furthermore, although trials are scarce, most of them have suggested that correction of vitamin D deficiency and treatment with bisphosphonates may reduce bone loss and fractures after transplantation [14–16], hence indicating these drugs as a therapeutic strategy in the pre- and posttransplant periods.

However, available data are insufficient to confirm that now there is a lower risk of fracture due to better metabolic bone mineral conditions, and there is not enough evidence that preventive measures have increased in patients with severe hepatic cirrhosis that may be susceptible to transplant in the future.

Therefore, in order to evaluate if at present patients undergoing LT may have better bone metabolic conditions than in previous years, we analyzed the incidence of bone pathology in patients awaiting LT and compared them with historical published data from liver transplant candidates prospectively evaluated between 1992 and 1993 [17].

Patients and Methods

Patients

We prospectively included 60 patients [mean age ± standard deviation (SD) 56 ± 9, range 31–69 years] with chronic advanced liver disease (male/female 41/19, 14 women were postmenopausal), who were consecutively evaluated in a screening pretransplant program for preventing bone disease after LT between January 2010 and July 2011.

Four patients had cholestatic liver diseases (two primary biliary cirrhosis, one primary sclerosing cholangitis, and one biliary cirrhosis), 12 patients had alcoholic cirrhosis, and 34 patients had cirrhosis of viral etiology (30 HCV and four HBV). The remaining patients had polycystic liver disease ($n = 3$), cryptogenic cirrhosis ($n = 3$), hemochromatosis ($n = 1$), primary portal hypertension ($n = 1$), congenital liver fibrosis ($n = 1$), and α1-antitrypsin deficiency ($n = 1$).

Data from these patients were compared with historical published data of 60 candidates for liver transplant prospectively evaluated in our department between 1992 and 1993 (mean age ± SD 50 ± 7.6, range 32–60 years; male/female 41/19, 15 women were postmenopausal). Six patients had primary biliary cirrhosis, 14 had alcoholic cirrhosis, and 39 had cirrhosis of viral etiology (36 HCV and 3 HBV) [17].

Patients excluded from the study were those younger than 18 years and those receiving a multiple organ transplant surgery or liver retransplant.

The Ethical Committee at Hospital Clínic approved the study protocol, and informed consent was obtained from all subjects. Moreover, the study was performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the 2008 Declaration of Istanbul.

Study Procedures

Demographic and clinical characteristics were assessed in all patients. Clinical assessment included evaluation of type and severity (Child-Pugh score) of the liver disease, alcohol consumption, menopausal status, concomitant treatments, and history of previous peripheral and vertebral fractures.

After an overnight fast, samples of venous blood were taken from all patients for measuring standard biochemical parameters. Liver function tests and serum values of calcium, phosphate, alkaline phosphatase, and creatinine were analyzed by standard procedures. Serum 25-hydroxyvitamin D [25(OH)D] was determined by an immunoassay (Liaison; DiaSorin, Saluggia, Italy). Serum values of 25(OH)D <20 and <10 ng/mL were considered indicative of vitamin D deficiency and severe deficiency, respectively [18].

Bone mineral density (BMD) at the lumbar spine and femur was measured by dual-energy X-ray absorptiometry (DXA) using a bone analyzer (DXA-Prodigy; Lunar, Madison, WI, USA). The coefficients of variation in the lumbar spine and femoral neck were 0.5 and 2.3 %, respectively. Osteopenia and osteoporosis were diagnosed in accordance with the World Health Organization criteria. Osteoporosis was defined as a BMD 2.5 SD or more below the young adult mean value (T score <-2.5) and osteopenia when the T score was between -1 and -2.5. To define the prevalence of osteoporosis, the lowest T score detected in each individual was considered. Standard X-rays of the thoracic and lumbar spine were obtained to disclose vertebral fractures. A vertebral fracture was defined as a reduction of 20 % or more in the anterior, middle, or posterior height of the vertebral body. Fractures attributable to major trauma (defined as a fracture caused by a fall higher than from standing height or by a car accident or other severe trauma) were not considered.

Statistical Analysis

Data are expressed as mean ± SD unless indicated otherwise. Normality was evaluated by the Kolmogorov–

Smirnov test. Student's t test was used to analyze differences in continuous variables. For comparisons of more than two quantitative variables, analysis of variance (ANOVA) was performed, using the Bonferroni method to adjust the p values. Chi squared and Fisher's exact tests were used to compare categorical variables. Correlations were evaluated by multiple regression analysis (stepwise). $p < 0.05$ was considered to indicate a significant difference. Statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical and laboratory data of patients included in the study are shown in Table 1.

Current transplant candidate (CTC) patients were significantly older than the historical group of candidates for transplantation historical transplant candidate (HTC). No differences between groups were found in the frequency of alcohol abuse, smoking status, and use of calcium or vitamin D supplements (calcium supplement 9 vs. 8.8 % and vitamin D supplement 9 vs. 3.5 % in the CTC and HTC groups, respectively). None of the HTC patients and only one patient in the CTC group (who was treated with alendronate) received treatment medication for pretransplant osteoporosis. Use of diuretics was more frequent in HTC patients (spironolactone 17 vs. 12 %, furosemide 10 vs. 5 %, and spironolactone and furosemide 23 vs. 54 % in the CTC and HTC groups, respectively; $p < 0.01$). CTC patients showed higher values of serum creatinine and calcium than HTC patients. In order to clarify the causes of low serum corrected calcium levels of HTC patients, we performed a multiple regression analysis (stepwise) including age, serum creatinine, and 25(OH)D. The analysis showed that corrected calcium values correlated with 25(OH)D levels ($r = 0.196$, $p < 0.05$). In addition, CTC patients had less severe liver disease with lower Child-Pugh scores at inclusion ($p < 0.01$). Consequently, CTC patients showed lower values of bilirubin and alanine

Table 1 Clinical and analytical data of the patients

	CTC ($n = 60$)	HTC ($n = 60$)	p
Age (years)	56.3 ± 9	50 ± 7.6	<0.01
Sex (M/F)	41/19	41/19	ns
Alcohol abuse (%)	45	37	ns
Smokers (%)	45	48	ns
Child-Pugh score			<0.01
Class A (%)	39	3.7	
Class B (%)	40	51.9	
Class C (%)	21	44.4	
Serum creatinine (mg/dL)	0.91 ± 0.3	0.76 ± 0.4	<0.05
Serum albumin (g/L)	33.4 ± 5.8	29.1 ± 5.5	<0.01
Serum calcium (mg/dL)	9.1 ± 0.7	8.5 ± 0.7	<0.01
Serum corrected calcium (mg/dL)	9.6 ± 0.5	9.3 ± 0.5	<0.05
Serum phosphate (mg/dL)	3.4 ± 0.5	3.5 ± 0.6	ns
Alkaline phosphatase (IU/L)	307.2 ± 157.2	359.3 ± 305.3	ns
Bilirubin (mg/dL)	2.7 ± 3.3	4.6 ± 4.5	<0.05
Aspartate aminotransferase (IU/L)	77.6 ± 79.8	73.2 ± 45.6	ns
Alanine aminotransferase (IU/L)	63.1 ± 52.8	99.5 ± 50.3	<0.01
Platelet count (10^9/L)	121.9 ± 64.1	78.6 ± 43.7	<0.01
Prothrombin time (%)	65.6 ± 17.1	57.22 ± 18.8	<0.05
25(OH)D (ng/mL)	13.4 ± 9.9	10.3 ± 9.1	ns
Lumbar BMD (g/cm^2)	1.027 ± 0.2	1.051 ± 0.16	ns
T score	−1.5 ± 1.4	−1.2 ± 1.4	ns
Z score	−0.96 ± 1.4	−1.07 ± 1.4	ns
Lumbar BMC (g)	45.2 ± 13.3	45.8 ± 9.5	ns
Femoral neck BMD (g/cm^2)	0.876 ± 0.1	0.867 ± 0.15	ns
T score	−1.3 ± 1.1	−0.75 ± 1.3	<0.05
Z score	−0.39 ± 0.9	−0.19 ± 1.3	ns
Femoral neck BMC (g)	4.6 ± 0.78	4.9 ± 1.2	ns
Patients with fractures	33 %	36 %	ns

Data are expressed as mean ± SD

CTC current transplant candidate, *HTC* historical transplant candidate, *BMD* bone mineral density, *BMC* bone mineral content

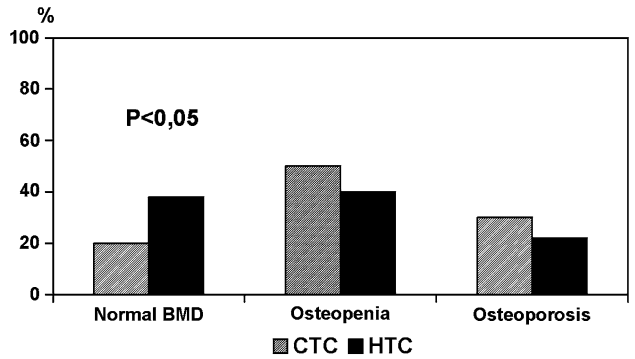

Fig. 1 Prevalence of normal BMD, osteopenia, and osteoporosis in CTH and HTC

aminotransferase and higher serum values of albumin, higher platelet count numbers, as well as higher prothrombin index.

CTC patients showed lower mean femoral neck *T* score than HTC patients with similar *Z* scores. No differences in lumbar BMD values were observed between the two groups (Table 1). Bone mineral content (BMC) values at the lumbar spine and femoral neck were similar in the two groups (Table 1). Moreover, only 20 % of patients in the CTC group and 38 % of patients in the HTC group had normal BMD values ($p < 0.05$), but no significant differences in the prevalence of densitometric criteria of osteoporosis or osteopenia between the groups were observed (Fig. 1). When evaluating the effect of the severity of the liver disease on bone mass, HCT patients with severe disease (child C) showed a significantly lower femoral neck *T* score than child B patients (child C -1 ± 1.3 vs. child B -0.3 ± 0.9; $p < 0.05$). No significant differences were observed in the CTC patients. Nonetheless, it should be noted that only 21 % of CTC patients had child C compared to 44 % of HTC patients (Table 1).

Bone fractures were present in 33 and 37 % of CTC and HTC patients, respectively (p = ns). Densitometric criteria of osteoporosis and/or fractures were present in 48 % of CTC patients and 52 % of HTC patients. As expected, CTC patients with fractures showed lower lumbar BMD and *T* scores than nonfractured patients (BMD: fractured patients 0.94 ± 0.8 vs. nonfractured 1.07 ± 1.2 g/cm^2, $p < 0.01$; *T* score: fractured -2.2 ± 1.5 vs. nonfractured patients -1.1 ± 1.5; $p < 0.01$). Moreover, lumbar BMD was lower than -2.5 *T* score more frequently in patients with fractures than in those without (40 vs. 11 %, $p < 0.05$).

CTC patients showed low mean serum values of 25(OH)D (13.4 ± 9.9 ng/mL). No differences in 25(OH)D mean values were observed between the CTC and HTC groups (Table 1). Nevertheless, 25(OH)D deficiency (<20 ng/mL) was more frequently observed in the HTC group (92 % in HCT patients vs. 77 % in the CTC group, $p < 0.05$). No significant differences were found in the prevalence of severe vitamin D deficiency (25[OH]D <10 ng/mL HTC 62 % vs. CTC 48 %, p = ns). HTC patients with alcoholic cirrhosis had lower 25(OH)D mean values than the group with viral cirrhosis (5.8 ± 2.7 vs. 10.6 ± 8.6 ng/mL, $p < 0.05$). These differences were not observed in the CTC patients, but in this group 25(OH)D values <10 ng/mL were more frequent in alcoholic patients than in patients with viral cirrhosis (83 vs. 32 %, $p < 0.01$).

Discussion

Our study shows that current candidates for LT have a similar rate of skeletal fractures than patients undergoing LT 20 years ago. CTC patients are older and have lower bone mass at the femoral neck and less severe liver disease than the HTC patients. In addition, vitamin D deficiency remains frequent, with nearly 80 % of CTC patients having low 25(OH)D serum values and fewer than 10 % of them receiving vitamin D supplementation.

Our results indicate that severe bone disease has a high prevalence among current candidates for LT. Thus, skeletal fractures were present in 33 % of patients awaiting LT, with only 20 % of them having normal BMD values. These data, together with the older age and the lower BMD values at the femoral neck in CTC patients, suggest that these patients still have a high risk for developing fractures in the posttransplant period. Indeed, recent studies have also shown that patients undergoing LT still present a high prevalence of skeletal fractures and low bone mass, with prevalence of osteopenia and osteoporosis reaching 48 and 38 % of patients, respectively [19–22].

In addition, the frequent and marked low vitamin D serum values observed in most of the CTC patients further increase the risk for developing skeletal complications in this clinical condition. Thus, nearly 50 % of patients showed a severe vitamin D deficiency [25(OH)D <10 ng/mL], with most patients (77 %) having a deficiency [25(OH)D values <20 ng/mL] of this vitamin, a well-known risk factor related to the development of fractures in individuals with osteoporosis. Nevertheless, in spite of having such a vitamin D deficiency and that this finding was also reported in HCT patients 20 years ago [17], supplementation with calcium and/or vitamin D was still uncommon in these patients. Fewer than 10 % of the CTC patients were supplemented with calcium and/or vitamin D, thereby indicating the necessity of treating this group of patients.

In the present study the differences in age and severity of liver disease could be explained by changes in the inclusion and prioritization criteria established in the current liver transplant programs. At present, the upper range of age has increased, and more patients with hepatocellular

carcinoma and less severe liver disease are submitted to liver transplant, changing the proportion of patients in the child classification. Consequently, BMD characteristics are influenced by age and liver function.

Vitamin D deficiency is more common in patients with alcoholic cirrhosis than in those with other liver diseases, as observed in CTC and HTC patients. Thus, Wibaux et al. [19] in a group of 99 patients with alcohol-induced cirrhosis awaiting LT also reported a prevalence of low vitamin D values [25(OH)D <20 ng/mL] in 88 % of patients.

The main limitation of the study is the difference in the characteristics of the two populations included. However, in both cases all patients evaluated for LT were consecutively referred; and therefore, we believe they are an example of the real candidates and reflect the characteristics and the real risk of our population. Unfortunately, free 25(OH)D levels were not assessed and might not be as low as suspected since DPB might also be low. Furthermore, the absence of serum parathyroid hormone and bone turnover marker determinations limits the information available to characterize bone remodeling in these patients.

Our study not only shows a high prevalence of bone disease in liver transplant candidates but also allows a direct comparison of current candidates for liver transplant with those submitted 20 years ago. The absence of a reduction in the risk factors associated with fractures in recent years reinforces the perception that bone disease is still a major problem, frequently undertreated in these patients.

In conclusion, the results of this study show that the prevalence of fractures among current candidates for LT is similar to that seen two decades ago, involving one-third of patients. As a consequence of changes in the inclusion criteria for LT, current patients awaiting LT are older and have lower femoral BMD. Moreover, although there are no significant differences in the proportion of patients with osteoporosis and osteopenia, the frequency of patients with normal BMD has been lower in recent years. Vitamin D deficiency remains extremely frequent, and calcium and/or vitamin D supplementation is still uncommon.

All of these data suggest that these patients are still a high-risk group for developing fractures in the posttransplant period and that health-care providers must be aware of the importance of addressing factors that may affect bone health in patients with chronic liver disease. Therefore, more efforts are needed to consider an earlier evaluation and adequate therapeutic approach in patients awaiting LT.

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