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Longitudinal Changes in BMD and Fracture Risk in Orthotopic Liver Transplant Recipients Not Using Bone-Modifying Treatment

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ABSTRACT

Osteoporosis is prevalent in end-stage liver disease, but data on long-term changes in bone mineral density (BMD) and related fracture incidence after orthotopic liver transplantation (OLT) are scarce. We evaluated BMD changes up to 5 years in consecutive recipients of a successful OLT at the Leiden University Medical Centre between 2000 and 2011, in whom sequential BMD data were available. Spinal radiographs were available at time of screening and at 6 and 12 months post-OLT and were assessed for vertebral fractures by two independent observers using Genant's semiquantitative method. Patients were excluded from the study when started on bisphosphonates. A total of 201 patients (71% men), median age 53 years (range, 18–70 years) were included in the study. Most common liver pathology was viral (27%) or alcoholic liver disease (25%). All patients received prednisone for at least 6 months after transplantation and the majority received either tacrolimus or cyclosporine for immunosuppression. At time of screening for OLT, osteoporosis and osteopenia were found in 18% and 36% of patients at the lumbar spine (LS), respectively, and in 9% and 42% at the femoral neck (FN), respectively. *T*-scores declined significantly at both sites 6 months after OLT, but increased thereafter at the LS, reaching pretransplantation values at 2 years and remaining stable thereafter. FN *T*-scores remained consistently lower than pretransplantation values. The prevalence of vertebral fractures increased from 56% at screening to 71% at 1 year after OLT, with a fracture incidence of 34%. BMD changes did not predict fracture risk. Osteoporosis, osteopenia, and vertebral fractures are prevalent in patients with end-stage liver disease. An overall decline in BMD is observed within the first 6 months after OLT, with subsequent recovery to pretransplantation values at the LS, but not at the FN. Vertebral fracture risk is high after OLT regardless of changes in BMD.

KEY WORDS: EPIDEMIOLOGY; DXA; OSTEOPOROSIS; INCIDENCE OSTEOPOROSIS; VERTEBRAL FRACTURES; FRACTURE RISK

Introduction

Osteoporosis is reported to be prevalent in end-stage liver disease, and accelerated bone loss associated with increased fracture risk has been observed in 25% to 35% of patients in the first 12 months after orthotopic liver transplantation (OLT).[1–11] The initial decline in bone mineral density (BMD), believed to be predominantly due to corticosteroid use for immunosuppression, is generally followed by a stabilization in bone mass between 6 and 12 months after OLT, with no further decrease in BMD thereafter, independently of the use of bone-modifying agents such as bisphosphonates.[1,3–6,8,9,12] Data on natural changes in BMD beyond the first year after OLT are scarce, however, and mainly based on small studies, or on studies in patients with exclusive cholestatic liver disease as underlying liver pathology.[1–9,12–16] Studies were also performed over a decade ago,[1–5,13–15] before the introduction of currently used immunosuppressive regimens, which enable the use of significantly lower corticosteroid doses post-OLT, thus precluding exposure to a high cumulative dose of these agents. Whether the spontaneous recovery of BMD within the first year after OLT is also associated with a decreased fracture risk has not been adequately addressed.

The aims of this study were to examine changes in BMD after OLT in a cohort of consecutive liver transplant recipients not receiving treatment with antiresorptive agents, to identify risk factors for bone loss after successful OLT and to examine the influence of changes in BMD on fracture risk within the first year after OLT.

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Patients and Methods

Patients

Consecutive patients who underwent a first OLT at the Leiden University Medical Centre between January 1, 2000 and January 1, 2011, and who had sequential BMD measurements after OLT, were eligible for the study, including 20 patients who had BMD measurements from 6 months onward after OLT. Immunosuppressive regimens for OLT consisted of corticosteroids for at least 6 months in all patients, with an additional calcineurin inhibitor: cyclosporine or tacrolimus in the majority, with mofetil mycophenolate (MMF) or sirolimus as additional second or third immunosuppressive agent in a few patients. International guidelines concerning immunosuppression were complied with in the case of new transplant patients, but established immunosuppressive regimens were not routinely altered in individual transplant patients. Corticosteroid schedules included methylprednisolone at a dose of 500 mg given during the OLT procedure, followed by oral prednisolone at a dose of 20 mg daily for 1 week, 10 mg daily for 3 months, slowly tapering to complete discontinuation of corticosteroids between 3 and 6 months after OLT in all but a few patients who required maintenance doses of prednisolone of 2.5 to 10 mg/d. Treatment with calcium and vitamin D supplements in a combined fixed dose of 500 mg elemental calcium and 400 IU cholecalciferol, and treatment with bisphosphonates were initiated at the discretion of the treating physician. Patients treated with bisphosphonates before or at the time of screening for OLT were excluded from the study. Patients receiving bisphosphonates after OLT were censored and thus excluded from further analysis from time of starting treatment.

Methods

Demographic and clinical data

Patients' demographic and clinical data were obtained from electronic hospital records. Data on age, gender, smoking, height, weight, and primary liver disease were collected. Concomitant or later renal transplantation was documented. Data were also collected on date and cause of death. Recorded medication included immunosuppressives, calcium and vitamin D supplements, and bone-modifying medications such as bisphosphonates.

Laboratory investigations

Laboratory data were also obtained from electronic hospital records. Biochemical data collected included serum calcium, corrected for an albumin of 40 g/L, phosphate, creatinine, parathyroid hormone (PTH), and 25-hydroxy-vitamin D (25-OHD) concentrations, which were measured at screening for OLT and at various time points thereafter. Severity of liver disease was determined using the laboratory Model for End-Stage Liver Disease (MELD) scores[17] calculated on the basis of serum creatinine, bilirubin, and international normalized ratio (INR) measurements obtained at time of screening for OLT. The following accepted formula was used to calculate the scores:

$$\begin{aligned} \text{MELD} = 10 \times \{&[0.957 \times \ln(\text{Creatinine}/88.4)] \\ &+ [0.378 \times \ln(\text{Bilirubin}/17.1)] \\ &+ [1.12 \times \ln(\text{INR})] + 6.43\} \end{aligned} \quad (1)$$

BMD measurements

BMD was measured at the lumbar spine and at the femoral neck using dual-energy X-ray absorptiometry (DXA Hologic QDR 4500; Hologic Inc., Waltham, MA, USA; equipped with reference values based on the National Health and Nutrition Examination Survey [NHANES III]). Absolute measurements of BMD in g/cm^2 as well as *T*-scores (matched to young adult reference populations at peak bone mass) and *Z*-scores (age-matched and sex-matched reference populations) were recorded. World Health Organization (WHO) criteria were used to define osteoporosis (*T*-score of -2.5 SD or less) and osteopenia (*T*-score between -1 SD and -2.5 SD). BMD measurements were performed at time of screening for OLT (baseline), at 6 and 12 months post-OLT, and yearly thereafter for up to 60 months after OLT. BMD measurements at 36 and 48 months post-OLT were not analyzed because too few measurements were available at these time points.

Vertebral fracture assessment

Spinal radiographs were routinely performed at time of screening and at 6 and 12 months post-OLT. Conventional anteroposterior and lateral radiographs of the thoracic spine and posteroanterior and lateral radiographs of the lumbar spine were performed by an experienced radiology technician following a standardized protocol, at a distance of 115 cm, with the film centralized on Th_7 for the thoracic spine and on L_3 for the lumbar spine.

All conventional radiographs of the thoracic and lumbar spine were blindly assessed for the prevalence and individually scored for the severity (grade) of vertebral fractures by two independent observers, an experienced musculoskeletal radiologist (HMK) and an experienced bone and mineral disorders specialist (NATH). Vertebral fractures were assessed using the Genant's semiquantitative method.[18] Using this method, a decrease in height of 20% to 25% is considered to be a "mild" grade I fracture, 25% to 40% a "moderate" grade II fracture, and >40% a "severe" grade III fracture. Uniform loss of vertebral height compared to adjacent vertebrae was additionally documented using the same grading scores. Radiographs were assessed in a random order, using random numbers generated by SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). A unique number was assigned to each series of radiographs. In case of discrepancy in scores, consensus was achieved by both observers reviewing the radiographs together.

Laboratory, BMD, and fracture data collected at time of screening for OLT were considered to be baseline data.

The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre.

Statistical analysis

For descriptive statistics, categorical variables were expressed as numbers and as percentages. Continuous variables were summarized using mean and SD in case of normal distribution of data; median and 5th and 95th percentiles were used otherwise. An extension of a generalized linear model, generalized estimation equations (GEEs), was used for calculation of differences in laboratory measurements and BMD, to account for repeated measurements. Patients treated with bisphosphonates were excluded from time of initiation of treatment for the duration of follow-up. Incidence rates for osteoporosis after OLT (number of new cases/person years at risk) were calculated with

follow-up time starting after transplantation. Patients already diagnosed as having osteoporosis at time of screening for OLT were not included in the calculation of osteoporosis incidence. An incident fracture was defined as the occurrence of a new vertebral fracture or an increase in grade of a prevalent fracture between serial radiographs before and during the first year after OLT. Follow-up duration until incident osteoporosis, or last measurement of BMD, was used to calculate person-years at risk. A GEE model was used to evaluate the influence of various factors on changes in BMD, corrected for age and gender, and accounting for repeated measurements.

Prevalence of fractures was calculated by dividing the number of patients with at least one vertebral fracture by the total number of patients with available spinal radiographs. A GEE model was used to evaluate the influence of change of BMD on fracture risk, corrected for age and gender, and accounting for repeated measurements. A univariate and multivariate logistic regression model was used to evaluate risk factors for incident fractures.

Calculations were performed using STATA/SE 12.0 software (Stata Corp LP, College Station, TX, USA).

Results

Baseline data

Demographic characteristics

Nine of the 223 eligible transplant recipients were not included in the study because bone densitometry data were not available after OLT and 13 patients were also not included because of treatment with bisphosphonates before or at time of screening for OLT.

Of the 201 patients included in the study, 142 were men (71%). Median age at time of OLT was 53 years (range, 18–70 years, with only 4 patients being younger than 20 years). The most common primary liver diseases were viral hepatitis (27%) and alcoholic liver disease (25%), followed by cholestatic liver disease (14%) (Table 1). At time of screening for OLT, 9 patients (5%) were using corticosteroids, and calcium and vitamin D supplements were prescribed as combination treatment to 21 patients (10%).

Laboratory data

Mean creatinine level was 92 ± 67 μmol/L (normal <104 μmol/L). Mean vitamin D level was 32 ± 23 nmol/L (normal, 50–250 nmol/L), 125 patients (83%) had 25-OH-vitamin D levels <50 nmol/L, 87 of whom had levels <30 nmol/L. Mean bilirubin level was 79 ± 140 mmol/L (normal <17 mmol/L).

Severity of liver disease

Severity of liver disease at screening for OLT, as expressed by laboratory-MELD score, could be calculated in 196 of the 201 patients (98%). Mean score was 14 ± 6 (range, 6–35).

BMD data

BMD measurements were available in 181 patients at time of screening for OLT, but were technically non-evaluable in 11 patients at the lumbar spine. Evaluation was precluded in these 11 patients by the presence of residual oral contrast material from abdominal CT scans, required as part of the screening protocol for OLT, but chronologically performed by error before DXA. Osteoporosis and osteopenia were respectively found in 18% and 36% of patients at the lumbar spine (LS) and in 9 and 42% of patients at the femoral neck (FN).

Table 1. Demographic Data at Time of Screening and After Liver Transplantation

Demographic data	
Patients, *n*	201
Gender, male patients, *n* (%)	142 (71)
Age at time of OLT, years, median (range)	53 (18–70)
Death during follow-up, *n* (%)	34 (17)
Time of death after OLT, months, median (5th–95th percentile)	10 (1–57)
BMI, kg/m^2, mean (SD)	26 (5)
Smoking, *n* (%)	64 (34)
Primary liver disease, *n* (%)	
Viral	54 (27)
Alcoholic	51 (25)
Combined alcoholic and viral	4 (2)
Cholestatic (PSC/PBC/overlap syndrome)	29 (14)
Malignancy	12 (6)
Autoimmune hepatitis	10 (5)
Metabolic	7 (3)
Other[a]	34 (17)
Previous or concomitant renal transplantation, *n* (%)	6 (3)
Time between screening and OLT, months, median (5th–95th percentile)	9 (1–27)
Second OLT	
n (%)	28 (14)
Time to second OLT, days, median (5th–95th percentile)	165 (2–1064)
Rejection episodes, number of episodes (cumulative incidence, %)	
6 months after OLT	27 (14)
12 months after OLT	30 (15)
24 months after OLT	42 (22)
60 months after OLT	42 (22)
Calcium and vitamin D supplements at time of screening, *n* (%)	21 (10)
Bisphosphonates after OLT, *n* (%)	
12 months	58 (32)
24 months	66 (43)
60 months	42 (48)
Corticosteroids at time of screening, *n* (%)	9 (5)
Immunosuppressive medication initiated at OLT, *n* (%)	
Prednisone, tacrolimus	88 (44)
Prednisone, cyclosporine	44 (22)
Prednisone, cyclosporine, and MMF	21 (10)
Prednisone, tacrolimus, and MMF	18 (9)
Other	30 (15

OLT = orthotopic liver transplantation; BMI = body mass index; PSC = primary sclerosing cholangitis; PBC = primary biliary cirrhosis; MMF = mycophenolate mofetil.

[a]Including cryptogenic cirrhosis, Budd-Chiari syndrome, portal vein thrombosis, hereditary polycystic liver-disease, acute liver failure of pregnancy, medically induced cirrhosis, Caroli disease, cystic fibrosis, and Rendu-Osler-Weber disease.

Fracture data

A total of 176 patients had available conventional spinal radiographs at time of screening for OLT. A total of 99 patients (56%) had one or more vertebral fractures, mostly grade 1 fractures (87%). Of the patients with documented prevalent vertebral fractures, 20 had osteoporosis (22%), 38 had osteopenia (42%), and 41 had a normal BMD (36%).

Data after OLT

Clinical data

Median time between screening and OLT was 9 months (range, 0–66 months; 5th–95th percentile 1–27 months). All patients received prednisone during the first 6 months after OLT. Prednisone was combined with tacrolimus in 44% of patients or with tacrolimus and MMF in 9% of patients. Cyclosporine was given to 22% of patients and combined with MMF in 10% of patients. Rejection episodes occurred mainly in the first 6 months after OLT (27 patients) with a cumulative incidence of 22% at 5 years after OLT. A second OLT was performed in 28 patients (14%) after a median time of 7 months (range, 0–37 months). Calcium and vitamin D supplements were increasingly prescribed after OLT, with 26 patients (14%) receiving these agents at screening, 107 (58%) at 1 year after OLT, and 68 patients (77%) at 5 years after OLT. Within the first year after OLT, bisphosphonate treatment was initiated in 58 patients (32%), and 42 patients (48%) were using these agents at 5 years after OLT. Median time of initiation of bisphosphonates was 12 months after OLT (range, 12–48 months).

Six patients (3%) received a previous or concomitant renal transplantation. Thirty-four patients (17%) died during the follow-up period, at a median time of 10 months after OLT (range, 1–58 months). The most common cause of death was infection ($n = 7$) and recurrence of hepatocellular carcinoma ($n = 5$). Other causes included myocardial infarction, hypoglycemia, and suicide.

Laboratory data

There was a significant improvement in liver function tests with time after OLT, with mean bilirubin level decreasing from 78 ± 141 mmol/L at screening to 20 ± 35 mmol/L ($p < 0.005$) at 12 months and to 20 ± 60 mmol/L at 2 years after OLT ($p < 0.005$), stabilizing thereafter with bilirubin levels of 15 ± 13 mmol/L at 5 years after OLT. There was a mild but significant decrease in renal function after OLT, with mean creatinine level increasing from 92 ± 67 μmol/L at time of screening for OLT to 113 ± 50 μmol/L at 12 months after OLT ($p < 0.005$), stabilizing thereafter with a mean creatinine level of 111 ± 66 μmol/L at 5 years after OLT. Mean vitamin D levels increased from 32 ± 23 nmol/L at time of screening to 51 ± 28 nmol/L at 12 months after OLT ($p < 0.005$) and to 60 ± 29 nmol/L at 5 years after OLT ($p < 0.005$).

Changes in BMD after OLT

Sequential changes in BMD were analyzed in the 201 patients included in the study. BMD measurements were not available at screening in 20 of these patients but sequential data were available from 6 months onward after OLT. BMD declined significantly at both LS and FN sites between screening and 6 months after OLT: LS -0.02 g/cm^2 (-2.5%), $p = 0.002$; FN -0.05 g/cm^2 (-6.5%), $p < 0.005$), stabilizing thereafter until 12 months after OLT (Fig. 1). Between 1 and 2 years after OLT, LS *T*-scores increased by 1.2% (0.02 g/cm^2, $p = 0.012$), reaching pretransplantation values at 2 years after OLT and subsequently remaining stable. In contrast, FN BMD remained consistently below pretransplantation values, but after the initial significant loss demonstrated no further decline up to 5 years of follow-up (Fig. 1). A second OLT did not influence the course of changes in BMD. Incidence rates of osteoporosis at the LS and FN were 4.2 and 4.7 per 100 person-years after OLT, respectively. The cumulative incidence of osteoporosis at the LS was 7% at 6 months, 12.1% at 12 months, and 14.7% at 5 years (Fig. 2). The cumulative incidence of osteoporosis at the FN was 8.5% at 6 months, 10.5% at 12 months, and 19.5% at 5 years after OLT.

Incidence of fractures after OLT

Spinal radiographs were available and evaluable in 115 patients at 6 months after OLT and in 106 patients at 12 months after OLT.

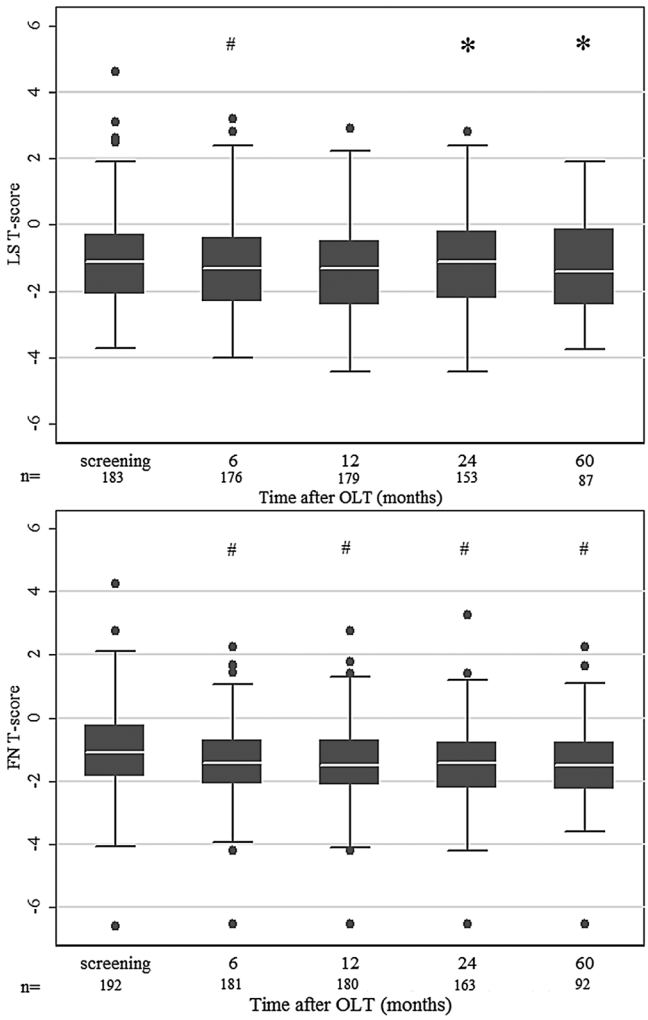

Fig. 1. Changes in LS and FN *T*-scores in patients not treated with bone-modifying agents after OLT. #Significant decrease $p < 0.05$ compared to values at the time of screening. *Significant increase $p < 0.05$ when compared to values at 12 months after OLT. LS = lumbar spine; FN = femoral neck; OLT = orthotopic liver transplantation.

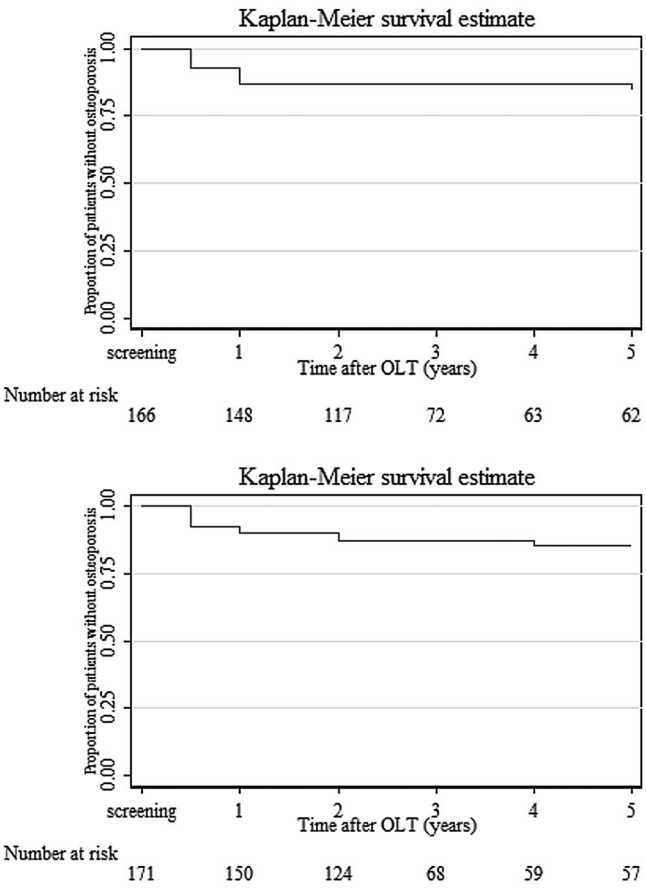

Fig. 2. Kaplan-Meier survival curve showing incident osteoporosis at the LS (upper panel) and FN (lower panel) after OLT. LS = lumbar spine, FN = femoral neck, OLT = orthotopic liver transplantation.

The prevalence of fractures increased from 56% at time of screening to 78 of 115 patients (68%) at 6 months after OLT, and to 75 of 106 patients (71%) at 12 months after OLT. Incident fractures occurred in 45 of 133 patients (34%) in whom a second spinal radiograph was available during the first year after transplantation.

Risk factors for bone loss and for vertebral fractures after OLT

We studied the effect of age, gender, primary liver disease, severity of liver disease, BMD at screening for OLT, and immunosuppressive regimens, including corticosteroids, on bone loss and fracture risk within the first year after OLT. Of these potential risk factors that may influence BMD, the only ones with a significant relationship with bone loss were age $\geq$52 years in women (pragmatic cutoff age for menopause) (odds ratio [OR] 0.89; 95% confidence interval [CI], 0.81–0.99; $p = 0.0024$), and the use of the calcineurin inhibitor tacrolimus for immunosuppression (OR 0.95; 95% CI, 0.91–0.98; $p = 0.003$). Vitamin D deficiency was not predictive for bone loss either at the LS (OR 0.95; 95% CI, 0.90–1.01; $p = 0.080$) or at the FN (OR 0.99; 95% CI, 0.95–1.04; $p = 0.674$). Patients with alcoholic liver disease demonstrated an increase, rather than a decrease, in LS BMD but not FN BMD after OLT (at LS: OR 1.08; 95% CI, 1.02–1.14; $p = 0.005$; at FN: OR 1.03; 95% CI, 0.99–1.08; $p = 0.187$).

Of the potential risk factors studied, only male gender (OR 5.15; 95% CI, 1.41–18.8; $p = 0.013$), and higher age (OR 1.06; 95% CI, 1.00–1.11; $p = 0.045$) were associated with an increased risk for incident fractures. Other factors, including cholestatic liver disease, severity of liver disease, LS BMD, and prevalent fractures at time of screening for OLT, were not predictive for increased fracture risk after OLT. There was no relationship between immunosuppressive medication and fracture risk. There was no difference in pattern of change in BMD at the LS or FN in patients with incident vertebral fractures within the first year after OLT compared to those who did not sustain a fracture (LS BMD: OR 0.97; 95% CI, 0.91–1.03; $p = 0.293$; FN BMD: OR 0.97; 95% CI, 0.93–1.02; $p = 0.272$).

Discussion

Our findings from this study of longitudinal changes in BMD and vertebral fracture incidence in a cohort of recipients of an OLT show a high prevalence of osteopenia/osteoporosis and vertebral fractures at time of screening for OLT. Of patients with diverse primary liver pathology, 54% had some degree of bone loss and 56% had prevalent vertebral fractures. Despite the high prevalence of skeletal pathology in these patients with end-stage liver disease awaiting liver transplantation, only a few received treatment with a bisphosphonate, which provided us the unique opportunity of studying sequential changes in BMD and fracture risk in a relatively large number of OLT recipients not receiving bone-modifying treatment. In keeping with previously published studies, with up to 2 years follow-up after OLT,[1–3,7,9,10,12,13,16] we observed significant bone loss at both the LS and FN sites between screening and 6 months after OLT. Spontaneous recovery of BMD to pretransplantation values was observed at the LS within 2 years after OLT, with our longer-term data showing stabilization of LS BMD thereafter for up to 5 years after OLT. In contrast to the increase in BMD observed at the LS after the initial rapid post-OLT decline in BMD, there was no similar recovery of BMD at the FN. Data on long-term changes in FN BMD after OLT are scarce and not always concordant.[1,5,9,13] Whereas some studies show an increase in FN BMD during the second year after OLT,[1,5] other studies show a persistently low FN BMD compared to pretransplantation values, or a further decline in bone mass at cortical sites.[6,9,13,15,16] The discrepancy in behavior of BMD between LS and FN sites is likely to be a result of the difference in proportion of trabecular and cortical bone between these two sites. Trabecular bone comprises 66% of total bone at the vertebrae, whereas cortical bone comprises >75% of the total bone composition of the FN. Trabecular bone is much more susceptible to changes in the bone microenvironment resulting from disease processes than cortical bone, just as it is more readily susceptible to pharmacologic interventions. BMD at the LS thus shows the greatest magnitude and speed of change in response to reversal of diseases processes as well as to pharmacological interventions, such as has been repeatedly demonstrated with the use of antiresorptives or anabolic agents in the management of osteoporosis. After successful OLT, reversal of cholestasis, vitamin D deficiency, and hypogonadism, which follows the restoration of liver function, is likely to significantly contribute to the spontaneous improvement in LS BMD, with recovery of FN BMD lagging behind that of LS BMD up to 5 years after OLT.

Corticosteroids form the mainstay of the induction and maintenance of immunosuppression after solid organ transplantation, and these agents are used in nearly all immunosuppressive protocols. An association between corticosteroid use and early posttransplantation bone loss has been observed in the early stages of solid organ transplantation.[8] However, the introduction of new immunosuppressive regimens has allowed the early tapering of corticosteroids, thereby substantially contributing to long-term recovery of bone mass after transplantation. Nonetheless, acute rejection episodes occur more commonly in the first 3 months after transplantation, so that corticosteroid withdrawal is only practical thereafter.

In our study, only few of the risk factors evaluated at screening for OLT, which may potentially influence BMD, were able to predict bone loss or its severity post-OLT. Alcoholic liver disease was, interestingly, but perhaps not surprisingly, associated with no decrease in BMD after OLT. Alcohol is toxic to the osteoblast and alcohol abuse is associated with a low turnover osteoporosis. Alcohol withdrawal is a prerequisite for liver transplantation, and candidates for OLT have to be completely dry for at least 6 months before being eligible for transplantation. In transplant recipients with alcoholic liver disease, removal of the toxic effect of alcohol on the osteoblast before transplantation, in addition to the improvement in nutritional status, when alcohol does no longer represent the major source of caloric intake, could well explain the lack of deterioration of bone mass after OLT in patients with this liver pathology.

We found no relationship between graft function, corticosteroid use, number of graft rejection episodes, or persistent vitamin D deficiency on the degree of bone loss after OLT. This is also in keeping with data from a number of studies addressing the role of these factors on post-OLT bone loss,[1,3,4,8,9,12–14] although some other studies did find an association between cholestatic liver disease, cumulative prednisone dose, and bone loss after OLT.[5,6,8]

Previously published data on fracture incidence after OLT show wide variability, ranging from 10% to 33% within the first year after OLT.[5,7,9,11,14,15,19] Our data on 1-year fracture incidence are in keeping with only one previously published study, in which a semiquantitative method of evaluation of vertebral fractures on routinely performed conventional spinal radiographs was also used, and the evaluation was performed by two independent observers on sequential radiographs.[9] Another reason for the discrepancy in fracture incidence between our study and that of others may be that previous studies were performed with smaller numbers of patients,[5,9,14,15,20] or in patients with only cholestatic liver disease as primary liver pathology.[19] Furthermore, although conventional spine radiographs were performed in some studies, these were not evaluated by semiquantitative methods, which may have also led to underestimation of fracture incidence since routine radiology reports tend to underreport specially mild grade fractures.

Data on risk factors for incident fractures after OLT are conflicting. BMD measurements have been found to be predictive in some studies,[9,14,15,19] but not in others.[7,11] In our study, both BMD at time of screening as well as changes of BMD within the first year after OLT were not predictive for fracture risk. Whereas some studies showed prevalent fractures before OLT to be associated with increased fracture risk after transplantation,[11,19,20] this was not the case in our study. These data suggest that the absence of low bone mass and of prevalent fractures before OLT does not preclude an increased risk for fracture after transplantation so that it is of significant clinical relevance that liver transplant recipients should be regularly screened for the presence of these fractures and treated accordingly.

Our study has a number of strengths as well as limitations. Its main strength lies in the relatively large representative cohort of patients studied, the availability of sequential BMD measurements as only inclusion criterion, providing a minimal selection bias, and the opportunity to study changes in BMD for a relatively long period after OLT without the confounding influence of bone-modifying treatment on BMD. Another strength of our study is the availability of serial spinal radiographs within the first year after transplantation in a large number of patients, and the blinded semiquantitative assessment of all spinal radiographs for vertebral fractures by two experienced independent observers.

Our study has also a number of limitations. There were no predefined treatment protocols for immunosuppressive regimens, or for indication for bisphosphonate therapy. These patient management decisions were left to the clinical judgment of the treating physician and may have provided some degree of bias. Another limitation may be our choice to exclude patients from the time of initiation of bisphosphonate treatment, using "last observation carried forward" to minimize the effect of this censoring on our data. Because patients excluded from further analysis owing to starting therapy were most likely to have continuing bone loss if left untreated, the increase in BMD reported in the remaining untreated patients may have been overestimated, although the number of patients treated is smaller than the number of untreated patients. Because treatment with different immunosuppressive regimens was not randomly assigned, the effect of these regimens on patterns of bone loss after OLT could also not be compared. A further limitation of our study is the variable time lag between screening for OLT and date of transplantation. Because the median time between screening and OLT was 9 months, it is conceivable that further bone loss and new fractures may have occurred between screening and transplantation, with possible further decrease in liver function and worsening cholestasis potentially contributing to worsening of skeletal pathology. However, this limitation is common to most published studies, with the majority failing to report time lag between pretransplantation and posttransplantation measurements.[1–5,7,12–14] Although the heterogeneity of the population studied may be perceived as a limitation, we did not consider this to be the case, because the distribution of primary liver pathology was fairly representative of OLT populations, patients receiving bisphosphonates were excluded from the analysis, and patients receiving a second liver transplant did not have a different course of changes of BMD. Only 12 patients (6%) were using corticosteroids at screening and use of these agents posttransplantation would override the effect of the pretransplantation use of these agents.

In conclusion, osteopenia, osteoporosis, and vertebral fractures are prevalent in prospective liver transplant recipients. An overall decline in BMD is observed within the first 6 months after OLT, with subsequent spontaneous recovery to pretransplantation values at the LS, but not at the FN, up to 5 years after OLT. The incidence of vertebral fractures is high within the first year after OLT with poor association between pretransplantation factors, changes of BMD, and fracture risk. Although our findings highlight the spontaneous recovery of BMD associated with restoration of liver function, and its maintenance in the long term after liver transplantation, our data also demonstrate that the spontaneous recovery in BMD was not associated with a

corresponding decrease in fracture risk, at least within the first year after OLT, suggesting a potentially persistent or irreversible effect of liver disease on bone quality and fracture risk. Whether treatment with bisphosphonates or other bone-modifying agents may be able to decrease or prevent fracture risk within the first year after liver transplantation and in the longer term thereafter remains to be established.

Disclosures

All authors state that they have no conflicts of interest.

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