No Association Between BMD and Prevalent Vertebral Fractures in Liver Transplant Recipients at Time of Screening Before Transplantation

Charlotte G. Krol, Olaf M. Dekkers, Herman M. Kroon, Ton J. Rabelink, Bart van Hoek,* and Neveen A. T. Hamdy*

Departments of Endocrinology and General Medicine (C.G.K., T.J.R., N.A.T.H.), Clinical Epidemiology (O.M.D.), Radiology (H.M.K.), and Gastroenterology and Hepatology (B.v.H.), Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands

Context: Osteoporosis and fractures are prevalent after orthotopic liver transplantation (OLT), but data on these skeletal complications are scarce in patients with end-stage liver disease awaiting liver transplantation.

Objective: To evaluate the prevalence of vertebral fractures (VFs) in OLT recipients at the time of screening for transplantation and to establish the association between bone mineral density (BMD) and these fractures before transplantation.

Design and Setting: We conducted a retrospective study of consecutive OLT recipients at the Leiden University Medical Centre between 2000 and 2011 at the time of screening for transplantation. Clinical, laboratory, and BMD data were extracted from electronic hospital records. Conventional spinal radiographs were assessed for VF by two independent observers using Genant's semiquantitative method.

Patients: In total, 162 of the 223 OLT recipients (median age, 51 y; 75% men) who had available BMD and spinal radiographs but who were not receiving bone-modifying treatment at screening for OLT were included in the study.

Main Outcome Measures: Association between BMD and VF before transplantation.

Results: Osteoporosis and osteopenia were prevalent at the lumbar spine in 19 and 38% of subjects, respectively, and in 10 and 42 % at the femoral neck. VFs, mostly grade 1, were prevalent in 56% of the subjects. There was no association between BMD and prevalent VF before transplantation.

Conclusions: VFs were prevalent in liver transplant recipients at the time of screening for transplantation, but there was no association between BMD and prevalent fractures. Spinal radiographs should be routinely performed as part of screening protocols before liver transplantation to enable identification of VF and allow timely intervention to potentially decrease or prevent skeletal morbidity after transplantation. **(*J Clin Endocrinol Metab* 99: 3677–3685, 2014)**

Osteoporosis and fractures are common after liver transplantation (1–3), but data on these skeletal complications are scarce in patients with end-stage liver disease awaiting orthotopic liver transplantation (OLT) (2, 4–6). Published data suggest low bone mass in over 50% of patients and prevalent vertebral fractures varying from 3.5 to 36% of patients before transplantation, depending on the method used for identification of these fractures (1, 4, 5, 7, 8). The liver plays an important role in bone and mineral metabolism. The etiology of bone loss

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received February 16, 2014. Accepted July 16, 2014.
First Published Online July 24, 2014

* B.v.H. and N.A.T.H. are joint senior authors.

Abbreviations: BMD, bone mineral density; CI, confidence interval; INR, international normalized ratio; LS, lumbar spine; MELD, Model for End-stage Liver Disease; 25-OHD, 25-hydroxyvitamin D; OLT, orthotopic liver transplantation; OR, odds ratio.

and increased fracture risk associated with disturbed liver function is multifactorial, including vitamin D deficiency, hypogonadism, decreased mobility, corticosteroid use (in autoimmune hepatitis), and alcohol toxicity where relevant. Candidates for liver transplantation with underlying skeletal pathology are potentially at higher risk for skeletal morbidity, particularly increased fracture risk, after transplantation (1, 2, 9). Cholestatic liver disease has been reported to be associated with osteoporosis and vertebral fractures (10–12), and alcohol abuse is a common cause of osteoporosis and increased fracture risk, particularly in men (5, 13), but less is known about these skeletal complications in other liver pathologies.

Prevalent vertebral fractures represent an important predictive factor for future fractures (1, 2, 14). Indeed, data show that risk of future fracture significantly increases with increasing number and/or grade of severity of vertebral fractures, also shown to be true for mild grade 1 vertebral fractures (15). Identification of these fractures before transplantation would thus be of significant clinical relevance, not only to predict future fracture risk, but also to allow timely initiation of therapeutic interventions potentially able to decrease or prevent skeletal morbidity after transplantation.

The main objectives of our study were to evaluate the prevalence of vertebral fractures in liver transplant recipients at the time of screening for transplantation and to establish the association between bone mineral density (BMD) and these fractures before transplantation.

Patients and Methods

Patients

Consecutive patients who underwent a first OLT at the Leiden University Medical Centre between January 2000 and January 2011 and who had available BMD measurements and conventional radiographs of the thoracic and lumbar spine (LS), performed at the time of their extensive in-hospital screening program before liver transplantation, were eligible for inclusion in the study. Patients treated with corticosteroids or bisphosphonates before or at the time of screening for transplantation were excluded from the present analysis because of the bone-modifying nature of these therapeutic agents. The Leiden University Medical Centre is a tertiary referral center for liver diseases, and often our first encounter with most patients is only at the time of screening for liver transplantation. Correction of vitamin D deficiency and treatment of osteoporosis with bone-modifying agents such as bisphosphonates has thus been very variable, despite clear guidelines, and is highly dependent on the clinical judgment of the referring physician, rather than being dictated by a specific protocol.

Methods

Demographic, clinical, laboratory, and BMD data at the time of screening before liver transplantation were obtained from electronic hospital records of individual patients. Availability of conventional spinal radiographs was ascertained from the records. Nonvertebral fractures were poorly documented, so that data on these fractures could not be analyzed.

Demographic data

Data on age, gender, smoking, height, weight, and primary liver disease were documented. Data on medication including the use of corticosteroids, calcium and vitamin D supplements, and bone-modifying agents such as bisphosphonates were recorded.

Biochemical investigations

Biochemical data extracted from the patients' records included serum calcium (corrected for an albumin of 40 g/L), phosphate, creatinine, total bilirubin, anticoagulant international normalized ratio (INR), PTH, and 25-hydroxyvitamin D (25-OHD) concentrations. Severity of liver disease was determined using the laboratory-based Model for End-stage Liver Disease (MELD) score, shown to be correlated with 3-month survival after transplantation in patients with cirrhosis. Scores were calculated on the basis of serum measurements of bilirubin, creatinine, and INR in SI units, using the following accepted formula (16):

$$MELD = 10*(0.957*ln(Creatinine/88.4)) + (0.378*ln(Bilirubin/17.1)) + (1.12*ln(INR)) + 6.43$$

BMD measurements

BMD was measured at the LS and the femoral neck (FN) using dual energy x-ray absorptiometry (Hologic QDR 4500; Hologic Inc; equipped with reference values based on the National Health and Nutrition Examination Survey [NHANES III]). Data collected included absolute measurements of BMD in g/cm^2, T-scores (SD above or below that of a young adult reference population at peak bone mass), and Z-scores (SD above or below that of an age- and sex-matched reference population). World Health Organization criteria were used to define osteoporosis: T-score of −2.5 or less; and osteopenia, T-score between −1 and −2.5 SD.

Due consideration was given to the need to adjust mean BMD scores of the LS in the presence of one or more lumbar vertebral fractures at the site of the LS BMD measurement (L1–L4).

Vertebral fracture assessment

Conventional anterior-posterior and lateral radiographs of the thoracic spine and postero-anterior and lateral radiographs of the LS were performed by an experienced radiology technician using a standardized protocol, at a distance of 115 cm, with the film centralized on Th7 for the thoracic spine and on L3 for the LS.

All radiographs were blindly assessed for the presence and severity (grade) of vertebral fractures by two independent observers, an experienced musculoskeletal radiologist (H.M.K.), and an experienced bone and mineral disorders specialist (N.A.T.H.). Fractures were assessed using Genant's semiquantitative method of vertebral fracture assessment (17). Using this method, a decrease in height of 20–25% is considered to be a

"mild" grade 1 fracture, a decrease of 25–40% is a "moderate" grade 2 fracture, and a decrease of > 40% is a "severe" grade 3 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 version 20 software (SPSS Inc). A unique number was assigned to each series of radiographs performed at screening for OLT. Radiographs were individually scored by the two independent observers, and in case of discrepancy in scores, mostly about fracture grading, consensus was achieved by both observers reviewing the radiographs together. Careful attention was given to the interpretation of vertebral deformities, excluding vertebral height reductions or deformities due to development abnormalities, degenerative changes, osteochondritis (Scheuermann's disease), or localized metabolic bone disorders such as Paget's disease of bone.

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. Data containing continuous variables were summarized using mean and SD in case of an estimated normal distribution. Median and 5th and 95th percentiles were used otherwise.

A regression model was used to evaluate the influence of potential risk factors for the development of osteoporosis and for the prevalence of vertebral fractures. A univariate regression model was first used, followed by a multivariate regression model with corrections for multiple variables including age and sex. A linear regression model was used in case of continuous variables and a logistic regression model in case of dichotomous variables.

We chose to calculate odds ratios (ORs) rather than risk ratios because of the regression models used. A P value $< .05$ was considered significant.

We evaluated the direct effect of various risk factors, such as cholestatic or alcoholic liver disease, on the outcome parameter, such as prevalence of fractures, as well as the indirect effect of the risk factor on the outcome of through various mediators, such as vitamin D deficiency, using a logistic regression model. We calculated confidence intervals (CIs) of the effect of mediators using the bootstrap method.

Calculations were performed using STATA/SE 12.0 software (StataCorp LP).

Results

Patient characteristics

In total, 162 of the 201 patients who received an elective OLT in the 10-year period between 2000 and 2011, who had available BMD measurements and conventional spinal radiographs performed at the time of screening before liver transplantation, but who were not treated with bisphosphonates, corticosteroids, or other bone-modifying agents were included in the study. Of the 39 excluded patients, 21 had for logistics reasons no BMD measurements and/or conventional spine radiographs at the time of screening for OLT, and 18 patients were using bone-modifying treatments. Details of patients included and excluded are shown in a study flow chart (Figure 1). Median age for the total population studied was 51 years (range, 17–69 y), and 122 of the 162 patients (75%) were men. Median age for women was also 51 years (range, 16–66 y), and 23 women were younger than 50 years. Menopausal status was not documented. The most common liver pathology was viral or alcoholic liver disease (31 and

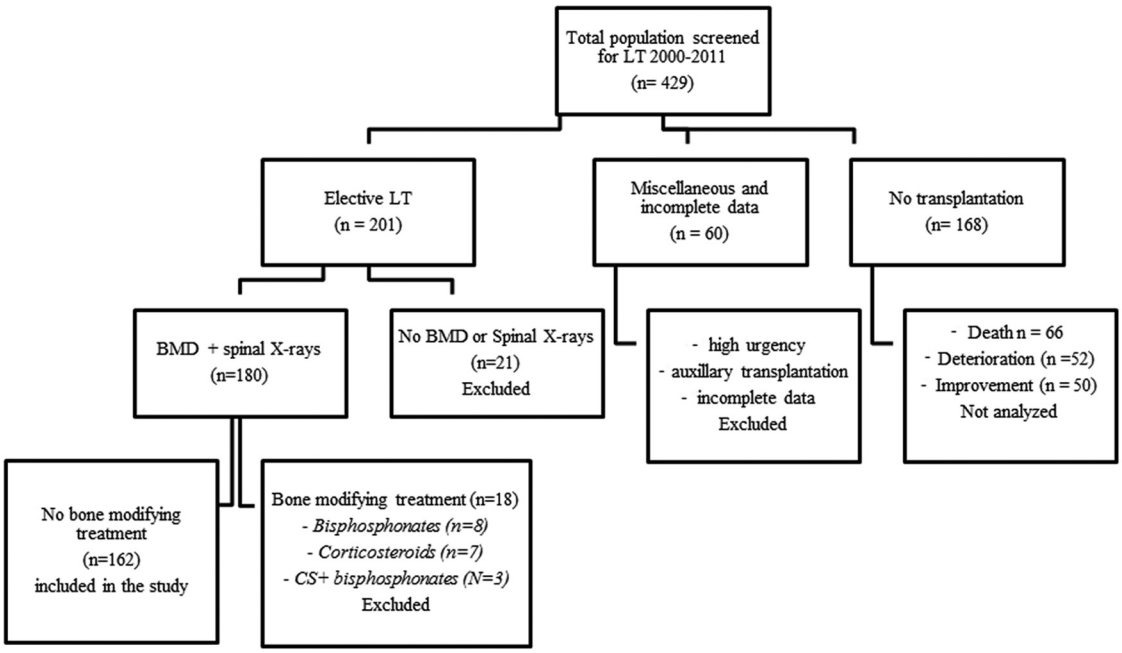

Figure 1. Study flow chart. CS, corticosteroids; LT, liver transplantation.

Table 1. Characteristics of Patients at Time of Screening for Liver Transplantation

Demographic Data	
No. of patients	162
No. of male patients (%)	122 (75)
Age at time of screening, median (5th–95th percentile), y	51 (30–65)
BMI, mean ± SD, kg/m^2	26 ± 5
Smokers, n (%)	54 (35)
Primary liver disease, no. of patients (%)	
Viral	50 (31)
Alcoholic	47 (29)
Combined alcoholic and viral	4 (2)
Cholestatic (PSC/PBC/overlap syndrome)	22 (14)
Malignancy	8 (5)
Autoimmune hepatitis	4 (2)
Metabolic	5 (3)
Other[a]	22 (14)
Severity of liver disease, mean lab MELD score ± SD	14 ± 6
Bone-specific medication, no. of patients (%)	
Calcium- and vitamin D supplements	12 (8)
Vitamin D supplements	2 (1)

Abbreviations: BMI, body mass index; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis.

[a] Other primary liver disease including cryptogenic cirrhosis, malignant tumor, vascular, rare metabolic disorders.

29%, respectively), followed by cholestatic liver disease (14%). Eight percent of patients were using calcium and vitamin D supplements, usually as a combination preparation at a fixed dose of 500 mg calcium and 400 IU cholecalciferol, which had been initiated at some stage before screening for transplantation. Details of patients' characteristics are shown in Table 1.

Biochemical data

Mean serum creatinine concentration was 89 ± 47 μmol/L (normal, <104 μmol/L). Median bilirubin level was 32 μmol/L (range, 4–1172; normal, <17 μmol/L). Mean INR was 1.3 ± 0.33. Mean 25-OHD level was 32 ± 23 nmol/L (normal, 50–250 nmol/L). 25-OHD levels were also low, with a mean of 31 ± 24 nmol/L in patients using vitamin D supplements. Of the 162 patients studied, 110 patients had 25-OHD levels < 50 nmol/L, of whom 54 patients had levels of < 25 nmol/L. Mean laboratory MELD score, reflecting the severity of liver disease, was 14 ± 6 SD (range, 6–35).

BMD measurements

Osteoporosis and osteopenia were prevalent in 19 and 38% of patients at the LS, respectively, and in 11 and 42% of patients at the FN. Mean T-score was −1.15 ± 1.44 at the LS and −1.06 ± 1.23 at the FN. Mean Z-score was −0.63 ± 1.49 at the LS and −0.15 ± 1.21 at the FN. Distributions of BMD at the LS and FN are shown for men and women in Figure 2.

Factors associated with a low BMD

We evaluated a number of potential risk factors for low BMD at the time of screening for transplantation (Table 2). Age and gender were not associated with increased risk for osteoporosis. Cholestatic liver disease was associated with significant increased risk for osteoporosis at the FN in the univariate model (OR, 1.23; 95% CI, 1.07–1.41; $P = .004$), but not in the multivariate model. There was no indirect effect of cholestatic liver disease through vitamin D deficiency on low bone mass (OR, 1.00; 95% CI, 0.96–1.05). Compared to other liver pathologies, alcoholic liver disease was not associated with an increased risk for low bone mass at the LS in the multivariate model (OR, 0.27; 95% CI, 0.08–0.87; $P = .028$), an effect independent of smoking (OR, 1.02; 95% CI, 0.98–1.06). Severity of liver disease as reflected by the laboratory MELD score, was associated with an increased risk of low bone mass at the FN in both the univariate and multivariate models (multivariate model, OR, 1.15; 95% CI, 1.02–1.29; $P = .021$), but not at the LS. Vitamin D deficiency (25-OHD levels < 25 nmol/L) was associated with an increased risk for osteoporosis at the LS in the univariate model (OR, 1.16; 95% CI, 1.01–1.32; $P = .029$), but not in the multivariate model or at the FN.

Prevalence of radiographic vertebral fractures

We documented 186 vertebral fractures in 90 patients, representing a prevalence of 56%. Forty-three patients (44%) had one prevalent fracture, 25 had two fractures (15%), and 22 had three or more fractures (14%). Over 50% of patients had one or more mild grade 1 fractures (52%), of whom 11 patients (10%) also had moderate grade 2 fractures. None of the patients studied had severe grade 3 vertebral fractures. The anatomical distribution of the fractures is shown in Figure 3; 47 patients had lumbar vertebral fractures, of whom 32 had one fracture, 24 of which were of the first lumbar vertebra. Five patients had two lumbar fractures, two patients had three, and two patients had fractures of all four lumbar vertebrae. Most of these fractures were single grade 1 fractures, with no significant impact on total LS BMD, so that they were not excluded from the analysis of total BMD.

Midthoracic compression fractures, usually involving two or three vertebrae, most commonly thoracic vertebrae 7 to 9, were prevalent in seven patients (6%).

Factors associated with radiographic vertebral fractures

We found no significant relationship between BMD and prevalent vertebral fractures using either univariate or

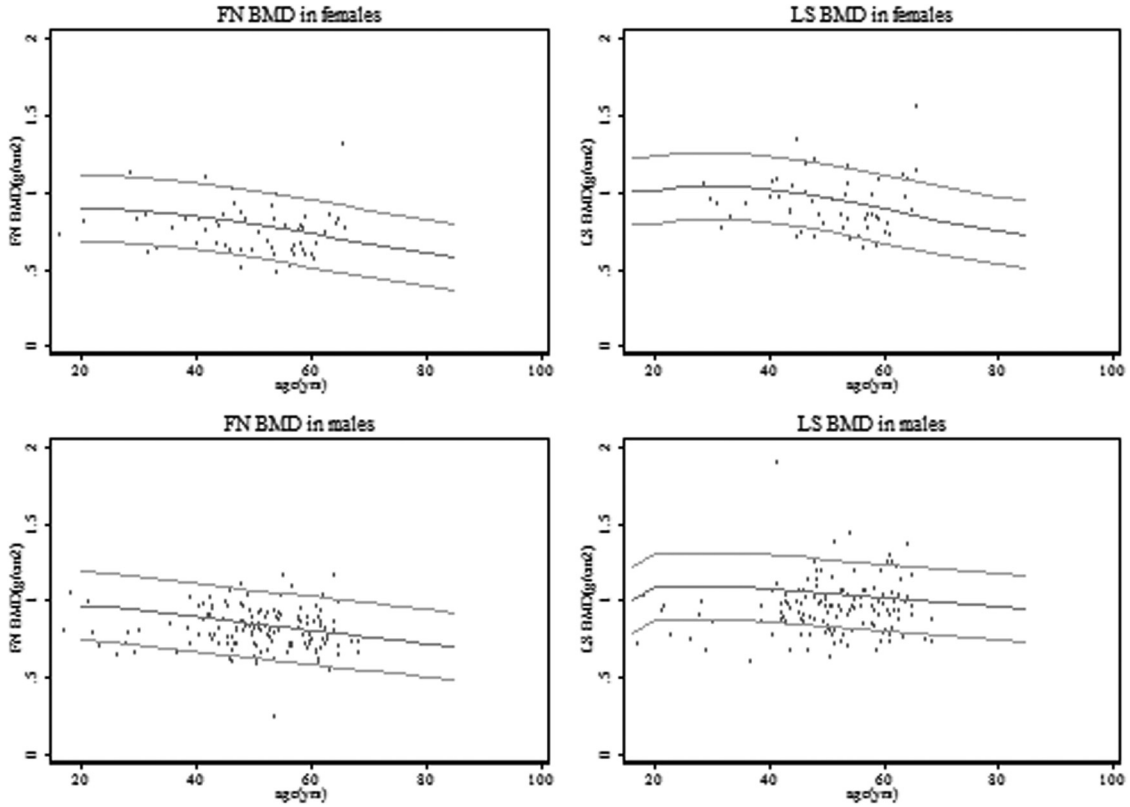

Figure 2. Distribution of BMD in 40 women (upper panels) and 122 men (lower panels) with end-stage liver disease awaiting liver transplantation. Middle, upper, and lower lines represent mean, + 1, and −1 SD of an age- and sex-matched reference population, respectively.

multivariate analysis. In patients with prevalent fractures, 38% had a normal BMD, 40% had osteopenia, and only 23% had osteoporosis. There was no significant association between BMD as a continuous variable, the presence or absence of low BMD, and the presence or absence of vertebral fractures, number of fractures per individual patient, or grade of severity of the fractures.

Male gender was associated with a higher prevalence of vertebral fractures than female gender, with an OR of 4.10 (95% CI, 1.73–9.67; $P = .001$), independent of age, un-

Table 2. Risk Factors for Osteoporosis

	Univariate				Multivariate			
	LS Osteoporosis		FN Osteoporosis		LS Osteoporosis		FN Osteoporosis	
Risk Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male gender	1.03 (0.89–1.20)	.660	0.88 (0.79–0.98)	.025[a]	1.90 (0.62–5.82)	.262	0.45 (0.13–1.55)	.208
Age, y	1.00 (0.97–1.05)	.675	1.00 (0.95–1.06)	.885	1.03 (0.98–1.08)	.216	0.99 (0.93–1.05)	.726
Smoking	1.05 (0.92–1.20)	.446	0.93 (0.85–1.03)	.153	1.78 (0.69–4.60)	.234	0.65 (0.15–2.77)	.562
Cholestatic liver disease	1.17 (0.97–1.42)	.106	1.23 (1.07–1.41)	.004[a]	1.38 (0.37–5.26)	.631	2.00 (0.45–8.85)	.363
Alcoholic liver disease	0.89 (0.77–1.02)	.086	0.91 (0.82–1.01)	.070	0.27 (0.08–0.87)	.028[a]	0.38 (0.07–2.16)	.276
Vitamin D deficiency[b]	1.16 (1.01–1.32)	.029[a]	1.01 (0.91–1.12)	.827	2.10 (0.83–5.28)	.116	0.73 (0.19–2.77)	.645
Bilirubin level, mmol/L	1.00 (1.00–1.00)	.676	1.00 (1.00–1.00)	.487				
Serum creatinine, μmol/L	1.00 (0.99–1.01)	.930	1.01 (1.00–1.01)	.151	1.00 (0.99–1.01)	.505	1.00 (0.99–1.01)	.896
Lab MELD score	1.032 (0.976–1.0910)	.531	1.10 (1.02–1.19)	.012[a]	1.07 (0.97–1.19)	.186	1.15 (1.02–1.29)	.021[a]

[a] Significant effect, *P* value < .05.

[b] Vitamin D deficiency, 25-OHD level < 25 nmol/L.

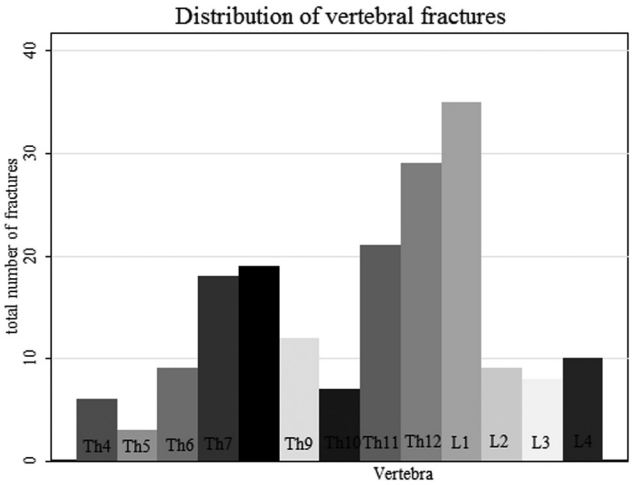

Figure 3. Distribution of 186 vertebral fractures in 90 patients with end-stage liver failure awaiting liver transplantation; Th, thoracic vertebra; L, lumbar vertebra.

derlying disease pathology, or severity of liver disease as expressed by the laboratory MELD score (Table 3). Age as a continuous parameter, vitamin D status, underlying liver disease, and severity of liver disease were not associated with an increased prevalence of vertebral fractures.

Discussion

Our data from this retrospective cohort study suggest a high prevalence of vertebral fractures, mostly grade 1 fractures, in 56% of liver transplant recipients at the time of screening for transplantation, independently of BMD measurements, although low bone mass, predominantly osteopenia, was documented in about two-thirds of these patients. Thus, at the time of screening for liver transplantation, there was no association between BMD as a continuous variable or the presence or absence of low BMD and the presence or absence of vertebral fractures, a higher number of fractures per individual patient, or a higher grade of fractures. Of all factors other than BMD potentially associated with increased fracture risk, only male gender was associated with increased fracture prevalence, independently of age, underlying liver disease, or severity of liver failure. The absence of a significant association between BMD and fracture prevalence suggests that factors affecting bone quality, rather than just bone quantity, may significantly contribute to fracture risk in patients with end-stage liver failure.

Our findings are in keeping with previously published studies, which report low bone mass in over 50% of patients awaiting liver transplantation, with the majority having osteopenia and 20–40% having osteoporosis (2, 5, 7, 8, 10, 11, 18–21). A high prevalence of osteoporosis and fractures reported in patients with cholestatic liver disease (10–12) is believed to be due to vitamin D deficiency and/or to the toxic effects of accumulated metabolites of cholestasis on bone remodeling. In our cohort, cholestatic liver disease also represented an increased risk for osteoporosis at the FN and for prevalent vertebral fractures in univariate but not multivariate analysis. We did not observe an increased prevalence of vertebral fractures in patients with alcoholic liver disease, possibly because of the removal of the inhibitory effect of alcohol on osteoblast function by the prerequisite alcohol abstinence for at least 6 months before screening for transplantation, which may also have contributed to the improvement in BMD at the time of screening (22).

The high prevalence of vertebral fractures of 56% observed in our cohort at the time of screening before transplantation is much higher than the overall prevalence of fractures of 7% observed in a recent Dutch population-based cohort of men and women aged > 55 years, in which all subjects were screened by conventional spinal x-rays (23). The observed prevalence of vertebral fractures in our study was also higher than that of previously published studies, which showed a widely variable and overall lower prevalence of these fractures (3 to 36%), in patients awaiting liver transplantation. (1–3, 5, 7, 8, 19, 24) The main reason for this discrepancy in the prevalence of vertebral fractures between our study and that of others probably lies in the method used for the identification of these fractures. Because vertebral fractures are often silent, actual fracture prevalence may have been underestimated in

Table 3. Risk Factors for Vertebral Fractures

	Univariate		Multivariate	
Risk Factor	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Male gender	1.36 (1.14–1.62)	.001[a]	4.10 (1.73–9.67)	.001[a]
Age, y	1.02 (0.99–1.06)	.136	1.03 (0.99–1.07)	.093
Smoking	0.91 (0.77–1.08)	.266	0.64 (0.30–1.38)	.256
Cholestatic liver diseases	0.76 (0.61–0.95)	.016[a]	0.33 (0.10–1.12)	.076
Alcoholic liver disease	1.07 (0.86–1.42)	.443	0.80 (0.35–1.86)	.607
Lab MELD score	1.01 (0.96–1.07)	.712	1.03 (0.96–1.11)	.361
LS BMD, g/cm^2	1.34 (0.21–8.21)	.755	0.78 (0.10–5.96)	.808

[a] Significant effect, *P* value < .05.

studies in which spinal radiographs were only performed in case of clinical suspicion of a vertebral fracture (5, 8, 25, 26). In contrast, conventional radiographs of the spine formed an integral part of the pretransplantation workup of our candidates for liver transplantation, and were consequently available in all but a few patients. In our study, we also judged it of clinical relevance to report grade 1 fractures, whereas mild grade fractures might have been underreported in previous studies. This is partly because radiologists have been generally reluctant worldwide to report mild vertebral fractures, so that relying on radiology reports for documentation of these fractures may have resulted in an underestimate of their true prevalence (27, 28). Mild grade fractures may have also been consciously under-reported because of doubt about their clinical relevance, although these mild fractures have also now been shown to be associated with increased fracture risk (15).

The relationship between BMD and prevalent fractures has been poorly studied in patients awaiting liver transplantation, and available data are not concordant. Some studies thus show an association between low BMD and prevalence of vertebral fractures (1, 29), but other studies found no such association (3, 30). In our study, there was intriguingly no association between BMD as a continuous variable or as low vs normal BMD and fracture prevalence. Thirty-three percent of patients with fractures thus had normal BMD, and 35% had osteopenia, suggesting that factors affecting bone quality independently of BMD may significantly contribute to increased skeletal fragility in patients with advanced liver disease. This may have significant implications in the management of skeletal complications of advanced liver disease before and after liver transplantation because tools to measure bone quality in vivo such as microindentation are just emerging and remain to be validated, and data on means to specifically improve bone quality with a view to decrease fracture risk are yet to be established.

Notwithstanding, the accurate identification of prevalent vertebral fractures is essential in fracture risk assessment because these fractures represent one of the strongest predictors of subsequent vertebral and nonvertebral osteoporotic fractures (31, 32). There is also evidence that mild grade 1 vertebral fractures are predictive for future fracture risk (15). Of further clinical relevance is that up to 50% of vertebral fractures, even high grade fractures, may be asymptomatic (34) and not necessarily associated with a decrease in BMD, so that they may not come to the attention of treating physicians. The small number of patients treated with bisphosphonates despite the high prevalence of osteoporosis and vertebral fractures and the overall poor vitamin D status of patients awaiting liver transplantation underscores the clinically unmet need for treating physicians to address the issue of skeletal health in patients with end-stage liver disease.

Our study has strengths as well as limitations. Its major strength lies in the evaluation of consecutive transplant recipients at the time of screening for transplantation in one center over a 10-year period, providing a representative pretransplantation cohort with available BMD measurements and conventional radiographs of the spine in all but a few patients. Another strength of our study is the blinded assessment of all spinal radiographs for vertebral fractures by two experienced independent observers using Genant's standardized semiquantitative method, advocated by the International Osteoporosis Foundation for evaluation of vertebral fractures in the clinic (35), rather than relying on routinely obtained radiology reports shown to often underestimate the true prevalence of fractures (25). In most other studies in liver transplantation so far reported, (semi-)quantitative assessments were performed by one observer (1, 7, 29, 30) or the method of evaluation of vertebral fractures is not mentioned (5, 6, 19, 33). A further strength of our study is the inclusion of the mild grade 1 vertebral fractures in the evaluation of prevalent fractures.

A limitation of our study is its retrospective design. However, the laboratory, radiological, and densitometric investigations were not randomly undertaken, but formed an integral part of a preplanned pretransplantation screening protocol for skeletal complications performed in patients with end-stage liver failure, who in this case went on to receive a liver transplant. Although most candidates for liver transplantation were screened for skeletal complications, we only studied those who subsequently received a liver transplant, which may have led to an underestimate of the true prevalence of skeletal pathology because the excluded patients would have been more likely to have had the more severe liver disease and thus potentially the more severe skeletal complications. We also chose to exclude patients using corticosteroids and/or bisphosphonates, which could also have led to the exclusion of patients with the worst skeletal pathology. However, because this was the case in a relatively small number of patients, this is unlikely to have affected the outcome of our study. The absence of prior spinal radiographs precluded the identification of the precise time of occurrence of a documented fracture, resulting in the association between BMD and prevalent fractures being potentially limited by the time lag between the development of a fracture and BMD measurement. We could collect no reliable data on nonvertebral fractures because these were poorly documented. However, previous studies report a generally low incidence of these fractures in end-stage liver disease (2, 5, 6, 8, 19, 29).

In conclusion, our finding of increased fracture risk independent of BMD in liver transplant recipients at the time of screening for transplantation adds to the accumulating body of evidence of the contributory role of bone quality rather than just bone quantity to fracture risk in patients with liver disease. This finding has significant clinical implications in the evaluation and management of prospective liver transplant recipients because it suggests that spinal radiographs should be routinely performed in these patients to enable identification of vertebral fractures and thus of skeletal fragility. Whether this pretransplantation skeletal fragility persists, worsens, or improves after liver transplantation and whether bone fragility could be modulated by available bone-modifying agents to decrease or prevent skeletal morbidity after transplantation remains to be established by long-term studies specifically addressing the issue of skeletal health in liver transplant recipients.

Acknowledgments

Address all correspondence and requests for reprints to: Neveen A. T. Hamdy, MD, PhD, Head Bone and Mineral Disorders Section, Department of Endocrinology and General Medicine, and Head Leiden Centre for Bone Quality, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. E-mail: N.A.T.Hamdy@lumc.nl.

Disclosure Summary: The authors have nothing to disclose.

References

1. **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(4):1198–1207.
2. **Leidig-Bruckner G, Hosch S, Dodidou P, et al.** Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. *Lancet*. 2001;357(9253):342–347.
3. **Monegal A, Navasa M, Guañabens N, et al.** Bone disease after liver transplantation: a long-term prospective study of bone mass changes, hormonal status and histomorphometric characteristics. *Osteoporos Int*. 2001;12(6):484–492.
4. **Alcalde Vargas A, Pascasio Acevedo JM, Gutiérrez D, et al.** Prevalence and characteristics of bone disease in cirrhotic patients under evaluation for liver transplantation. *Transplant Proc*. 2012;44(6): 1496–1498.
5. **Carey EJ, Balan V, Kremers WK, Hay JE.** Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. *Liver Transpl*. 2003;9(11):1166–1173.
6. **Guichelaar MM, Malinchoc M, Sibonga JD, Clarke BL, Hay JE.** Bone histomorphometric changes after liver transplantation for chronic cholestatic liver disease. *J Bone Miner Res*. 2003;18(12): 2190–2199.
7. **Monegal A, Guañabens N, Suárez MJ, et al.** Pamidronate in the prevention of bone loss after liver transplantation: a randomized controlled trial. *Transpl Int*. 2009;22(2):198–206.
8. **Premaor MO, Das TK, Debiram I, et al.** Fracture incidence after liver transplantation: results of a 10-year audit. *QJM*. 2011;104(7):599–606.
9. **Hardinger KL, Ho B, Schnitzler MA, et al.** Serial measurements of bone density at the lumbar spine do not predict fracture risk after liver transplantation. *Liver Transpl*. 2003;9(8):857–862.
10. **Bai XL, Liang TB, Wu LH, et al.** Elevation of intact parathyroid hormone level is a risk factor for low bone mineral density in pretransplant patients with liver diseases. *Transplant Proc*. 2007; 39(10):3182–3185.
11. **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(9):1390–1402.
12. **Trautwein C, Possienke M, Schlitt HJ, et al.** Bone density and metabolism in patients with viral hepatitis and cholestatic liver diseases before and after liver transplantation. *Am J Gastroenterol*. 2000; 95(9):2343–2351.
13. **González-Reimers E, Alvisa-Negrín J, Santolaria-Fernández F, et al.** Prognosis of osteopenia in chronic alcoholics. *Alcohol*. 2011;45(3): 227–238.
14. **Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M.** Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721–739.
15. **Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Krege JH.** Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporos Int*. 2007;18(6):761–770.
16. **Kamath PS, Wiesner RH, Malinchoc M, et al.** A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001; 33(2):464–470.
17. **Genant HK, Wu CY, van Kuijk C, Nevitt MC.** Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137–1148.
18. **Dolgos S, Hartmann A, Isaksen GA, et al.** Osteoporosis is a prevalent finding in patients with solid organ failure awaiting transplantation - a population based study. *Clin Transplant*. 2010;24(5):E145–E152.
19. **Millonig G, Graziadei IW, Eichler D, et al.** Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. *Liver Transpl*. 2005;11(8):960–966.
20. **Ninkovic M, Love SA, Tom B, Alexander GJ, Compston JE.** High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. *Calcif Tissue Int*. 2001;69(6):321–326.
21. **Sokhi RP, Anantharaju A, Kondaveeti R, Creech SD, Islam KK, Van Thiel DH.** Bone mineral density among cirrhotic patients awaiting liver transplantation. *Liver Transpl*. 2004;10(5):648–653.
22. **Peris P, Parés A, Guañabens N, et al.** Bone mass improves in alcoholics after 2 years of abstinence. *J Bone Miner Res*. 1994;9(10): 1607–1612.
23. **Van der Klift M, De Laet CE, McCloskey EV, Hofman A, Pols HA.** The incidence of vertebral fractures in men and women: the Rotterdam Study. *J Bone Miner Res*. 2002;17(6):1051–1056.
24. **Ninkovic M, Love S, Tom BD, Bearcroft PW, Alexander GJ, Compston JE.** Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. *J Hepatol*. 2002;37(1):93–100.
25. **Floreani A, Fries W, Luisetto G, et al.** Bone metabolism in orthotopic liver transplantation: a prospective study. *Liver Transpl Surg*. 1998; 4(4):311–319.
26. **Pennisi P, Trombetti A, Giostra E, Mentha G, Rizzoli R, Fiore CE.** Pamidronate and osteoporosis prevention in liver transplant recipients. *Rheumatol Int*. 2007;27(3):251–256.
27. **Delmas PD, van de Langerijt L, Watts NB, et al.** Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. *J Bone Miner Res*. 2005;20(4):557–563.
28. **Kim N, Rowe BH, Raymond G, et al.** Underreporting of vertebral

fractures on routine chest radiography. *AJR Am J Roentgenol*. 2004; 182(2):297–300.
29. **Giannini S, Nobile M, Dalle Carbonare L, et al.** Vertebral morphometry by x-ray absorptiometry before and after liver transplant: a cross-sectional study. *Eur J Gastroenterol Hepatol*. 2001;13(10): 1201–1207.
30. **Ninkovic M, Skingle SJ, Bearcroft PW, Bishop N, Alexander GJ, Compston JE.** Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. *Eur J Gastroenterol Hepatol*. 2000;12(8):931–935.
31. **Black DM, Arden NK, Palermo L, Pearson J, Cummings SR.** Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1999;14(5):821–828.
32. **Melton LJ 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL.** Vertebral fractures predict subsequent fractures. *Osteoporos Int*. 1999;10(3):214–221.
33. **Meys E, Fontanges E, Fourcade N, Thomasson A, Pouyet M, Delmas PD.** Bone loss after orthotopic liver transplantation. *Am J Med*. 1994;97(5):445–450.
34. **Melton LJ 3rd, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL.** Prevalence and incidence of vertebral deformities. *Osteoporos Int*. 1993;3(3):113–119.
35. **Hernlund E, Svedbom A, Ivergård M, et al** Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013;8:136.