Alendronate in Combination With Calcium and Vitamin D Prevents Bone Loss After Orthotopic Liver Transplantation: A Prospective Single-Center Study

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Bone loss is a common complication in patients before and after liver transplantation (LT). The aim of this study was to investigate the efficacy of prophylactic treatment with bisphosphonates after LT in preventing progressive bone loss in LT patients. We included 136 patients with end-stage liver diseases awaiting LT. Bone mineral density (BMD) (by dual X-ray absorptiometry) and markers of bone metabolism were determined before, and 4, 12, 24, 36, and 48 months after LT. All patients received vitamin D and calcium supplementation before and after LT, those with osteopenia or osteoporosis prior to LT were additionally treated with alendronate following LT. Decreased BMD was seen in a high percentage of patients undergoing LT (osteopenia 48.5%, osteoporosis 23.5%). Reduced BMD before LT was not related to gender, underlying liver disease, or Child-Turcotte-Pugh classification. Body mass index (BMI) prior to LT, however, correlated significantly with the fracture risk. Alendronate prevented the ubiquitously observed bone loss after LT in patients with osteoporosis and osteopenia and, in addition, led to an increase in BMD in patients with osteoporosis within 24 months after LT. In conclusion, our study suggests that alendronate is efficacious in preventing the natural course of bone loss associated with LT. (*Liver Transpl 2005;11:960-966.*)

Osteoporosis is an important and common complication in individuals with advanced stage liver disease characterized by reduced bone mass and architecturally-flawed bone tissue with resulting increased fracture rate. Osteoporosis also affects a high percentage of patients with end-stage liver disease who undergo orthotopic liver transplantation (LT), causing significant morbidity, immobility, and markedly reduced quality of life.[1,2]

The etiological mechanisms of hepatic osteodystrophy are multifactorial and remain undefined. Pretransplant factors such as malnutrition,[3] immobility,[4] vitamin D deficiency,[5,6] and hypogonadism[7,8] may contribute to low bone mineral density (BMD) prior to LT. After LT, immunosuppressive agents, in particular corticosteroids, tacrolimus and cyclosporine A, are responsible for further deterioration of bone metabolism.[9–11] Numerous studies have shown a dramatic decrease of BMD in the first 3 to 12 months after LT.[12–17] The need for therapy of transplantation-related bone loss has been recognized, but no guidelines based on controlled clinical trials dealing with larger cohorts of LT recipients are yet available.

Most of our knowledge about osteoporosis is derived from studies with postmenopausal women and steroid-induced bone loss. In these patients, treatment with bisphosphonates not only prevented deterioration in BMD but also decreased the fracture rate.[18–21] Other therapy options for postmenopausal osteoporosis are calcitonin,[22] selective estrogen receptor modulators (raloxifene),[23] and hormone replacement therapy,[24–26] most of them in conjunction with adequate calcium and vitamin D intake.

Only recently, Shane et al.[27] showed that patients after heart transplantation treated with alendronate or vitamin D3 had less bone loss than the untreated control group.

Based on the recommendations of the American College of Rheumatology for prevention and treatment of steroid-induced osteoporosis,[28] we initiated a prospective uncontrolled study with patients awaiting LT. All patients on the waiting list received 1,000 mg calcium and 400 IE vitamin D daily. Oral bisphosphonate (alendronate 70 mg/week) was commenced after LT in those with osteopenia and osteoporosis prior to LT at

Abbreviations: LT, liver transplantation; BMD, bone mineral density; BMI, body mass index.

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Table 1. Patients' Baseline Characteristics

	Osteoporosis	Osteopenia	Normal BMD
Number of patients	32	66	38
Female	10	19	14
Male	22	47	24
Chi-squared test	No statistical significance ($P = 0.8$)		
Child A	8	15	12
Child B	18	43	21
Child C	6	8	5
Chi-squared test	No statistical significance ($P = 0.8$)		
Viral	12	23	16
Alcoholic	16	31	11
Cholestatic	3	4	3
Other causes	1	8	8
Chi-squared test	No statistical significance ($P = 0.2$)		

Abbreviation: Child, Child-Turcotte-Pugh class.

the time of LT. Those patients that showed an initially normal BMD but deteriorated at the first reevaluation 4 months after LT were started on alendronate at that time.

The aim of the study was to evaluate the efficacy of alendronate to prevent further bone loss after LT and reduce fracture rates in patients with preexisting osteoporosis, osteopenia, or those with initially normal BMD that decreased after LT. In addition, we analyzed bone metabolism parameters to evaluate if they add information to that derived from imaging techniques regarding bone remodeling after LT.

Patients and Methods

Patients

Between January 1999 and December 2003 a pre-LT osteoporosis assessment was performed in 156 patients. Subsequently, 136 patients, who underwent LT were eligible for this analysis (for patients' demographics according to their BMD status see Table 1). The study was approved by the local ethics committee and informed consent was given by all patients.

All patients were evaluated for osteoporosis before LT and consecutively at 4, 12, 24, 36, and 48 months after LT. The mean follow-up was 27.6 months after LT.

At the time of evaluation for LT, the mean age of patients (43 female, 93 male) was 55 ± 9 years (range 23-73 years).

The major underlying liver diseases were alcohol-related cirrhosis in 58 patients (42.6%) followed by chronic viral hepatitis in 51 (37.5%), and primary biliary cirrhosis and primary sclerosing cholangitis in 10 (7.4%). The remaining 17 patients (12.5%) had miscellaneous liver diseases, such as autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, and polycystic liver disease.

According to the Child-Turcotte-Pugh classification, the degree of liver disease was as follows: 35 patients (25.7%) presented with class A (listed for LT because of a hepatocellular carcinoma), 82 (60.3%) with class B, and 19 (14.0%) with class C.

Immunosuppressive regimens after LT consisted of cyclosporine A (82 patients; 60.3%) or tacrolimus (52 patients; 38.2%). Sirolimus was administered to 2 patients (1.5%). Some of the patients received interleukin-2-receptor antagonist instead of calcineurin-inhibitors in the early postoperative period because of initially poor renal function. At the time of LT all patients received corticosteroids, which were gradually tapered and discontinued within 3 months post-LT.

Nutritional Status

Nutritional status was assessed by the body mass index (BMI) before LT and at the time of reevaluation for osteoporosis. Before LT, 6.1% of the patients were underweight (BMI <19), 50% were within normal ranges (BMI 20-25), and 43.9% were overweight (BMI >25). The mean BMI of 25.2 (±3.7) prior to LT decreased slightly 4 months after LT (BMI 24.7 ± 4.1) but increased to 26.0 ± 4.3 after the first year post-LT and remained stable thereafter.

Determination of BMD and Metabolism

BMD was measured by dual X-ray absorptiometry (Hologic DQR-4500W [Hologic, Inc., Bedford, MA] or Lunar DPX [Lunar Radiation Corp., Madison, WI]; all data were converted according to the manufacturer's instructions into Hologic BMD).

To detect vertebral fractures, conventional radiographs of the thoracic and lumbar spine were performed pre-LT, and 4, 12, 24, 36, and 48 months post-LT.

Osteoporosis and osteopenia were defined according to international guidelines. Osteoporosis was classified by a t-score of below −2.5 in either lumbar spine or femur, and osteopenia by a t-score between −2.5 and −1.

Several laboratory parameters of bone and calcium metabolism were measured in order to analyze bone resorption and bone formation (intact parathyroid hormone [immunoluminometric assay; Nichols Institute Diagnostics, San Clemente, CA], osteocalcin [immunoradiometric assay; BioCis, Gif-sur-Yvette Cedex, France], bone-specific alkaline phosphatase [radioimmunoassay; Beckmann Coulter, Krefeld, Germany], insulin-like growth factor 1 [immunoradiometric assay; Nichols], insulin-linked growth factor binding protein 3 [radioimmunoassay; Nichols], sex hormone binding protein [immunoradiometric assay; Biochemical Immunosystems, Rome, Italy], free testosterone [radioimmunoassay; DPC Buehlmann, Salzburg, Austria], and free deoxypyridinoline [enzyme-linked immunoabsorbent assay; Metra-Biosystems, Inc, Mountain View, CA]). All tests were performed according to the manufacturers' instructions in a routine laboratory.

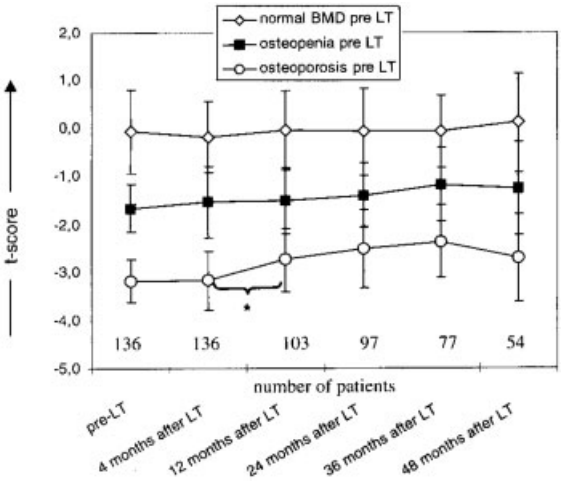

Figure 1. Follow-up of the t-score in the lumbar spine. *$P < 0.05$.

Treatment

All patients received 1,000 mg calcium and 400 IE vitamin D3 supplementation prior to and post-LT. Patients with osteoporosis or osteopenia in either the lumbar spine or the femoral neck received oral bisphosphonate therapy (Alendronate [Fosamax]; Merck, Sharp & Dohme, Vienna, Austria), if tolerated. A total of 98 patients (72%) received alendronate after LT. Alendronate therapy was continued until the end of follow-up.

Statistical Methods

Data were analyzed using the SPSS program version 11.0 (SPSS, Chicago, IL). Chi-squared, paired *t*-test or Mann-Whitney-U-test, 1-way ANOVA or Kruskal-Wallis test, and Spearman's correlations coefficient were used to analyze differences between the subgroups. Tests were chosen depending on the distribution of the data. Log-transformation was used to achieve better approximation to normal distributions. Statistical significance was defined for $P < 0.05$.

Results

Baseline Evaluation (Prior to LT; 136 Patients)

A decreased BMD, defined as a t-score lower than 1 standard deviation below the normal range either in the lumbar spine or in the femur (trochanter and neck), was seen in 72% of patients prior to LT; osteoporosis was seen in 23.5% of patients, osteopenia in 48.5%. Only 28% showed a normal BMD. Compared to the age-matched population, patients with end-stage liver disease showed an increased prevalence of osteopathy. A z-score lower than 1 standard deviation below the age-matched range was found in 43.4% of patients.

Interestingly, there were no differences between male and female patients in the prevalence of either osteoporosis or osteopenia. In addition, no statistically significant differences in the BMD were seen between the 4 major groups of liver diseases, namely viral, alcohol-related, cholestatic, and miscellaneous. The stage of liver disease according to the Child-Turcotte-Pugh classification showed no statistically significant correlation with the BMD prior to or after LT.

A low BMI at the time of evaluation for LT, however, significantly correlated ($P < 0.01$) with decreased BMD and increased risk of fractures before LT ($P = 0.04$), whereas a gain in BMI after LT failed to correct the previously noted decline in BMD and therefore, did not show a correlation with the course of the BMD.

Post-LT Evaluation

Lumbar BMD After LT (Lumbar Vertebrae 1-4)

Patients with osteoporotic spinal BMD before LT did not lose BMD, as known from the natural history of BMD after LT. Moreover, they gained BMD significantly within 24 months after LT and remained stable thereafter. Patients with osteopenia before LT did not show a decrease in BMD after LT and remained stable throughout the study period (Fig. 1).

Femoral BMD after LT (Trochanter and Neck)

Patients with osteoporotic femoral neck BMD before LT significantly gained BMD between 4 and 12 months after LT and showed a continuous gain of BMD thereafter. Patients with osteopenia remained stable within the first 2 years after LT and then gained BMD significantly between the second and the third year after LT (Fig. 2).

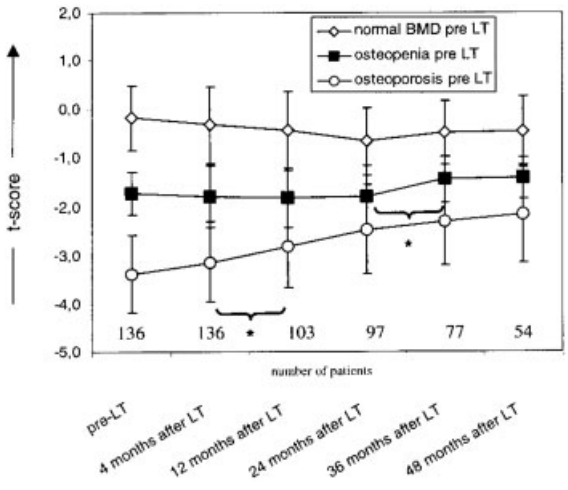

Figure 2. Follow-up of the t-score in the femoral neck. *$P < 0.05$.

Table 2. Changes in Bone Mineral Density at the End of Follow-Up

	Loss of BMD*	Stable BMD*	Gain of BMD*
Number of patients	8	102	26
Female	3	33	7
Male	5	69	19
Chi-squared test	No statistical significance ($P = 0.8$)		
Child A	4	28	3
Child B	4	63	15
Child C	0	11	8
Chi-squared test	Statistically significant difference ($P = 0.04$)		
Viral	2	40	16
Alcoholic	5	40	6
Cholestatic	1	7	2
Other causes	0	15	2
Chi-squared test	No statistical significance ($P = 0.3$)		

Abbreviations: BMD, bone mineral density; Child, Child-Turcotte-Pugh class.
*Patients are counted if they changed to another BMD category (osteoporosis, osteopenia, normal BMD).

Patients Without Alendronate

Patients with a normal BMD in both femoral neck and lumbar spine were treated only with calcium and vitamin D3. They lost BMD in the femoral neck within the first months; however, without reaching statistical significance ($P = 0.08$). BMD at the lumbar spine remained stable throughout the whole study period.

Response to Alendronate

At the end of follow-up (mean follow-up 27.6 months after LT) we assessed the number of patients who changed their BMD category (e.g., from osteoporosis to osteopenia) (Table 2). The majority of patients remained stable (102 / 136 patients; 75%), while 8 patients significantly lost BMD (5.8%) and 26 patients gained BMD, moving to the superior category (19.1%). Gender and diagnosis did not influence the change in BMD, but patients presenting with Child-Turcotte-Pugh C more frequently improved their BMD ($P = 0.04$).

Risk of Fractures Prior to and After LT

A total of 15 patients (11.0%) presented with fractures before LT (3 had traumatic rib fractures, 1 of them with an accompanying fracture of the clavicle; 12 had vertebral compression fractures). There was no significant difference between men and women, but patients with alcohol-related liver disease were more prone to fractures than patients with other underlying liver diseases.

The risk of fractures after LT was 5.8%, with no significant differences between male and female patients, underlying liver disease or the stage of liver disease before LT. Most fractures were vertebral compression fractures (6 / 8 fractures; 75%), 2 of 8 fractures were traumatic (1 fracture of the humerus, 1 fracture of the os sacrum). Interestingly, there was no fracture of the femoral neck, even though the mean BMD in the femur was significantly lower than in the spine. All fractures occurred within the first year after LT.

Low BMD seen 12 months after LT correlated with the incidence of fragility fractures after LT. Prior to LT, a low BMI and alcohol-related liver cirrhosis were risk factors for fractures, but BMD, Child-Turcotte-Pugh classification, or gender had no predictive values.

Correlation Between Laboratory Parameters and BMD

Laboratory parameters showed a high between-patient variability. No significant correlation between BMD or fractures and laboratory parameters could be demonstrated at any time. Even when categorized in quartiles, laboratory parameters showed no significant correlation with BMD or fractures pre- or post-LT. There was no significant correlation between changes in BMD and changes in log-transformed laboratory parameters.

Besides the expected difference in the free testosterone concentration, there was no consistent gender difference in the bone metabolism parameters.

Side Effects

No patients developed severe gastroesophageal reflux disease, which has been reported for alendronate use.[29] Alendronate had to be discontinued in only in 2 patients (1.8%) due to abdominal discomfort including mild reflux esophagitis. In these patients, pamidronate (Aredia; Novartis, Vienna, Austria) was given at a dose of 30 mg intravenously once a month.

Discussion

Osteoporosis has been found in a significant number of patients with end-stage liver disease; a regimen of immunosuppressive drugs including steroids leads to a further deterioration of this condition after LT in almost all patients, causing pronounced morbidity and reduced quality of life. Several studies have addressed this problem and different therapeutic approaches have been used; however, without much efficacy.[30]

Recently, alendronate has shown its positive effect in the treatment of postmenopausal women and in steroid-induced osteoporosis.[18–21] Based on these data, this prospective study was conducted to evaluate the efficacy and safety of alendronate in the treatment of post-LT osteoporosis.

Patients with end-stage liver disease awaiting LT were included, and bone density and fractures were analyzed by dual X-ray absorptiometry and conventional radiographs pre- and several times post-LT (4, 12, 24, 36, and 48 months). Patients with osteoporosis, osteopenia, or a normal BMD but significant decrease in BMD within the first 4 months after LT received oral alendronate in addition to calcium and vitamin D3 supplementation to prevent the almost inevitable bone loss after LT.[12,13,16,31–33] Treatment with alendronate was started immediately after LT, whereas calcium and vitamin D3 supplementation was instituted while patients were waiting for LT. If tolerated, alendronate was continued as long as BMD showed osteopenic or osteoporotic values.

In our cohort the prevalence of osteoporosis (BMD < -2.5 standard deviations below normal) and osteopenia (BMD between -2.5 and -1 standard deviations below normal) was 23.5 and 48.5%, respectively. Only 28% presented with normal BMD values. These rates are in agreement with the previously published data reporting a decreased bone density in end-stage liver disease varying between 16 and 56%.[34–38]

The striking result of this study was that alendronate combined with calcium and vitamin D almost completely prevented further bone loss in the first 4 months after LT. This is a significant improvement compared to the natural course of bone loss within the first few months after LT as reported in numerous publications.[12,13,16,39–41] Furthermore, both osteoporotic and osteopenic patients treated with alendronate remained stable following LT throughout the first 4 months after LT and improved their BMD significantly thereafter (osteoporotic patients showed a significant increase between 1 and 2 years after LT, osteopenic increased their BMD between year 2 and year 3 after LT).

With our results, we are in agreement with the study by Shane et al.,[27] in which they found that patients after heart transplantation receiving alendronate or vitamin D3 showed less bone loss than untreated patients.

Underlying liver disease, stage of liver cirrhosis, and gender did not correlate with the prevalence of bone loss prior to or post-LT, which is in agreement with previous publications.[7,42–44]

In our cohort we can corroborate the correlation between BMI and BMD in pretransplantation patients, which had already been shown in both postmenopausal women[45] and in patients with end-stage liver disease.[46] Presumably this is due to metabolic and endocrinologic activities of the adipose tissue. Nutritional therapy (enteral or parenteral hyperalimentation) has been shown to be beneficial in the treatment of complications of liver cirrhosis (infection, encephalopathy, ascites, and prolonged hospitalization). This approach might be usefully employed in patients having been underweight before LT with the intention to improve BMI and secondarily BMD.[47]

The fracture incidence, the final and most debilitating complication of osteopathy, was very low in our study with 5.8% (8 / 136 transplanted patients). Previous publications with large cohorts of LT recipients reported fracture rates between 7.5% and 65%.[1,48–50] In agreement with other studies, the majority of our patients who showed fractures developed vertebral compression fractures and traumatic fractures of peripheral bones. None of our patients had a hip fracture, which is in contrast to other studies reporting a 10% prevalence of hip fractures.[49,51] Patients with alcohol-related liver cirrhosis were more prone to fractures, mostly before LT. This might be associated with a higher prevalence of falls in this population.

So far, the role of antiresorptive therapy in patients with liver disease and those after LT has not yet been defined. Controversial results have been reported for pamidronate.[52–54] However, only a single infusion of pamidronate was used in these studies. Other regimens consisted of hormone replacement therapy as recommended for treatment of osteoporosis in postmenopausal women.[55] But the reported increased risk of breast cancer in women treated with hormone replacement therapy has markedly limited the use of this therapeutic approach.[56]

Although bisphosphonates prevented a significant decline of the BMD in LT patients, led to some improvement in spinal BMD after 24 months in osteopenic and osteoporotic patients, and were associated with a low fracture risk when initiated immediately after LT, it was not possible to reach normal BMD for patients with osteoporosis or osteopenia before LT except for 4 in whom alendronate was discontinued because of normal BMD. This phenomenon of incomplete recovery has already been demonstrated in the natural course of BMD, where patients gained BMD after the initial loss within the first 3 months after LT but never reached a higher BMD than before LT.[57]

One drawback of this study is that it is not a randomized investigation. However, numerous studies have shown a significant reduction of bone density within a short time after LT. In addition, alendronate and other bisphosphonates have recently demonstrated their great efficacy in treating osteoporosis, in particular that induced by corticosteroid treatment.[18–21] Based on this evidence, it appeared reasonable to administer alendronate to patients presenting with osteopenia / osteoporosis prior to LT.

There was no significant correlation between laboratory parameters such as intact parathyroid hormone, osteocalcin, insulin-linked growth factor binding pro-

tein 3, bone-specific alkaline phosphatase, insulin-like growth factor 1, sex hormone binding protein, free testosterone, free deoxypyridinoline, and actual BMD, changes in BMD, or the risk of fractures in patients with end-stage liver disease or after LT. Therefore, these parameters appear to be of limited use in patients after LT, a fact that is in agreement with previously published works.[58] In our study the limitation of the bone turnover markers seemed to be the high variability within the same individual. This might be due to the previously described influences of the circadian rhythm, seasonal changes, or differences between fasting and nonfasting periods.[59–61]

Our study suggests that oral alendronate therapy immediately after LT in patients with osteoporosis / osteopenia is effective in preventing bone loss subsequent to LT. However, these results can only be interpreted as hypothesis-generating for the present time, and further randomized studies are needed.

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