Decrease in Bone Mass in Women After Liver Transplantation: Associated Factors

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ABSTRACT

Background. In the future, an increasing number of female liver transplant recipients will reach the climacteric with osteoporosis as a common complication. We evaluated the factors associated with decreased bone mass among women after liver transplantation.

Methods. A prospective, cross-sectional study of 23 outpatient transplant recipients followed from February 2009 to March 2010 included women of age ≥35 years after liver transplantations ≥1 year prior. We recorded patient histories, liver enzyme levels, as well as bone mineral densities measured at the lumbar spine and femur. Statistical analysis used Fisher's exact test, simple odds ratio (OR), and Spearman's rank correlation coefficient.

Results. The mean patient age was 52.5 ± 11 years with 30.4% premenopausal, and 69.6% perimenopausal or postmenopausal. Approximately 21% showed osteoporosis and 35%, a low bone mass. Postmenopausal women: OR 69.0 (95% CI 2.89–1647.18; $P < .0001$), aged ≥49 years: OR 13.33 (95% CI 1.78–100.15; $P = .0123$) and receiving a transplant after 44 years of age: OR 49.50 (95% CI 3.84–638.43; $P < .0001$) were associated with a lower bone mass. Having undergone transplantation for more than 5.8 years lowered the risk of bone mass change: OR 0.11 (95% CI 0.02–0.78; $P = .0361$). Clinical and laboratory variables, including corticosteroid use, were not associated with decreased bone mass.

Conclusion. Understanding the prevalence and factors associated with osteoporosis among female liver transplant recipients is important to enhance the strategies to diagnose and treat these women, seeking to improve their quality of life.

IN THE LAST few decades, liver transplantation has become widely accepted as an established form of therapy worldwide. Considerable progress in clinical transplantation has produced good long-term results, resulting in a significantly increased survival of patients who experience severe liver disease.[1] Despite improved survival, their morbidity has been known to increase, impairing quality of life among transplant recipients.[2] Women represent approximately one third of liver transplant patients. Their major indications for liver transplantation include primary biliary cirrhosis, posthepatitis cirrhosis, and autoimmune hepatitis.[3] In Brazil, transplantation is mainly indicated for hepatitis virus C and alcoholism.[4] Osteoporosis is a severe complication after liver transplantation. As a result of preexistent chronic liver disease and the high doses of immunosuppressive agents, the majority of liver transplant patients show accelerated loss of bone mass within the first 3 or 6 months after surgery, resulting in a greater fracture risk.[5] Other factors such as vitamin D deficiency, hypogonadism, malnutrition, and reduced physical activity, which are common among patients with end-stage liver disease, also contribute to decreased bone mineral density.[6] Cholestatic diseases such as primary biliary cirrhosis and primary sclerosing cholangitis have also been identified as risk factors for changes in bone mass, perhaps owing to malab-

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sorption of calcium and vitamin D, as well as to interference of hyperbilirubinemia with osteoblast function.[7]

In addition to all of the factors associated with liver transplantation, climacteric women have a greater decrease in serum levels of estrogen. However, a previous study identified age and severity of liver disease, and not menopausal status, as the main risk factors for the development of osteoporosis among women with primary biliary cirrhosis who did not undergo liver transplantation.[8]

In the future, an increasing number of women undergoing liver transplantation will reach the climacteric. However, there are relatively few studies related to hypogonadism after liver transplantation. The existing reports are often limited to the male population.[9] With the purpose of identifying possible risk factors associated with bone mass changes in liver transplant recipients and enhancing the strategy for managing osteoporosis among these patients, we performed a study of women who had undergone liver transplantation.

METHODS

This prospective, cross-sectional study included female liver transplant recipients followed from February 2009 to March 2010. All women aged ≥35 years who had received a liver transplant ≥1 year prior were included in the study. Women with amenorrhea for ≥12 months or follicle-stimulating hormone measurements (FSH) > 23 mUI/mL were considered postmenopausal. Perimenopause was established when menstrual irregularity had occurred without any anatomic cause. Women with regular menstrual cycles were considered to be premenopausal.[10] We excluded from the study physically debilitated patients, those with a personal history of bilateral oophorectomy, and those who used hormonal medications to treat menopausal symptoms within 3 months before enrollment. Of the 33 women who met the inclusion criteria, 6 did not respond to our telephone contact and 4 declined to participate in the study, leaving 23 subjects.

Women were interviewed in the Menopause Outpatient Clinic by the same investigator, who ascertained: age, race, education, marital status, date of transplantation, time since transplantation, disease that caused liver failure, type of immunosupressive drug currently used, history of high blood pressure or diabetes mellitus, date of menarche, date of last menses, menstrual pattern, and history of active sex life. We also measured weight (kg), height (m), and blood pressure (mmHg) of these women, as well as performing a general physical and gynecological examination. After the interview, the women underwent laboratory tests for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl-transferase (GGT), and bilirubin and bone densitometry of the lumbar spine and femur. All subjects signed a written informed consent form before the interview. The study was approved by our Research Ethics Committee (number 721/2008) and financed by FAPESP (number 2008/09726-6).

Bone Mineral Density

Bone mineral density was measured at the lumbar spine (L1–L4), total femur and femoral neck using dual energy x-ray absorptiometry (DXA; Hologic, Discovery, Wisc). The effective coefficient of variation (CV) of the device is 0.45%. Bone mineral density measurements were expressed in grams by cm^2 and as *T*- and *Z*-scores. For the diagnosis of osteoporosis by densitometry, we used the *T*-score value for postmenopausal and perimenopausal women. For premenopausal women, we used the *Z*-score.[11] Osteoporosis was defined as *T*-score values ≤ −2.5 standard deviations. Low bone mass was diagnosed when the *T*-score values measured between −1 and −2.5 standard deviations. Bone mass was considered normal when *T*-score values were > −1 standard deviation.[12] *Z*-score values >−2 standard deviations were considered within the expected value and *Z*-scores < −2 standard deviations were classified as bone mass changes.[11]

Biochemical and Hormonal Measurements

Laboratory tests were drawn from 7 to 10 AM on the day of the interview after an overnight fast. Samples were stored in a freezer at −20°C until the tests. FSH measurement was obtained by chemiluminescence (Advia, Centauro-Siemens), where the minimum concentration detected was 0.3 mUI/mL and concentrations > 23 mUI/mL were defined as postmenopausal. AST and ALT measurements were obtained by the kinetic UV test (Liquiform-Labtest); alkaline phosphatase was measured by the modified Bowers and McComb method (Liquiform-Labtest); GGT was measured by the modified Szasz method (Liquiform-Labtest); bilirubin by the Jendrassik method (Liquiform-Labtest).

Statistical Analysis

Data were evaluated by the mean values with standard deviations and medians. Correlations between interval measurements were evaluated by Spearman's rank correlation coefficient. For laboratory or interval measurements, the median value was used as the cut-off. Analysis of categories above or below the median was performed using Fisher's exact test and simple odds ratio (OR). The adopted significance level was 5%; The SAS version 9.1.3 (SAS, Inco, Chicago, Ill) was the software used for the analysis.

RESULTS

The mean age of the women was 52.5 ± 10.9 years (median, 49.2; range, 35.0–69.6). There were 4 (17.4%) of 35–40 years of age; 1 (4.3%) of 40–45; 7 (30.4%) of 45–50; 4 (17.4%) of 55–60; 3 (13%) of 60–65; and 4 (17.4%) of 65–70 years. The mean age of the women at liver transplantation was 46.7 ± 12 years (median, 44.7; range, 25.7–63.9). The mean time since transplantation was 5.8 ± 3.1 years (median, 5.8; range, 1–11.9). Mean body mass index was 27.0 ± 4.6 (median, 27.3; range, 18.8–38.2). Of the 23 women, 7 (30.4%) were premenopausal, 3 (13%) perimenopausal, and 13 (56.5%) postmenopausal. Corticosteroids were administered for immunosuppression in 7 women (30.5%); therefore, 16 (69.5%) were not prescribed corticosteroids.

Of 23 women included in the study, 13 had bone mass changes (56.5%), including 5 (21.7%) who had osteoporosis detected by densitometry with 3 (13%) ≥1 site and 2 (8.7%) in the lumbar spine, femoral neck, and total femur. Eight had low bone mass in ≥1 site (34.8%; Table 1).

Being postmenopausal was significantly associated with a decreased bone mass: OR, 69.0 (95% confidence interval [CI], 2.89–1647.18; $P < .0001$). Age at the time of liver transplantation showed a significant relationship. For those >44 years at the time of the surgical procedure, the risk was

Table 1. Bone Mineral Density According to WHO Criteria (n = 23)

Measurement Site	n	%
Lumbar spine (L1–L4)		
Osteoporosis (T score < -2.5)	4	17.4
Low bone mass (T score from -1 to -2.5)	8	34.8
Normal (T score from -1 to $+1$/Z-score until -2)	11	47.8
Femoral neck		
Osteoporosis (T score < -2.5)	3	13.0
Low bone mass (T score from -1 to -2.5)	9	39.1
Normal (T score from -1 to $+1$/Z-score until -2)	11	47.8
Total femur		
Osteoporosis (T score < -2.5)	2	8.7
Low bone mass (T score from -1 to -2.5)	7	30.4
Normal (T score from -1 to $+1$/Z-score until -2)	14	60.9

WHO, World Health Organization.

49.50 (95% CI, 3.84–638.43; $P < .0001$). The age of a woman at the time of the interview also showed a significant correlation. There was a higher risk of bone mass changes when the age was > 49 years: OR, 13.33 (95% CI, 1.78–100.15; $P = .0123$). Time since transplantation also had a significant relationship to bone mass, and time after liver transplantation >5.8 years was a protective factor against bone mass changes: OR, 0.11 (95% CI, 0.02–0.78; $P = .0361$).

All women included in the study were taking immunosuppressive drugs. Of these, 8 (34.8%) were prescribed tacrolimus and mycophenolate; 4 (17.4%), tacrolimus alone; 3 (13%) cyclosporine alone; 3 (13%), tacrolimus and prednisone; 1 (4.3%), cyclosporine and prednisone; 1 (4.3%), cyclosporine and mycophenolate; 1 (4.3%), tacrolimus, prednisone, and mycophenolate; 1 (4.3%), cyclosporine, prednisone, and mycophenolate; and 1 (4.3%), tacrolimus, prednisone, and azathioprine. Due to the small number of women, the various combinations of immunosuppressive drugs and the fact that glucocorticoids are the group of immunosuppressants most closely related to decreased bone mass, we subdivided the women into 2 groups; Corticosteroid use (30.5%), and no use of these drugs (69.5%). No difference was observed between groups regarding bone mass (OR, 0.18; 95% CI, 0.03–1.28; $P = .1688$).

Disorders responsible for transplantation were classified into 2 groups: Cholestatic (primary biliary cirrhosis and primary sclerosing cholangitis) and noncholestatic (the remaining disorders). There was no evidence of a difference between groups regarding bone mass (OR, 0.13; 95% CI, 0.01–1.38; $P = .1269$). Analysis of the association between bone mass and liver enzyme levels (AST, ALT, alkaline phosphatase, and GGT) and bilirubine also failed to show any difference. There were no associations between bone mass and race, education, marital status, arterial hypertension, presence of diabetes, age at menarche, sexual activity, body mass index, or parity (Table 2).

To quantify a correlation between variables in which we observed a significant association we used Spearman's correlation coefficient. There was an inverse correlation between the total lumbar spine bone mineral density in grams per square centimeter and present chronological age ($P < .01$; $R = -0.58$); age at the time of transplantation ($P < .01$; $R = -0.66$); and time since onset of menopause expressed in months after the last menses ($P < .01$; $R = -0.62$). There was a direct correlation between total lumbar spine bone mineral density in grams per square centimeter and time since transplantation ($P = .02$; $R = 0.45$; Fig 1)

DISCUSSION

The purpose of this study was to evaluate bone mass as well as factors associated among liver transplanted women aged ≥ 35 years. We observed a decreased bone mass in 56.5% of the subjects: 34.8% with a low bone mass and 21.7% with osteoporosis. The prevalence of observed bone mass changes agreed with previously reported data, which described bone mass changes in 65.5% of cases[13] and osteoporosis among 25% to 50% of women receiving a liver transplantation.[14,15]

We observed a significant association of older patient age at the time of liver transplantation with a low bone mass. Regarding age at transplantation, previous studies have reported an inverse relationship between bone mass and chronological age before the performance of the surgical procedure.[16,17] Low bone density before transplantation proved to be the major risk factor for the development of osteoporosis and pathologic fractures after surgery.[18] In contrast, Guichelaar et al[16] described younger age and having greater bone mass before surgery as risk factors for greater bone loss in the first 4 months posttransplantation. However, despite greater bone loss, this group of patients did not develop densitometry values compatible with low bone mass after undergoing liver transplantation. The study group of Guichelaar et al[16] was heterogeneous including both men and women of various age groups. Therefore, a comparison between their results and ours is hampered.

The relationship between menopausal status and bone mass is yet to be clarified among patients with chronic liver disease. In the present case study, 30.4% of the patients were premenopausal, 13% were perimenopausal, and 56.6% were postmenopausal. In perimenopausal and postmenopausal women, we observed an 81.2% rate of bone mass change, including 50% with low bone mass and 31.2% with osteoporosis.

In this study, the rate of low bone mass in climacteric women undergoing liver transplantation was similar to that reported in women not undergoing a liver transplantation, which is estimated to be 37%–50%.[19] The rate of osteoporosis observed among transplanted climacteric recipients was similar to that observed in the postmenopausal population with no liver disease, namely approximately 30%.[20] In the present study, the prevalence of osteoporosis in climacteric patients undergoing a liver transplantation was lower than that reported by Isoniemi et al,[15] who described osteoporosis in 50% of postmenopausal patients undergoing liver transplantation. However, it is worth mentioning

Table 2. Factors Associated With Bone Mass Changes in Women Undergoing Liver Transplantation (n = 23)

	Bone Mass					
	Changed		Unchanged			
	n	%	*n*	%	*P*-Value	OR (95% CI)
Age (y)					.0123*	
≤49	3	23.1	8	80.0		1.0
>49	10	76.9	2	20.0		13.33 (1.78–100.15)
Race					1.0000*	
White	11	84.6	9	90.0		0.61 (0.05–7.88)
Non-white	2	15.4	1	10.0		1.0
Hypertension					.5596*	
Yes	1	7.7	2	20.0		0.33 (0.03–4.32)
No	12	92.3	8	80.0		1.0
Diabetes mellitus					.3394*	
Yes	4	30.8	1	10.0		4.00 (0.37–43.14)
No	9	69.2	9	90.0		1.0
Menopausal status					<.0001*	
Premenopausal	0	0.0	7	70.0		1.0
Perimenopausal	2	15.4	1	10.0		25.00 (0.75–833.00)
Menopausal	11	84.6	2	20.0		69.00 (2.89–1647.18)
Menarche (y)					.2138*	
≤13	5	38.5	7	70.0		1.0
>13	8	61.5	3	30.0		3.73 (0.65–21.58)
Time since transplantation (y)					.0361*	
≤5.8	9	69.2	2	20.0		1.0
>5.8 y	4	30.8	8	80.0		0.11 (0.02–0.78)
Age at transplantation (y)					<.0001*	
≤44	2	15.4	9	90.0		1.0
>44 y	11	84.6	1	10.0		49.50 (3.84–638.43)
BMI (kg/m^2)					.6802*	
≤27	7	53.8	4	40.0		1.0
>27	6	46.2	6	60.0		0.57 (0.11–3.04)
Immunosuppression					.1688*	
Without corticosteroids	11	84.6	5	50.0		1.0
With corticosteroids	2	15.4	5	50.0		0.18 (0.03–1.28)
Liver disease					.1269*	
Cholestatic	1	4.3	4	17.4		0.13 (0.01–1.38)
Others	12	52.2	6	26.1		1.0

*Fisher's Exact Test.

that in the study of Isoniemi et al,[15] approximately 94% of climacteric women who underwent liver transplantation were prescribed glucocorticoids, in contrast to the only 19% in the present study.

We confirmed an inverse correlation between bone mineral density and time since amenorrhea as expressed in months after the last menstrual period; that is, the longer time since the onset of menopause, the lower the bone mineral density. Monegal et al[2] observed correlations between menopausal status and chronological age, but this variable did not significantly influence bone mass. In a study of nontransplanted patients with primary biliary cirrhosis, Guanabens et al[8] concluded that menopausal status was not, although chronological age, severity of liver disease, advanced histologic stage, and low body mass index, were independent risk factors for osteoporosis.

In the present study, none of the premenopausal women undergoing liver transplantation displayed bone mass changes, a finding in agreement with the results of Guichelaar et al,[16] which indicated a gain in bone mass during the first 2 years after transplantation that was significantly higher among premenopausal than perimenopausal and postmenopausal patients, probably owing to the high estrogen levels in the latter groups of women. However, there is a scarcity of studies to elucidate more clearly the role of hypoestrogenism in bone mass changes after liver transplantation.

Previous data have shown that the loss of bone mass occurs mainly in the first 3–6 months after liver transplantation owing to an uncoupling between bone formation and bone resorption.[2,16,18] Bone histology studies have described that bone loss ceases approximately 6 months after liver transplantation. Bone formation tended to increase, especially in the lumbar spine, resulting in the recovery of bone mass within 2 years after the procedure.[2] Our study corroborated the results of previous studies. There was a

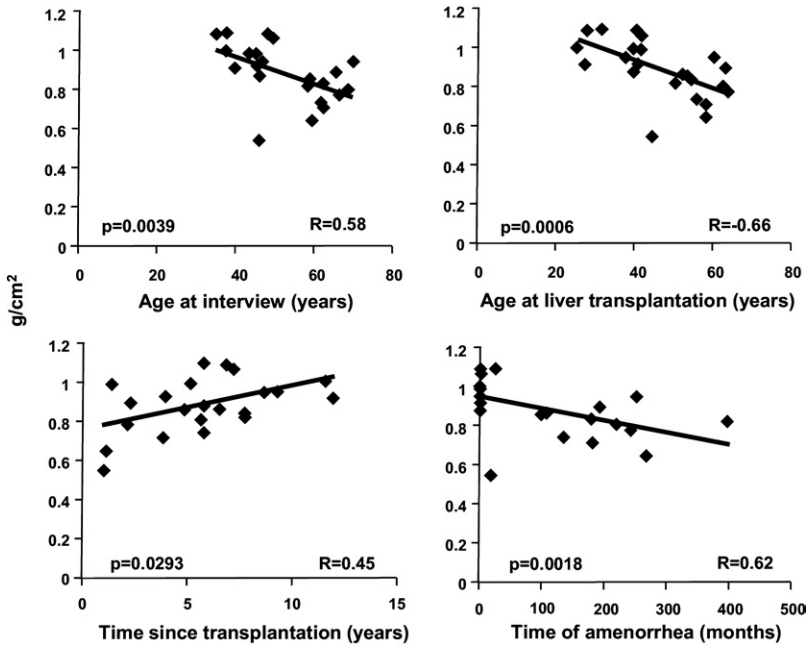

Fig 1. Correlation between lumbar bone mass and age, time since transplantation, age at transplantation, and menopausal status.

clear tendency for an increased bone mass in the lumbar spine with time. A longer time after transplantation corresponded to a higher bone mass. In contrast, we noticed a less close correlation between bone mass and time since transplantation in the femur. Previous studies had suggested the same observation, concluding that the recovery of bone mass occurred more slowly in the femoral neck than in the lumbar spine, probably because cortical bone needs more time to recover than trabecular bone.[2,13]

The deleterious effects of glucocorticoids on bone mass have already been demonstrated.[21–29] In this study, the current use of corticosteroids as an immunosuppressive drug did not affect the bone mass, probably owing to the time elapsed since liver transplantation. Similar results were also obtained in previous studies.[2,13,16] An explanation for this finding may be that high corticosteroid doses are used mainly in the first months posttransplantation, producing a higher loss of bone mass at that time.[26] In the near future, the doses of glucocorticoids will tend to decrease, for combinations with tacrolimus[28,30] have lessened the necessity of glucocorticoid treatment.

Cholestatic diseases were associated with a greater prevalence of osteoporosis among patients who were not liver transplant recipients.[31] Malabsorption of calcium and vitamin D, in addition to the interference of bilirubin levels in osteoblast function have been cited as risk factors.[7] Analysis of women with pretransplantation cholestatic disorders was also performed to investigate whether these women were at higher risk for bone mass changes after transplantation. However, no differences were observed, probably because of the small number of cases in our study. The nature of this study did not permit the establishment of a cause and effect relationship. We also measured liver enzymes and bilirubin to confirm whether their increase could influence bone mass in these women. The results were not significant, probably owing to the same limitations.

We highlight that this study evaluated only women older than 35 years. The group was heterogeneous concerning menopausal status and other characteristics. Therefore, these results should not be generalized to other liver transplant groups. However, we believe that the evaluation of a group of liver transplant recipients consisting of only women is crucial for an enhanced understanding of posttransplant hypogonadism and its interference with bone mass. We believe that in the near future the results of this initiative will contribute toward a broader understanding of the need to focus on the female population, who deserve a better quality of life.

This study showed that menopausal status, older chronological age at the time of transplantation, less time since transplantation, and older recipient age at the present time were the main factors associated with decreased bone mass among women receiving a liver transplantation. This subject has not been well studied and is yet to be fully understood. We believe that the data reported may help to elucidate the behavior of bone mass in female liver transplant recipients.

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