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ORIGINAL ARTICLE

Trabecular bone score in patients with liver transplants after 1 year of risedronate treatment

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Summary

The aim of this study was to analyse the effect of risedronate on Trabecular Bone Score in liver transplant patients with low bone mass, during 1-year follow-up. In this retrospective cohort study, trabecular bone score (TBS) was calculated from dual X-ray absorptiometry images of the lumbar spine (LS), collected from a prospective randomized open-label 1-year trial performed in liver recipient patients. A total of 89 patients with osteopenia or osteoporosis were randomized to receive RIS plus calcium and vitamin D3 or calcium and vitamin D3. TBS was low in both groups at baseline, 6 and 12 months. Baseline TBS at the LS showed degraded microarchitecture in 22.8% of patients, partially degraded in 40.3%, and normal values in 36.8% of the patients. After 1 year of treatment, no difference in TBS was observed between both groups. No correlations were found between bone mineral density (BMD) and TBS values at any follow-up time point. No relationship was found between BMD, TBS or immunosuppressive drugs with incidental fracture. No significant effect in TBS was observed in liver transplant patients treated with RIS or calcium and vitamin D3 after 1 year of follow-up. In these patients, the clinical usefulness of this new tool should be established.

Introduction

Bone loss after liver transplantation (LT) is well recognized, and results in considerable morbidity with an increased risk of fractures [1]. An overall decline in bone mineral density (BMD) has been observed within the first 6 months after LT, with subsequent recovery in some patients to pretransplantation values at the lumbar spine (LS), but not at the femoral neck (FN). However, vertebral fracture risk is high after LT regardless of changes in BMD [2]. Fracture rates of 15–27% have been reported, with most fractures occurring within the first 2 years of transplantation [3]. Meta-analysis has shown that bisphosphonates treatment during the first year after solid organ transplantation is associated with a 47% reduction in the number of subjects with fractures [4]. Therefore, bisphosphonates are probably a first-line option for the treatment of these patients.

Currently, the gold standard for the diagnosis of osteoporosis has been based on the evaluation of BMD [5]. However, considerable overlap exists in BMD values between individuals who develop fractures and those who do not [6]. The utility of BMD values in predicting fracture risk in organ transplant patients is still unclear, suggesting that factors affecting bone quality (geometry, microarchitecture and the intrinsic properties of bone tissue) rather than just bone quantity may significantly contribute to fracture risk in patients with end-stage liver failure [2].

In this way, it should be appropriate to develop an ideal surrogate for identifying the risk of post-transplant fracture. The trabecular bone score (TBS) is a new grey-level

texture measurement that is derived from the exploitation of experimental variograms of 2D projection images. TBS measures the mean rate of local variation of grey levels in 2D projection images. TBS is obtained after reanalysing a dual X-ray absorptiometry (DXA) examination and can be compared directly with a BMD because both evaluate the same region of the bone [7–9]. In previous cohort studies, TBS was related to fracture risk, particularly when showing degraded architecture (TBS below 1.200) [10], and discriminated patients with fragility fractures from those without fracture, independently of BMD [11–13]. TBS has been shown to predict current and future fragility fractures in primary osteoporosis, to be a helpful adjunct to BMD and clinical risk factors for fracture detection and prediction, and for monitoring treatment effect [14]. In addition, a number of studies have shown that TBS has value in secondary causes of osteoporosis [15].

The aim of this study was to analyse the effect of RIS on TBS in liver transplant patients with low bone mass, during 1-year follow-up. There have been several prospective and randomized trials using different bisphosphonates in LT patients with conflicting reports regarding fracture incidence and BMD changes. To our knowledge, RIS has not been tested in liver transplant patients, even though RIS is indicated for postmenopausal and glucocorticoid-induced osteoporosis treatment [16,17]. RIS has shown early and significant reductions regarding fracture risk in patients at high risk for fracture [18] within the first year of treatment.

Patients and methods

Subjects

In this retrospective cohort study, TBS was calculated from DXA images of the lumbar spine, collected from a prospective randomized open-label 1-year trial performed in liver recipient patients at '12 Octubre' University Hospital, Madrid. They were recruited between January 2006 and March 2008. Exclusion criteria were age <18 years; *T*-score >−1 SD at lumbar spine and hip, positive human immunodeficiency virus (HIV) serology; severe gastrointestinal disease (such as oesophageal diseases, gastritis and ulcers); creatinine clearance <30 ml/min; previous treatment with antiresorptive agents; other metabolic bone disease; and LT more than 15 days before recruitment study [19].

A total of 212 patients were transplanted in this period. Of these, 89 patients were included and were randomized to RIS (RIS group, $n = 45$) or no RIS (control group, CON, $n = 44$). Randomization was performed by a simple random sampling from survey select of SAS enterprise guide. All patients gave informed consent. RIS group received oral RIS 35 mg once weekly, plus oral calcium (500 mg twice daily) and vitamin D_3 (800 IU daily), whereas CON group received only calcium and vitamin D_3 at same dosages. Six patients died during the study (four RIS, two CON) because of major LT complications (acute rejection, liver failure or infection) and two withdrew from the study (CON group) for personal reasons.

We chose to include patients with abnormal BMD, excluding those with normal BMD, because pre-existing low bone mass at the time of LT has been shown to be a major risk factor for post-transplant skeletal complications [20].

All patients received immunosuppression after LT with tacrolimus and glucocorticoids. In selected patients, mycophenolate mofetil or cyclosporine was added as per protocol. Perioperative intravenous methylprednisolone (500 mg) was followed by oral prednisone doses of 20 mg/day. Glucocorticoids were progressively tapered, aiming to withdraw after 3 months. Tacrolimus was initially given at 0.15 mg/kg/day divided into two doses, thereafter adjusting for level (5–10 ng/ml). Data were collected from a data base for LT of our centre.

Biochemical parameters

Fasting serum samples were obtained at baseline, 3, 6 and 12 months after LT and were immediately processed and kept frozen at −70 °C until the assays were performed. 25-hydroxyvitamin D_3 (25(OH)D) was assessed by enzyme immunoassay (IDS). Bone remodelling markers, procollagen type 1 amino-terminal propeptide (P1NP) and β-CrossLaps (β-CTX), were analysed by electrochemiluminescence technique (Roche Diagnostics, Mannheim, Germany) (reference values of 20–100 ng/ml and 0.200–0.704 ng/ml, respectively). The coefficient of variation for each one of these assays was <10%. Estimating glomerular filtration rate (eGFR) was calculated using the abbreviated MDRD-4 equation [21]: estimated GFR (ml/min per 1.73 m^2) = 186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if African American).

Bone densitometry

Bone mineral density was measured at 0, 6 and 12 months of post-LT, at lumbar spine (L1-L4) and femoral sites, with a DXA densitometer (QDR 4500; Hologic, Waltham, MA, USA). Precision error was <1.5%. The least significant change (LSC) calculated as recommended by the International Society for Clinical Densitometry (ISCD) for DXA was 3.54%, which is an acceptable value [22]. Using the WHO classification, patients were classified as normal (*T*-score >−1), osteopenic (−1 ≥ *T*-score >−2.5) or osteoporotic (*T*-score ≤−2.5). Interval between basal DXA and transplantation was <15 days.

TBS analysis

Trabecular bone score is a method for noninvasive assessment of bone microstructure. The finding of more numerous and connected and less sparse trabeculae translates into a high TBS value, whereas a low trabecular number and connectivity and high trabecular separation translate into a low TBS, independent of BMD.

Trabecular bone score was applied retrospectively to DXA examination and was assessed using the TBS INSIGHT2.0 software (Med-Imaps, Geneva, Switzerland). TBS examination was performed by the same author. LS TBS was calculated as the mean value of individual measurements for vertebrae L1-L4. We use as reference values, the mean value of TBS in a group of healthy Spanish controls ($n = 87$), mean TBS 1.372 ± 0.170 (unpublished data). This value is similar to those reported by other authors, in postmenopausal women: TBS ≥ 1.350 is considered normal; between 1.200 and 1.350 is consistent with partially degraded microarchitecture, and ≤1.200 with degraded microarchitecture [14].

Fracture evaluation

Standard X-rays (posteroanterior and lateral) of thoracic and lumbar spine were obtained at baseline and 12 months after transplantation. Evaluation was performed using the Genant semi-quantitative approach. Fracture assessments were performed by one observer. 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 LT. All organ transplantation subjects of the study were follow-up regularly in our centre. In case of a traumatic fracture, we had access to the image and include this in the analysis.

Statistical analysis

Categorical variables are described as percentage and continuous variables as mean and standard deviation. Variables were tested for normality (with the Kolmogorov–Smirnov test). The normality assumption was confirmed in all the variables. For between-group comparisons, unpaired Student's *t*-test or chi-square test was used accordingly. Correlation analysis between various parameters was performed by Pearson correlation coefficient.

Changes in parameters compared with baseline (e.g. BMD and TBS) were analysed using paired Student's *t*-test. Changes in BMD and TBS were evaluated through mixed effects ANOVA (group × time design with repeated determinations in time factor). Dropouts were not included in the analysis, and missing values were not replaced. Adjustments for gender, age, vitamin D level, cumulative corticosteroid dose, primary liver pathology and postmenopausal status were made by double classification ANOVA. BMD changes between baseline, 6 and 12 months were presented as a percentage.

Statistical analyses were conducted using the SPSS program (version 14.0; SPSS, Chicago, IL, USA).

Results

Baseline characteristics are summarized in Table 1. There were no differences in mean age at transplantation or body mass index between the two study groups.

As we previously reported [19], osteoporosis at either lumbar spine or femoral level was present at baseline in 39% of patients (lumbar spine and/or femoral *T*-score ≤−2.5). There were no statistically significant differences between RIS and CON groups in terms of the number of osteoporotic patients (44.4% RIS group, 34.1% CON group; $P = 0.317$) (Table 2).

After 6 months, in the RIS group, there was an increase in spine BMD (compared with baseline) which was significant ($P = 0.014$). One-year lumbar spine BMD showed a significant increase in both groups (Table 3). Changes in femoral neck were no significant in any of the groups. Comparisons between RIS and CON group showed no significant differences at 6 or 12 months. Gender factor did not modify the treatment effect on BMD change.

We found significant differences between the mean baseline TBS of the whole group (1.298), and the mean TBS in healthy controls (1.372) ($P < 0.001$). Baseline TBS at the lumbar spine showed degraded microarchitecture (TBS ≤ 1.20) in 22.8% of the patients, partially degraded (TBS > 1.20 and <1.35) in 40.3% and normal values (TBS ≥ 1.35) in 36.8% of the patients (Fig. 1). These low values were not correlated with age ($P = 0.35$), vitamin D status ($P = 0.33$), underlying liver disease ($P = 0.69$), sex ($P = 0.36$) or the presence of prior diabetes mellitus ($P = 0.12$). We found that lumbar spine TBS was negatively correlated with BMI ($r = -0.53$, $P = 0.0001$). TBS was low in both groups at baseline (RIS 1.291 ± 0.122; CON 1.306 ± 0.126, $P \geq 0.84$), 6 months (RIS 1.276 ± 0.139; CON 1.309 ± 0.103, $P = 0.75$) and 12 months (RIS 1.275 ± 0.111; CON 1.293 ± 0,128, $P = 0.98$) (Table 4, Fig. 2). MANOVA test showed no significant evolution in TBS over the year of the study ($P = 0.490$). There were no significant differences between groups ($P = 0.454$). The time × group interaction was no significant ($P = 0.801$).

No correlations were found between BMD and TBS values, at any follow-up time point (baseline: $r = -0.005$, $P = 0.90$; 6 months: $r = 0.117$, $P = 0.38$; 12 months: $r = -0.016$, $P = 0.90$).

A total of 19 patients (44%) in RIS group and 13 (30%) patients showed vertebral fracture baseline, without differ-

Table 1. Baseline characteristics of patients randomized at inclusion.

	RIS plus calcium and vitamin D (n = 45)	Calcium and vitamin D (n = 44)	P-value
Age (years)	57.9 ± 6.5	54.6 ± 8.8	0.052
Gender (%) males/females	32 (71%)/13 (29%)	38 (86%)/6 (14%)	0.079
Postmenopausal females	100% (13/13)	67% (4/6)	**0.028**
BMI(kg/m^2)	24.6 ± 4.5	25.2 ± 4.3	0.524
Aetiology (%)			
Alcoholic	15 (37)	11 (30)	0.142
HCV	14 (35)	12 (32)	
HBV	2 (5)	6 (16)	
Miscellaneous	9 (23)	8 (22)	
Time since diagnosis of liver disease (years)	8.3 ± 8.8	11.9 ± 11.7	0.133

Data are represented as mean ± SD. HBV, hepatitis B virus; HCV, hepatitis C virus. Miscellaneous includes viral-alcoholic, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune and cryptogenic liver disease. Bold value indicates statistically significant values.

Table 2. Baseline bone mineral density (BMD), *T*-score, *Z*-score and trabecular bone score (TBS) for study population (mean ± SD). Bold values indicates statistically significant values.

	Risedronate (n = 45)	Control (n = 44)	P value
BMD(g/cm^2)			
Lumbar spine	0.792 ± 0.104	0.844 ± 0.089	**0.012**
Femoral neck	0.691 ± 0.106	0.713 ± 0.135	0.389
T-score			
Lumbar spine	−2.61 ± 0.87	−2.14 ± 0.75	**0.008**
Femoral neck	−1.68 ± 0.86	−1.58 ± 0.99	0.611
TBS			
Lumbar spine	1.291 ± 0.122	1.306 ± 0.126	0.840
Lumbar spine and/or femoral			
Osteoporosis	20 (44.4%)	15 (34.1%)	0.317
Osteopenia	25 (55.6%)	29 (65.9%)	

Table 3. Lumbar spine bone mineral density (BMD) change (%) at 6 and 12 months from baseline (mean ± SD).

	RIS group	CON group	P value
BMD % change LS 6 months	2.82 ± 6.92*	1.46 ± 4.88	0.319
BMD % change LS 12 months	4.81 ± 8.81†	3.35 ± 5.76†	0.385

*P = 0.014 vs. baseline.
†P = 0.001 vs. baseline.

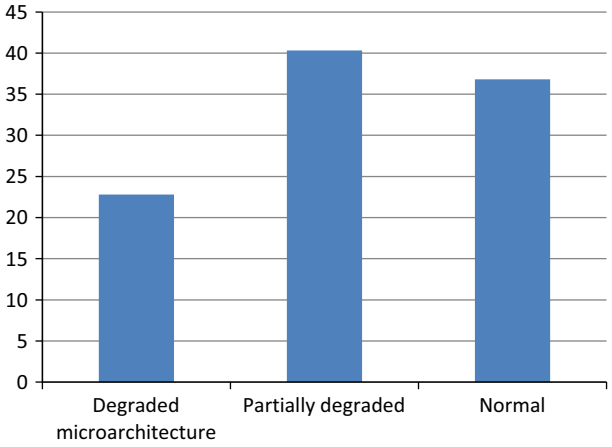

Figure 1 Baseline trabecular bone score (TBS) at the lumbar spine in the study population showed degraded microarchitecture (TBS ≤1.200) in 22.8% of the patients, partially degraded (TBS > 1.200 and <1.350) in 40.3% and normal values (TBS > 1.350) in 36.8% of the patients.

Table 4. Trabecular bone score at baseline, 6 and 12 months (mean ± SD).

	RIS group	CON group	P value
LS trabecular bone score			
Baseline	1.291 ± 0.122	1.306 ± 0.126	0.84
Six months	1.276 ± 0.139	1.309 ± 0.103	0.75
Twelve months	1.275 ± 0.111	1.293 ± 0.128	0.98

ences between groups (P = 0.181). Twelve months after LT, 10% (4) of the patients in the RIS group and 21% (8) in the CON group had developed vertebral fractures (P = 0.178).There was no difference in pattern of change in BMD (LS or FN) or TBS in patients with incident vertebral fractures within the first year after LT compare to those who did not developed a fracture. All vertebral fractures were diagnosed morphologically. Fracture analyses according to severity (Genant classification) also showed no intergroup differences. There were no peripheral fragility fractures.

At baseline, serum 25(OH)D was below 30 ng/ml in 91% of patients. 25(OH)D levels significantly increased at 3 months (P < 0.0001) in both groups and remained stable during the 12-month follow-up. At the end of the study, 52% of patients showed vitamin D sufficiency (>30 ng/ml).

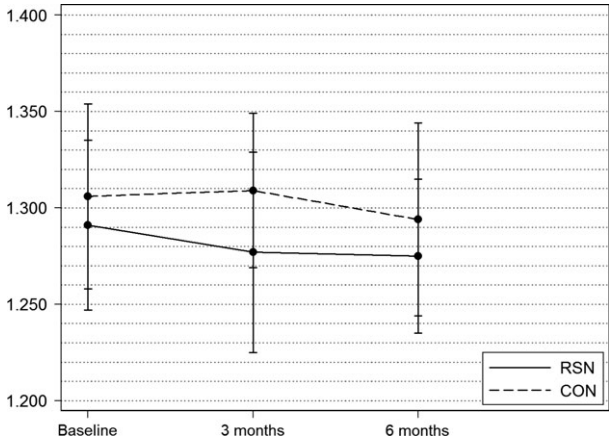

Figure 2 Evolution of trabecular bone score at baseline, 6 and 12 months in RIS and CON groups (mean ± SD).

Regarding bone remodelling markers (P1NP and β-CTX), no significant differences were observed between groups throughout the study. No correlation was found between TBS values and 25(OH)D levels, P1NP or β-CTX.

After 3 months, steroid treatment was discontinued in 53% (RIS) and 42% (CON) of the patients. Six months later, these percentages increased to 83% (RIS) and 80% (CON). Mean cumulative doses of prednisone, tacrolimus and mycophenolate mofetil were calculated at baseline, 6 and 12 months of the study. No relationship was found between BMD and TBS change or incident vertebral fracture and doses of immunosuppressive drugs (steroids, tacrolimus or mycophenolate mofetil).

Discussion

The evaluation of TBS in addition to BMD is of interest in a number of conditions associated with increased fracture risk. Most of the time, secondary osteoporosis results from the combination of risk factors and chronic diseases and their treatment. The impact of these risk factors, treatment and diseases on BMD is usually well documented, while studies demonstrating their impact on bone micro-architecture are scarce. The increase in fracture risk is largely independent of BMD by DXA in different settings as post-transplantation or long-term glucocorticoid therapy [23], which could be related to alterations in bone microarchitecture. To the best of our knowledge, this is the first study that evaluates the usefulness of TBS in LT patients.

Our study could not detect changes in terms of TBS during 1 year of treatment with RIS combined with calcium and vitamin D3 compared with patients receiving only calcium and vitamin D3, after LT. These results contrast with those observed in spine BMD in the same patients. As we reported in a previous study, lumbar spine BMD significantly increased in both groups at 12 months, whereas did not change at the hip [19].

In general, the impact of antiresorptive therapy on TBS is smaller in magnitude than on BMD. This is not surprising, because one would expect a greater improvement in BMD, particularly with antiresorptive therapy, due to increased mineralization and filling of the remodelling space, than improvement in trabecular microstructure as estimated by TBS [14].

In the present study, we observed that patients with low BMD and TBS values who receive either RIS combined with calcium and vitamin D3 or calcium and vitamin D3 alone showed a significant increase in spine BMD at 12 months compared with baseline values, without significant changes on TBS after 1 year of follow-up. This is consistent with other observations that antiresorptive therapy is expected to provide a 'positive maintenance' of bone micro-architecture rather than a major improvement in micro-architecture [24,25]. Krieg *et al.* [24] investigated the effects of different antiresorptive agents (bisphosphonates, raloxifene and calcitonin) on TBS in women age 50 and older. Relative to baseline, there was a significant improvement in BMD (+1.86% per year, 95% CI +1.71 to +2.02%), and a small increase in TBS (+0.20% per year, 95% CI +0.04 to +0.37%) in women treated for 3.7 years. Similar results have been found in other groups. Hans *et al.* [25] noted that spine TBS significantly increased by 2.3 and 3.1% over 1 and 2 years, respectively, in those on strontium, but not significantly (by 0.5 and 1.0%, respectively) in those given alendronate. Recently, Popp *et al.* [26] have found an increased in BMD of 9.6% versus only 1.4% in TBS in 53 postmenopausal women after 3 years of treatment with zoledronate, consistent with the notion that the two indices represent independent measures. Our study, in a population with elevated bone loss and high risk of fracture, suggests that more than 1 year may be necessary to demonstrate a significant increase in bone microstructure measured by TBS in LT patients.

On the other hand, we observed that baseline TBS values in the two groups were not correlated with age, sex, vitamin D status or underlying liver disease, but showed a negative correlation with BMI. Leslie *et al.* [27] found, in 29.407 women ≥50 years, that lower TBS was associated with older age, higher BMI, recent glucocorticoid use, prior major fracture, rheumatoid arthritis, chronic obstructive pulmonary disease and alcohol abuse. They showed that LS TBS was negatively correlated with BMI ($r = -0.15$). This correlation may reflect technical difficulties in performing texture analysis in obese subjects.

Compared with initial estimates of bone loss and fracture after transplantation, recent studies have reported lower rates [4]. Most of these studies were performed in the nineties, before the introduction of current used immunosup-

pressive regimens, which enable the use of significantly lower corticosteroid doses, probably allowing recovery of LS-BMD. In a recent study, Shane *et al.* [28] found that zoledronate and alendronate prevent bone loss at the hip and increase spine BMD in liver transplant patients after 12 months of treatment. Incidence of fractures in our study is similar to other previously published. Bodingbauer *et al.* [29] reported an incidence of fragility fractures of 8.5% in LT patients treated with iv zoledronate and 22.5% in patients treated with calcium and vitamin D3 for 2 years. Krol *et al.* [2], in 201 patients undergoing LT, observed a higher incidence of vertebral fractures (34%) 1 year after LT. However, in the last study, patients on treatment with bisphosphonates were excluded from the study and radiographs were blindly assessed by two experienced independent observers, which could explain the higher frequency of fractures found. Interestingly, these authors found that the recovery in LS-BMD was not associated with a corresponding decrease in fracture risk, suggesting a potentially persistent or irreversible effect of liver disease on bone quality and fracture risk.

As for the aetiology of liver disease, one-third of our patients had alcoholic liver disease (ALD). As it is known, alcohol has a toxic effect on bone mediated by decreased bone formation and increased bone degradation that are, in turn, influenced by nutritional, hormonal and proinflammatory factors [30]. In a previous meta-analysis, Bang *et al.* [31] have found associations between bone fractures and ALD, independent of BMD or the presence of osteoporosis. In our study, no significant differences were found in terms of TBS, BMD or fractures, regarding the aetiology of liver disease. No previous studies have examined the relationship of TBS with aetiology of liver disease.

Furthermore, our study could not find evidence that immunosuppression and corticosteroid therapy induce bone microarchitecture degradation, as measured by TBS, after 1-year follow-up in these patients. Few studies have analysed the long-term impact of GC therapy on TBS. Colson *et al.* [32] studied this impact in women treated with for 1 or more years. LS-BMD and TBS were evaluated in 136 women, from 45 to 80 years old. GC-treated patients had a 4% decrease in TBS ($P < 0.0001$) compared with the age-matched normal values, while no change in BMD was observed ($P = 0.49$). They conclude that GCs-treated women have significant deterioration of bone microarchitecture as assessed by TBS independently of the BMD level. Paggiosi *et al.* [33] confirmed that women with recent fractures had lower LS-BMD and TBS that women without fractures and that GC-treated women had lower TBS that GC naïve women, although their BMD did not differ.

Our study has some limitations to be considered. The findings of our TBS analysis are limited by the retrospective nature of the study. Although TBS analysis was carried out by one experienced physician, we have to point out that it was performed in a single centre and therefore cannot be extrapolated to the entire population. The study has not been designed to study the relation between prevalent or incident fractures and TBS. There was also a wide range of age in the study population that does not allow us to study the relationship between TBS and age variations. The main strength of our study is that its results contribute to better understanding of bone metabolism in this setting. There are scarce dates with regard to the damage in bone microarchitecture as measured by TBS in patients with terminal liver disease, post-transplant patients and bisphosphonate treatment.

In conclusion, our results point that RIS does not induce significant changes in trabecular bone score in liver transplant patients during 1 year of follow-up. Changes in BMD and TBS at lumbar site from baseline were not correlated, indicating different response to bone therapy. A longer duration of follow-up in LT recipients on bisphosphonate therapy is needed so potential improvements on TBS could be assessed.

Authorship

SL and SG: were involved in patient data management, analysis and writing of the manuscript. GM and FH: conceptualized the original idea, protocol draft, analysis and writing of the manuscript. GA: patient data management and technical support. DL: was the statistical advisor. CJ: was involved in liver transplantation and critical review.

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