Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Effect of bisphosphonates on bone mineral density in liver transplant patients: a meta-analysis and systematic review of randomized controlled trials

Krishna S. Kasturi,[1] Swapna Chennareddygari[2] and Rajasekhara R. Mummadi[1]

1 Division of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, TX, USA
2 Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA

Keywords
bisphosphonates, bone mineral density, liver transplant, meta-analysis.

Correspondence
Krishna S. Kasturi MD, MPH, Division of Gastroenterology and Hepatology, UTMB, 301 University Blvd, Rt 0570, Galveston, TX 77555, USA. Tel.: +1 409 772 1501; fax: +1 409 772 4789; e-mail: kskastur@utmb.edu

Received: 25 June 2009
Revision requested: 30 July 2009
Accepted: 1 September 2009

doi:10.1111/j.1432-2277.2009.00976.x

Summary

Bone mineral density (BMD) loss after liver transplantation (LT) results in considerable morbidity with the increased risk of fractures. Data on the efficacy of bisphosphonate use in post LT patients is scarce. This meta-analysis aims to summarize the results from published randomized controlled trials (RCTs) on the topic of interest. Electronic databases were searched to identify relevant publications. A total of 157 articles were identified and reviewed. Individual authors were contacted from relevant RCTs to obtain individual patient data where necessary to uniformly quantify BMD values post LT pre- and post LT. A total of six RCTs were used for final data extraction. (i) *Lumbar Spine*: In 364 patients (six studies, 182 in intervention and control groups each), bisphosphonate therapy improved BMD by 0.03 g/cm^2 (95% C.I. 0.01–0.05 g/cm^2; $P = 0.02$) at 12 months post LT. (ii) *Femoral neck*: In 268 patients (four studies, 130 bisphosphonate, 138 control), bisphosphonate use did not result in a statistically significant change in BMD at the end of 1 year. None of the studies noted serious adverse effects related to bisphosphonate administration. Data on incident fractures could not be pooled because of heterogeneity. Bisphosphonate therapy during the first year in LT recipients appears to reduce accelerated bone loss and improve bone mineral density at the lumbar spine.

Introduction

Bone mineral density (BMD) loss after liver transplantation (LT) is well recognized and results in considerable morbidity with the increased risk of fractures. Bone loss is most pronounced in the first 3–6 months after liver transplantation [1] with fracture rates up to 40% in the first couple of years post liver transplantation [1,2]. Several risk factors for osteoporosis can be identified in patients with chronic liver disease including excess alcohol intake, poor nutrition, hypogonadism, and biliary disease. These risks are compounded with the use of immunosuppressive therapy and steroids in the post-transplant patients leading to accelerated bone loss. Increased bone turnover is seen in the first few months after LT and theoretically bisphosphonates which inhibit or reduce osteoclast-mediated bone resorption could be of benefit to LT patients. However, published reports on the efficacy of bisphosphonates in preventing BMD loss and fracture incidence after LT have come up with conflicting results. Several studies reported a beneficial effect [1,3–12] as opposed to studies with limited or no effect of bisphosphonate use [13,14] in preventing bone loss or fractures after successful LT. There are also no clear guidelines on the indications, optimum duration and dosage of bisphosphonates in LT patients. This meta-analysis is an attempt to systematically summarize published literature on the topic and pool the data from randomized controlled trials (RCTs) for an overall estimate of effect size.

Methods

Electronic databases (MEDLINE, EMBASE, Cochrane Controlled Trials Register and ISI Web of Science) were searched from inception till February 2009 by two independent investigators (K.K. and M.R.) to identify studies that provided information on bone mineral density in liver transplant patients. Search terms used were 'bisphosphonates', 'liver transplant', 'bone mineral density', 'hepatic', 'zolendronate', 'pamidronate', 'alendronate', 'etidronate', 'risedronate' and 'ibandronate'. Boolean logic was used to combine the search terms. Initially, all studies with information on BMD in patients undergoing liver transplantation along with the use of bisphosphonates were reviewed. RCTs that investigated the use of bisphosphonates in liver transplant patients were selected for the final meta-analysis. Eligible RCTs included studies using bisphosphonate in any dose/route of administration/duration/drug either alone or in combination with calcium and vitamin D supplementation with the control group receiving a placebo/no treatment either alone or in combination with calcium and vitamin D. Studies were excluded if patients had a prior history of organ transplantation, or chronic kidney disease, had treatment with agents that could influence bone metabolism (such as bisphosphonates, calcitriol, sex hormones and glucocorticoids). Reference lists of all the selected articles were hand-searched for any additional studies. Abstracts from national meetings (Digestive Disease Week, American Association for the Study of Liver Diseases, American College of Gastroenterology, and the European Association for the Study of the Liver annual scientific meetings) were reviewed to identify unpublished data. None of the abstracts were eligible for inclusion in the final analysis. The study attrition diagram is shown in Fig. 1.

Quality of the included studies was assessed using the Jadad scale [15]. Our main outcome measure was BMD change 12 months after successful liver transplantation in RCTs comparing bisphosphonates to a control group. Data regarding incident fractures were collected and tabulated as detailed in the articles. The authors of the RCTs included in our meta-analysis were contacted to obtain individual patient data on BMD values (in g/cm^2) if it was not possible for us to extract information on BMD prior to and 12 months after liver transplantation from the published article. In this manner, we calculated the paired BMD values in the lumbar spine and femoral neck as mean ± standard deviation (SD) at baseline and at 12 months after liver transplantation for each study. Weighted mean differences were calculated and data pooling was done using statistical methods [Review Manager (RevMan) [Computer program] Version 5.0.18 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008]. One RCT had to be completely excluded from the meta-analysis resulting from unavailability of individual patient data from the authors at the time of submission of this article for publication [10]. Heterogeneity among the studies was assessed using chi-squared test and I^2 inconsistency statistic. Funnel plots were generated to identify publication bias in the included studies. Sensitivity analysis was performed by

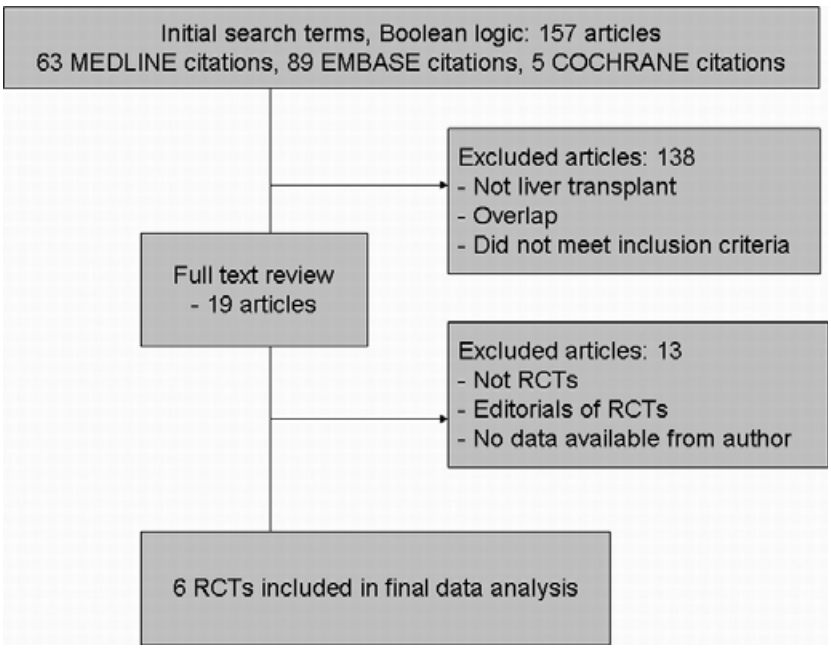

Figure 1 Study attrition diagram.

removing the studies with lowest quality score to assess the changes in overall effect.

Results

Electronic literature search using the terms mentioned earlier initially yielded 157 relevant articles. A comprehensive full text review was done for 19 articles. A total of seven RCTs met our inclusion criteria and the individual authors were contacted wherever the BMD values pre- and post liver transplant were not extractable from the published article in g/cm^2. After excluding one study because of nonresponse from the authors, we were able to obtain data from six RCTs [1,3,4,6,13,16] for the final data analysis. Characteristics of included studies are shown in Table 1.

Two of the studies were double-blind and multi-center when compared with the rest [1,6]. Two studies used oral bisphosphonates, alendronate [16] and etidronate [4]. Intravenous (i.v.) zolendronate was used in two studies [1,3] and i.v. pamidronate was used in two studies [6,13]. The doses and duration of bisphosphonate administration differed among the studies as shown in Table 1. All patients in the included studies used calcium and vitamin D supplementation except for the study by Ninkovic *et al.* where neither groups were given calcium and vitamin D supplementation [13]. Immunosuppressive regimens did not differ considerably across studies. Data made available by individual authors enabled BMD determination (mean ± SD in g/cm^2) at baseline and 12 months post LT at the lumbar spine, and four studies provided similar data on BMD at the femoral neck region.

BMD change at lumbar spine

In 364 study patients from six RCTs (182 in intervention: 130 male, 52 female patients; and 182 in control group: 123 male, 59 female patients), bisphosphonate therapy improved BMD by 0.03 g/cm^2 (95% C.I. 0.01–0.05 g/cm^2; $P = 0.02$) at 12 months post LT compared to the control group (Fig. 2). The studies were homogeneous allowing us to use the fixed effects model in effect size estimation.

Sensitivity analysis: To assess the robustness of our study, we performed sensitivity analysis by removing the study by Valero *et al.* because of low quality score. This did not have a significant impact on the overall results.

BMD change at femoral neck

In the 268 patients (130 bisphosphonate, 138 control), bisphosphonate use did not result in a statistically significant change in BMD at the end of 1 year when compared with the control group [change in BMD was 0.02 g/cm^2 (95% C.I. −0.01–0.05 g/cm^2); however, the *P*-value was nonsignificant at 0.19] (Fig. 3).

There was no observed heterogeneity among the four included studies for this data analysis.

Fracture incidence

Although data on incident fractures were provided by five of the included studies, pooling of the numbers was not done because of heterogeneity. Moreover, not all studies were adequately powered to estimate the fracture incidence. The details on fractures are summarized in Table 2.

Adverse effects related to bisphosphonates

None of the studies noted serious adverse effects related to bisphosphonate administration. The most severe adverse effects were noted by Atamaz *et al.* who used oral alendronate where two patients initially included in the study discontinued from the trial because of persistent gastrointestinal distress [16]. The most common side-effects across the studies were mild fever, myalgia, arthralgia, and temporary hypocalcemia. No major adverse effects on renal function were seen irrespective of the dose of bisphosphonates.

Discussion

Chronic liver disease predisposes to bone disorders by a multitude of mechanisms including impaired bile salt production and vitamin D metabolism, poor nutrition, and hypogonadism [17]. Accelerated bone loss subsequent to orthotopic LT is a well-recognized but less well-understood entity, likely resulting from the use of steroids and other immunosuppressive agents and postoperative immobility [2,18]. Metabolic bone disease and the resultant increase in fracture risk contribute to significant morbidity and mortality in LT recipients [3]. Bisphosphonates act by inhibiting the apoptosis of osteoclasts and osteoblasts and are the cornerstone of antiresorptive therapy in postmenopausal and steroid-induced osteoporosis [19]. BMD measurements are widely accepted in clinical practice to guide therapy with bisphosphonates, although it has been shown that BMD values do not accurately predict fracture risk in individuals [20]. Likewise, the utility of BMD values in predicting fracture risk in organ transplant patients is still unclear. There has been a recent surge of interest in the use of bisphosphonates in LT patients because of the increasing survival rates. However, there are no established guidelines on antiresorptive therapy in LT patients till date. Results from several prospective and randomized trials have given conflicting reports

Table 1. Baseline characteristics of included RCTs.

Study, year, location	Bisphosphonate group	Control group	Bisphosphonate N; M/F	Control N; M/F	Mean age (SD) bisphosphonate/ control	BMD measurements	Immunosuppression	Jadad quality score	Primary end-point
1. Crawford *et al.*, 2006; Australia and NZ [1]	i.v. Zolendronic acid 4 mg within 7 days of LT and at 1,3,6 and 9 months + calcium carbonate 600 mg/ day and ergocalciferol 1000 U/day from time of transplant listing throughout study	Saline + calcium carbonate 600 mg/day and ergocalciferol 1000 U/day from time of transplant listing throughout study	29; 23/6	25; 18/7	47.4 (9.7)/ 49.0 (6.8)	0,3,6,12 L2–L4, femoral neck, total hip	Tacrolimus or cyclosporine, azathioprine and methylprednisolone	5	BMD change at 3 months post LT
2. Bodingbauer *et al.* 2007, Austria [3]	i.v. Zolendronic acid 4 mg once monthly for 6 months, then 9,12 months + calcium carbonate 1000 mg/ day and vit D3 800 IE/day po	Calcium carbonate 1000 mg/day and vit D3 800 IE/day po	21; 17/4	20; 15/5	52 (8.2)/ 54 (7.9)	0,6,12 L1–L4, femoral neck, trochanter, total	Cyclosporine or tacrolimus, dexamethasone/ methylprednisolone	3	Rate of pts first bone # within 24 months
3. Atamaz *et al.* 2006; Turkey [5]	Alendronate 70 mg weekly + calcium 1000 mg/day and calcitriol 0.5 mcg/ day	Calcium 1000 mg/ day and calcitriol 0.5 mcg/day	44; 32/12	48; 35/13	43.7 (9.8)/ 45.0 (8.9)	0,6,12,18,24 L1–L4, proximal femur	Cyclosporine or tacrolimus, prednisone	2	Effect on BMD and # risk
4. Ninkovic *et al.* 2002; UK [13]	i.v. Pamidronate 60 mg once prior to LT (admission or listing) majority within 4 weeks	None	33; 16/17	38; 19/19	52.8 (10.5)/ 49.3 (12.3)	0,3,6,12 L1–L4, femoral neck	Cyclosporine or tacrolimus, prednisolone	3	Effect on BMD and # rate in 1 year after LT
5. Valero *et al.* 1995; Spain [4]	p.o. etidronate 400 mg/day for 15 days q 3 months + 1000 mg po calclium/day for 12 months	40 IU/day i.m. calcitonin + 1000 mg po calcium/day for 12 months	23; 16/7	17; 10/7	40.4 (12.8)/ 52.1 (6.2)	0,12 Vertebral spine	Cyclosporine, prednisone, azathioprine	1	Efficacy of both on rx for osteoporosis in LT pts

Table 1. continued

Study, year, location	Bisphosphonate group	Control group	Bisphosphonate N; M/F	Control N; M/F	Mean age (SD) bisphosphonate/ control	BMD measurements	Immunosuppression	Jadad quality score	Primary end-point
6. Monegal *et al.* 2009; Spain [6]	i.v. Pamidronate 90 mg within 2 wks of LT and at 3 months + calcium 1000 mg/day and Vit D 16000 IU q 15 D	i.v. glucose + calcium and vit D	32; 26/6	34; 26/8	52.8 (11.2)/ 53.6 (10)	0,6,12 L2–L4, proximal femur	Cyclosporine, prednisone, mycophenolate mofetil	3	Change in BMD and side effects, fractures

on fracture incidence and BMD changes with the use of bisphosphonates. This meta-analysis was done to systematically review available data on RCTs and generate an estimate of cumulative effect size on bisphosphonate efficacy in LT patients.

Our results show that there is a statistically significant increased mean BMD of 0.03 g/cm^2 in the bisphosphonate group when compared with the control/placebo group at the lumbar spine 12 months after LT (six studies). At the femoral neck, the decline in mean BMD comparison was not statistically significant, but was reduced by 0.02 g/cm^2 in the bisphosphonate group (four studies). A meta-analysis of RCTs on the effects of bisphosphonates in renal transplant patients reported that the loss of BMD at the lumbar spine was lesser by 0.06 g/cm^2 in the bisphosphonate group compared to the control group by 6–12 months post renal transplant [21].Our meta-analysis shows that BMD values at the lumbar spine in fact improve by 0.03 g/cm^2 post LT from bisphosphonate use when compared with the 'lesser decline' in BMD at the lumbar spine post renal transplant.

None of the studies reported major adverse effects from any dose or form of bisphosphonate therapy despite the presence of chronic liver disease. The primary study endpoints differed across studies, but all the studies assessed BMD changes and fracture rates in LT patients. With the exception of one study that only administered a single dose of i.v. pamidronate to the intervention group [13], all the other studies noted increase in lumbar BMD values at 1 year post LT. Crawford *et al.* noted a positive effect on BMD at the lumbar spine despite the intervention group requiring more steroid therapy as a result of acute rejection compared with the control group [1]. Their study also points out that average BMD at the lumbar spine recovered above the pretransplant levels by 12 months in both the intervention and control groups. However, this effect was not seen at the hip region where patients in the zolendronic acid group had no loss of bone when compared with the placebo group that could only regain partial BMD at 12 months post LT. Similar improvements at the control/placebo group lumbar spine BMD values from baseline levels at 12 months post LT were seen in the studies by Valero *et al.*, Ninkovic *et al.* and Atamaz *et al.* [4,13,16]. This finding serves as a confirmation to continued bone recovery after the initial decline in the first few months post LT and could very well be from improvements in general health and mobility, liver function and nutritional status. However, a majority of the included studies show that mean BMD levels at the femoral neck are lower than pre-LT values after 12 months in both the treatment and control groups. The study by Atamaz *et al.* is the only RCT that showed that mean BMD at the femur neck persistently moved in a

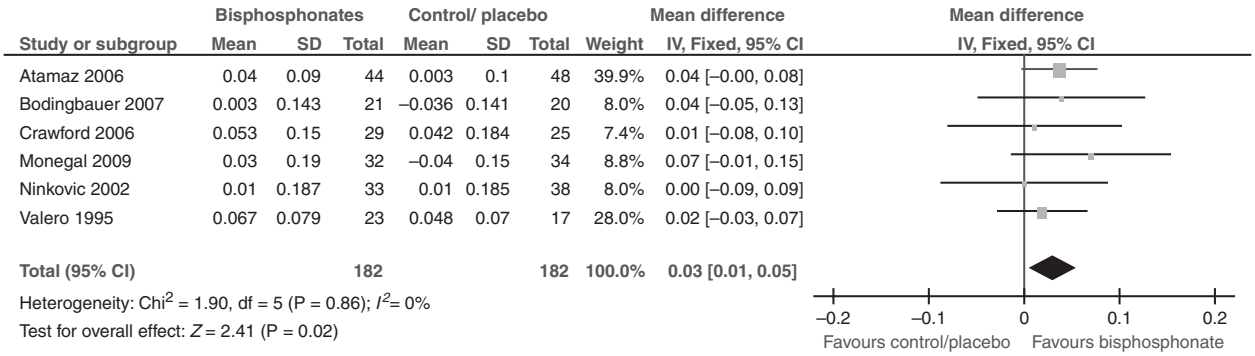

Figure 2 Forest plot of the weighted mean differences of BMD changes at lumbar spine after bisphosphonate therapy versus controls; fixed effects model.

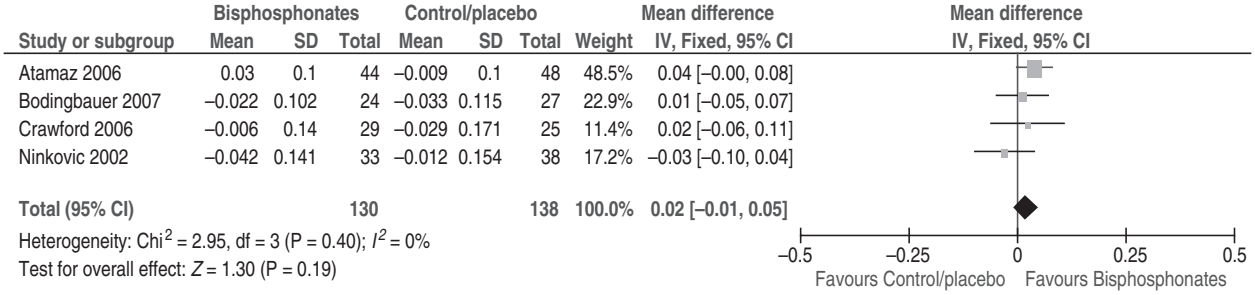

Figure 3 Forest plot of the weighted mean differences of BMD changes at femoral neck after bisphosphonate therapy versus controls; fixed effects model.

positive direction in the bisphosphonate group unlike the placebo group post LT. In their study, the mean BMD at the femoral neck started to improve in the placebo group after 6 months and then had a persistent improvement over a period of 2 years to reach values above pre-LT BMD [16]. It is likely that bone recovery at the femoral region is slower than at the vertebral spine [22].

The study by Bodingbauer *et al.* is the only study among the included RCTs that primarily assessed bone fracture incidence in the intervention and control groups [3]. Four patients in the zolendronic acid group sustained vertebral fractures when compared with the control group (11 patients; $P = 0.5$). In our meta-analysis, fracture data could not be pooled for a summary estimate as a result of the heterogeneity among the studies (Table 2). Considering vertebral fractures to be causing more morbidity than nonvertebral fractures, the included RCTs show that more vertebral fractures were seen in control/placebo group studies by Crawford *et al.* (five doses of i.v. zolendronic acid 4 mg), Bodingbauer *et al.* (eight doses of i.v. zolendronic acid 4 mg) and Atamaz *et al.* (weekly 70 mg p.o. alendronate); more vertebral fractures were seen in

Table 2. Incident fracture data.

Study, year	Number of fractures – bisphosphonate group	Number of fractures – control group	Duration (months)
Crawford *et al.* 2006 [1]	2 pts with single nonvertebral fracture	2 pts with multiple vertebral fracture and 1 pt wrist fracture	12
Bodingbauer *et al.* 2007 [3]	4 pts had vertebral fracture	11 pts had vertebral fracture	24
Atamaz *et al.* 2006 [5]	3pts had ≥1 vertebral fracture and 0 pts had ≥2vertebral fracture	7pts had ≥1 vertebral fracture and 2 pts had ≥2 vertebral fracture	24
Ninkovic *et al.* 2002 [13]	2 pts had 2 vertebral fractures each and 1 pt had 1 vertebral fracture and 1 pt had 1 extravertebral fracture	1 pt had 2 vertebral fractures and 1 pt had 1 extravertebral fracture	4
Monegal *et al.* 2009 [6]	6 pts vertebral fractures and 1 pt extravertebral fracture	2 pts vertebral and 1 pt extravertebral fracture	12

the intervention group in the studies by Ninkovic *et al.* (single dose i.v. pamidronate 60 mg) and Monegal *et al.* (two doses of i.v. pamidronate 90 mg). Individual patient factors need to be taken into account prior to summarizing the fracture incidence relative to brand, dose and duration of bisphosphonate therapy. This would be a limitation of our present meta-analysis. As the studies did not include patients who were already on bisphosphonates prior to being considered for liver transplantation, we have not been able to assess the efficacy of bisphosphonate use in this particular patient group after OLT.

Conclusions

Bisphosphonate therapy in LT recipients appears to reduce accelerated bone loss and improve bone mineral density at the lumbar spine during the first year post LT. The indications, optimum duration and dosage of bisphosphonate therapy in LT patients need to be determined. Higher doses appear to be safe in these patients despite chronic liver disease. Future studies in LT patients should focus on precise estimation of fracture incidence and interventions to reduce such fractures. There is a need for the development of an ideal surrogate for identifying post-transplant fracture risk as BMD values appear to be poor predictors of fracture risk. The present meta-analysis cannot justify the role of bisphosphonates in preventing fractures post LT despite a positive effect on mean BMD. A longer duration of follow-up in LT recipients on bisphosphonate therapy is needed so that long-term sustainability of the initial improvements in bone health can be assessed.

Authorship

KK: Conceived the project, contacted other authors for data, literature review, statistical analysis, writing the manuscript. SC: assisted with literature review and manuscript editing. RM: literature review, assisted with statistical analysis and interpretation, writing the manuscript and providing expert critique.

Acknowledgements

We are grateful to the authors of the studies who provided individual data of all participating study patients.

References

1. Crawford BA, Kam C, Pavlovic J, *et al.* Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2006; **144**: 239.
2. Collier J. Bone disorders in chronic liver disease. *Hepatology* 2007; **46**: 1271.
3. Bodingbauer M, Wekerle T, Pakrah B, *et al.* Prophylactic bisphosphonate treatment prevents bone fractures after liver transplantation. *Am J Transplant* 2007; **7**: 1763.
4. Valero MA, Loinaz C, Larrodera L, Leon M, Moreno E, Hawkins F. Calcitonin and bisphosphonates treatment in bone loss after liver transplantation. *Calcif Tissue Int* 1995; **57**: 15.
5. Atamaz F, Hepguler S, Karasu Z, Kilic M, Tokat Y. The prevention of bone fractures after liver transplantation: experience with alendronate treatment. *Transplant Proc* 2006; **38**: 1448.
6. Monegal A, Guanabens N, Suarez MJ, *et al.* Pamidronate in the prevention of bone loss after liver transplantation: a randomized controlled trial. *Transpl Int* 2009; **22**: 198.
7. Vedi S, Ninkovic M, Garrahan NJ, Alexander GJ, Compston JE. Effects of a single infusion of pamidronate prior to liver transplantation: a bone histomorphometric study. *Transpl Int* 2002; **15**: 290.
8. Reeves HL, Francis RM, Manas DM, Hudson M, Day CP. Intravenous bisphosphonate prevents symptomatic osteoporotic vertebral collapse in patients after liver transplantation. *Liver Transpl Surg* 1998; **4**: 404.
9. Dodidou P, Bruckner T, Hosch S, *et al.* Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporos Int* 2003; **14**: 82.
10. Hommann M, Abendroth K, Lehmann G, *et al.* Effect of transplantation on bone: osteoporosis after liver and multivisceral transplantation. *Transplant Proc* 2002; **34**: 2296.
11. Pennisi P, Trombetti A, Giostra E, Mentha G, Rizzoli R, Fiore CE. Pamidronate and osteoporosis prevention in liver transplant recipients. *Rheumatol Int* 2007; **27**: 251.
12. 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**: 960.
13. 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**: 93.
14. Riemens SC, Oostdijk A, van Doormaal JJ, *et al.* Bone loss after liver transplantation is not prevented by cyclical etidronate, calcium and alphacalcidol. The Liver Transplant Group, Groningen. *Osteoporos Int* 1996; **6**: 213.
15. Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1.
16. Atamaz F, Hepguler S, Akyildiz M, Karasu Z, Kilic M. Effects of alendronate on bone mineral density and bone metabolic markers in patients with liver transplantation. *Osteoporos Int* 2006; **17**: 942.

17. Leslie WD, Bernstein CN, Leboff MS. AGA technical review on osteoporosis in hepatic disorders. *Gastroenterology* 2003; **125**: 941.
18. Karges W, Trautwein C. Liver transplantation and osteoporosis: securing ''bone-fied'' success. *Liver Transpl* 2006; **12**: 1322.
19. Ruf KM, Johnson NK, Clifford T, Smith KM. Risk factors, prevention, and treatment of corticosteroid-induced osteoporosis in adults. *Orthopedics* 2008; **31**: 768.
20. 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**: 857.
21. Mitterbauer C, Schwarz C, Haas M, Oberbauer R. Effects of bisphosphonates on bone loss in the first year after renal transplantation – a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21**: 2275.
22. Giannini S, Nobile M, Ciuffreda M, *et al.* Long-term persistence of low bone density in orthotopic liver transplantation. *Osteoporos Int* 2000; **11**: 417.

