META-ANALYSIS

Bisphosphonate therapy after liver transplant improves bone mineral density and reduces fracture rates: an updated systematic review and meta-analysis

Owen Tsung Wen Ho[1], Winston Cheng Ann Ng[1], Zachariah Gene Wing Ow[1], Yeung Jek Ho[1], Wen Hui Lim[1], Jie Ning Yong[1], Renaeta Shiqi Wang[1], Keng Lin Wong[1,2], Cheng Han Ng[1], Mark D. Muthiah[1,3,4,*] & Claire Min-Li Teo[5,*]

1 Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
2 Department of Orthopedics Surgery, Sengkang General Hospital, Singapore, Singapore
3 National University Centre for Organ Transplantation, National University Health System, Singapore, Singapore
4 Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore
5 Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, Singapore

Correspondence
Mark D. Muthiah MBBS (S'pore), MRCP (UK), MMED (S'pore), Division of Gastroenterology and Hepatology, Tower Block Level 10, 1E Kent Ridge Road, Singapore 119228, Singapore.
Tel.: +65 6772 4354;
fax: +65 6775 1518;
e-mail: mdcmdm@nus.edu.sg
and
Zachariah Gene Wing Ow, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 10 Medical Dr, Singapore 117597, Singapore.
Tel.: +65 6772 3737;
fax: +65 6778 5743;
e-mail: zachariahowgenewing@u.nus.edu

*Equal supervision.

SUMMARY

To investigate the efficacy of bisphosphonates and compare oral and IV formulations on bone mineral density (BMD) and fracture incidence in post-orthotopic liver transplant (OLT) patients. Electronic databases were searched, and six RCTs and three cohort studies were included out of 711 articles. Main outcomes included post-OLT BMD changes, fracture incidence, and treatment adverse reactions. Pairwise meta-analysis was conducted for binary and continuous outcomes, while pooled fracture incidence utilized single-arm meta-analysis. Post-OLT fracture incidence was reported in nine studies (n = 591). Total fracture incidence was 6.6% (CI: 3.4–12.4%) in bisphosphonate group and 19.1% (CI: 14.3–25.1%) in calcium and vitamin D group. Total fractures were significantly lower in patients on bisphosphonate, compared to calcium and vitamin D (n = 591; OR = 0.037; CI: 0.18–0.77; P = 0.008). Overall fractures were significantly lower in the oral group (n = 263; OR = 0.26; CI: 0.08–0.85; P = 0.02) but not in the IV group (n = 328; OR = 0.45; CI: 0.16–1.26; P = 0.129). Both oral and IV bisphosphonates are effective in reducing fracture incidence post-OLT compared to calcium and vitamin D. Oral formulations may also have an advantage over IV in reducing bone loss and fracture incidence post-OLT.

Transplant International 2021; 34: 1386–1396

Key words
bone density, bone density conservation agents, bone diseases, liver transplantation, osteoporosis

Received: 9 February 2021; Revision requested: 17 March 2021; Accepted: 16 April 2021;
Published online: 1 July 2021

doi:10.1111/tri.13887

Introduction

Metabolic bone disease is a common complication faced by liver transplant patients, with many experiencing bone mineral density (BMD) loss in the first 12 months post-orthotopic liver transplant (OLT) [1]. General pre-transplant risk factors of osteoporosis, including advanced age, vitamin D deficiency, smoking, post-menopausal status, etiology of liver disease such as alcoholic and cholestatic cirrhosis, and female gender, predispose these individuals to developing bone loss and fractures post-OLT [2,3]. Post-OLT risk factors such as immunosuppressants further increase bone resorption, worsening post-OLT osteoporosis, and its complications faced by these patients [2]. Although there is conflicting literature on the effects of steroid use on post-OLT fracture rates [4–6], risks of fractures in transplant recipients remain high, ranging from 24% to 65% [6–10].

Interventions to reduce post-OLT bone density loss and fracture incidence include lifestyle modifications, calcium and vitamin D supplementation, and anti-resorptive therapies including bisphosphonates. Bisphosphonates have been shown to be more efficacious in preventing post-OLT bone loss and reducing fracture incidence as compared to other interventions [11]. Currently, both oral and intravenous (IV) bisphosphonates are routinely used in the management of post-OLT bone loss, with limited evaluation of newer agents such as denosumab and teriparatide in post-OLT patients. A greater efficacy of IV bisphosphonates over oral bisphosphonates has been reported in one study [12].

A previous meta-analysis attempted to evaluate the efficacy of bisphosphonates on reducing bone loss in post-OLT patients [13]. However, the study did not explore the effect of bisphosphonate therapy on fracture incidence nor did it investigate the difference between oral and IV routes on post-OLT osteoporosis outcomes. Hence, this meta-analysis aims to investigate the efficacy of bisphosphonates in reducing fracture incidence, as well as to explore the differences between oral and IV bisphosphonates on BMD and fracture incidence in post-OLT patients.

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used in the synthesis of this review [14]. An electronic database search of MEDLINE and Embase was performed on December 7, 2020, using keywords and terms synonymous with "Osteoporosis" and "liver transplant" (Appendix S1). The search strategy used was "(((liver* OR hepat*) adj3 (transplan* OR graft*)).tw. or exp Liver Transplantation/AND (exp osteoporosis/or (osteoporo* or osteopeni*).tw. or bone demineralization/or (bone* adj fragil*).tw. or fracture*.tw.)". References were managed and duplicates were removed with EndNote X9.

Study selection and extraction

Studies evaluating the effect of bisphosphonates compared to calcium and vitamin D on BMD change or fracture incidence in post-OLT patients were included in this review. Studies which did not have BMD data at the time of 12 months post-OLT, studies without BMD data in g/cm^2, and those that initiated bisphosphonate treatment before OLT were excluded. The decision to only include BMD data at 12 months post-OLT was based on increasing study homogeneity [15–20], since only two included articles provided follow-up data until 24 months [21,22] and only one article evaluated patients up till 36 months [23]. The inclusion of an article was evaluated by an independent blinded pair of authors (OTWH and CAWN), with any disagreements being resolved by obtaining the consensus of a third author.

The main outcomes in this meta-analysis include post-transplant bone mineral density changes, fracture incidence, and treatment adverse reactions. For post-OLT bone density changes, two main anatomical areas were assessed, namely the lumbar spine and the neck of femur (NoF). BMD changes were quantified using the change in bone density (g/cm^2) of the individuals 12 months after initiating postoperative bisphosphonate or calcium and vitamin D treatment regimens. Fractures were defined by the individual studies as the obtaining of pairwise independent observer agreement on the semiquantitative evaluation of plain radiographs of patients. Data extraction was performed to extract study characteristics (study location, year, country, follow-up times, bisphosphonate regimen), baseline characteristics (age, gender, body mass index, disease etiology, immunosuppression therapy), and post-OLT outcomes (BMD change in g/cm^2, fracture incidence). Means and standard deviations were extracted for the pooling of continuous outcome data, and data were converted to mean and standard deviation using pre-existing formulae as described by Wan et al. when unavailable [24].

Statistical analysis and quality assessment

All analyses were carried out using STATA 16.1 and RSTUDIO, version 1.3.1093 (RStudio, Boston, MA, USA)

[25]. Statistical significance was considered for outcomes with *P*-value <0.05. A single-arm analysis of binary outcomes was pooled in random effects using the generalized linear mixed model (GLMM) with Clopper–Pearson intervals to stabilize the variance [26,27]. Simulation studies have found that the GLMM provides the most accurate estimate in single-arm meta-analysis [26]. Next, a pairwise meta-analysis of dichotomous and continuous outcomes was performed and presented as odds ratios (OR) and weighted mean differences (WMD), respectively, with the Dersimonian and Laird random effects model [28,29]. A continuity correction of 0.5 was done for zero events to account for pairwise comparisons of dichotomous events [30]. As mentioned, BMD data were analyzed at the 12 months of follow-up timepoint. Fractures, in turn, were analyzed based on the last follow-up date of the study as fractures require a longer follow-up duration for events to be significant, before a sensitivity analysis was performed at 12 months of follow-up. In addition, subgroup analysis based on oral and IV formulations of bisphosphonate therapy was conducted to account for the differences in total fracture incidence, vertebral fracture incidence, and BMD changes at LS and NoF. When insufficient data were present for a meta-analysis, a systematic synthesis of literature was the preferred method to summarize the evidence. Statistical heterogeneity was assessed via I^2 and Cochran *Q* test values, where an I^2 value of 0–40% indicates low heterogeneity, while values of 30–60%, 50–90%, and 75–100% were classified as moderate, substantial, and considerable heterogeneity, respectively [31]. A Cochran *Q* test of $P < 0.10$ was significant for heterogeneity. Random effects model was used in all analyses regardless of heterogeneity as it provides more robust outcome measures compared to the alternative fixed effects models [32]. Where applicable, publication bias was assessed with Egger and Harbord regression [33] for continuous and dichotomous variables, respectively. Quality assessment of studies was performed using the Newcastle–Ottawa Scale (NOS) [34] and Jadad Scale [35] for cohort studies and randomized controlled trials (RCTs), respectively.

Results

Summary of included articles

A systematic search of the literature utilizing our search strategy yielded a total of 711 references, of which 25 articles underwent full text review. Nine articles were subsequently included in the meta-analysis (Fig. 1). Two articles originated from Turkey [15,21], Spain [18,19], and Austria [16,23] each, while one article originated from each of Germany [22], Australia [17], and Switzerland [20]. Of the studies, three were prospective in study design and six were randomized controlled clinical trials [15–23]. A total of 645 patients underwent OLT and were treated with either bisphosphonates ($n = 340$) or calcium and vitamin D ($n = 305$). In summary, majority of the included studies were of good quality, as evaluated by the Jadad [35] and NOS [34] scales. Tables S1 and S2 summarize the individual studies and quality assessment, respectively.

Indication for treatment

In total, 226 patients were started on bisphosphonate therapy regardless of BMD status post-OLT [15–17,19,21,22], while 84 patients were started on bisphosphonate therapy only if they were osteoporotic or osteopenic post-OLT [18,20], and a further 30 patients were started on bisphosphonates only if they were osteoporotic and had survived more than 12 months after OLT [23].

Post-OLT bone mineral density

A total of seven studies [15–19,21,23] consisting of 645 patients reported BMD changes following OLT. There was a significant improvement in lumbar spine bone density of patients on bisphosphonate following OLT as compared to those on calcium and vitamin D (WMD = 0.038 g/cm^2; CI: 0.014–0.063; $P = 0.002$; Fig. 2). Similarly, bone density of the NoF regions was also observed to be significantly higher in the bisphosphonate group (WMD = 0.023 g/cm^2; CI: 0.001–0.044; $P = 0.023$; Fig. 3).

Post-OLT fracture incidence

Post-OLT fracture incidence was reported in eight studies consisting of 591 patients [15,16,18–23]. Total fracture incidence in patients following OLT was 6.6% (CI: 3.4–12.4%; Fig. 4) in bisphosphonate group and 19.1% (CI: 14.3–25.1%; Fig. 5) in calcium and vitamin D group. Pooled incidence of vertebral fractures was 5.3% (CI: 2.4–11.5%) in patients on bisphosphonate compared to 14.2% (CI: 8.4–23.1%) in patients on calcium and vitamin D regimen. There was a significant reduction in total fractures ($n = 591$; OR = 0.37; CI: 0.17–0.77; $P = 0.008$; Fig. 6) and vertebral fractures ($n = 591$;

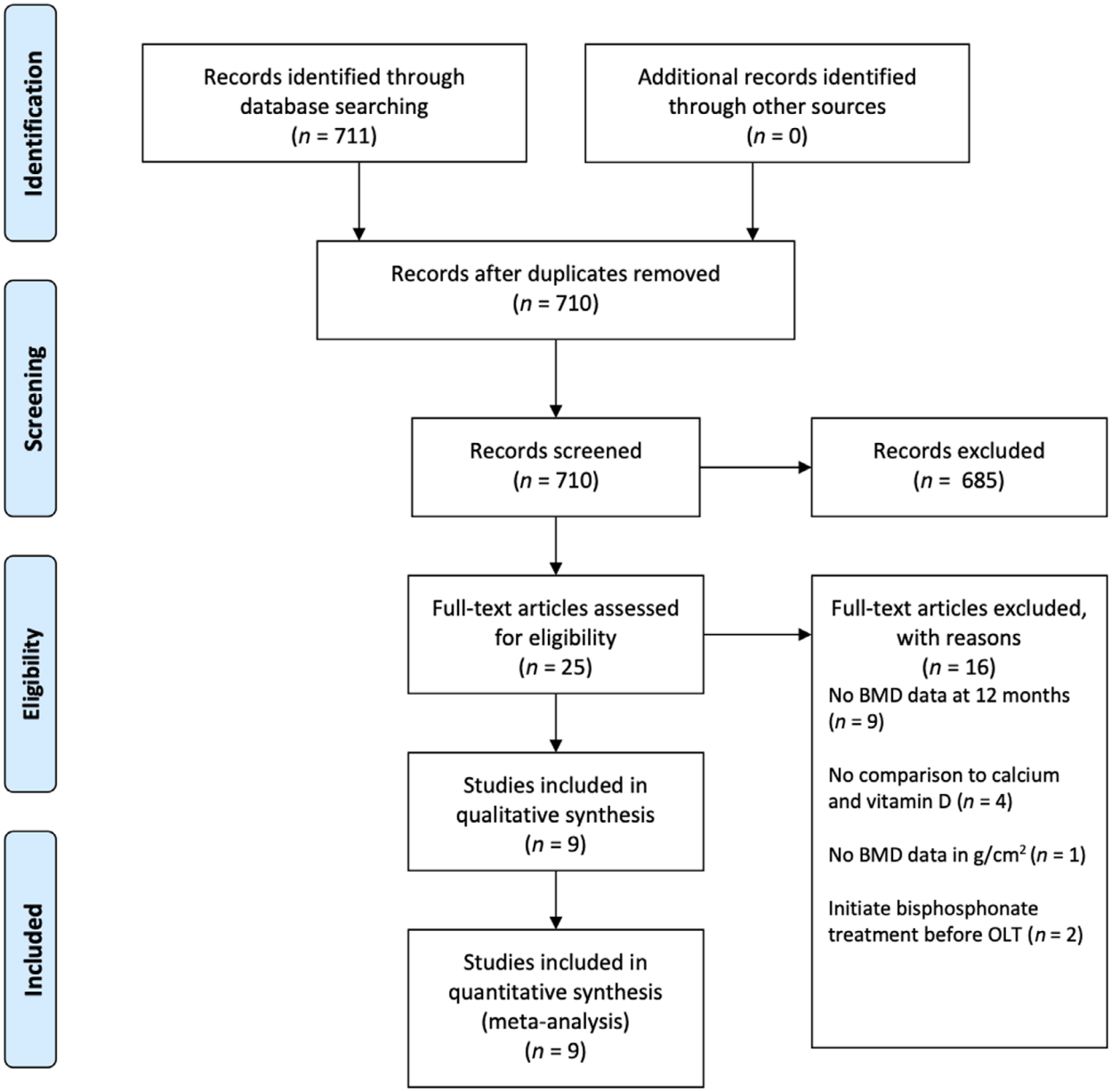

Figure 1 PRISMA flow diagram.

OR = 0.42; CI: 0.19–0.90; $P = 0.027$) in the bisphosphonate group as compared to calcium and vitamin D.

A sensitivity analysis was conducted for fracture incidence at 12 months ($n = 5$) [15,18–21]. Total fracture incidence was 3.9% (CI: 1.0–14.5%) in patients on bisphosphonates compared to 13.7% (CI: 9.4–19.7%) in patients on calcium and vitamin D regimen. Pooled incidence of vertebral fractures was 2.5% (CI: 0.4–15.1%) in patients on bisphosphonate compared to 9.1% (CI: 3.7–20.7%) in patients on calcium and vitamin D regimen. There was a nonsignificant decrease in fractures at 12 months comparing patients on bisphosphonates to calcium and vitamin D regimen ($n = 410$, OR: 0.38; CI: 0.09–1.52; $P = 0.170$). Similarly, there was a nonsignificant decrease in vertebral fractures at 1 year ($n = 410$, OR: 0.46, CI: 0.101–2.106; $P = 0.319$).

Adverse reactions

Six studies reported adverse reactions to bisphosphonate therapy [15–19,21]. The most common adverse reactions were musculoskeletal pain ($n = 49$), gastrointestinal discomfort ($n = 38$), hypocalcemia ($n = 20$), and

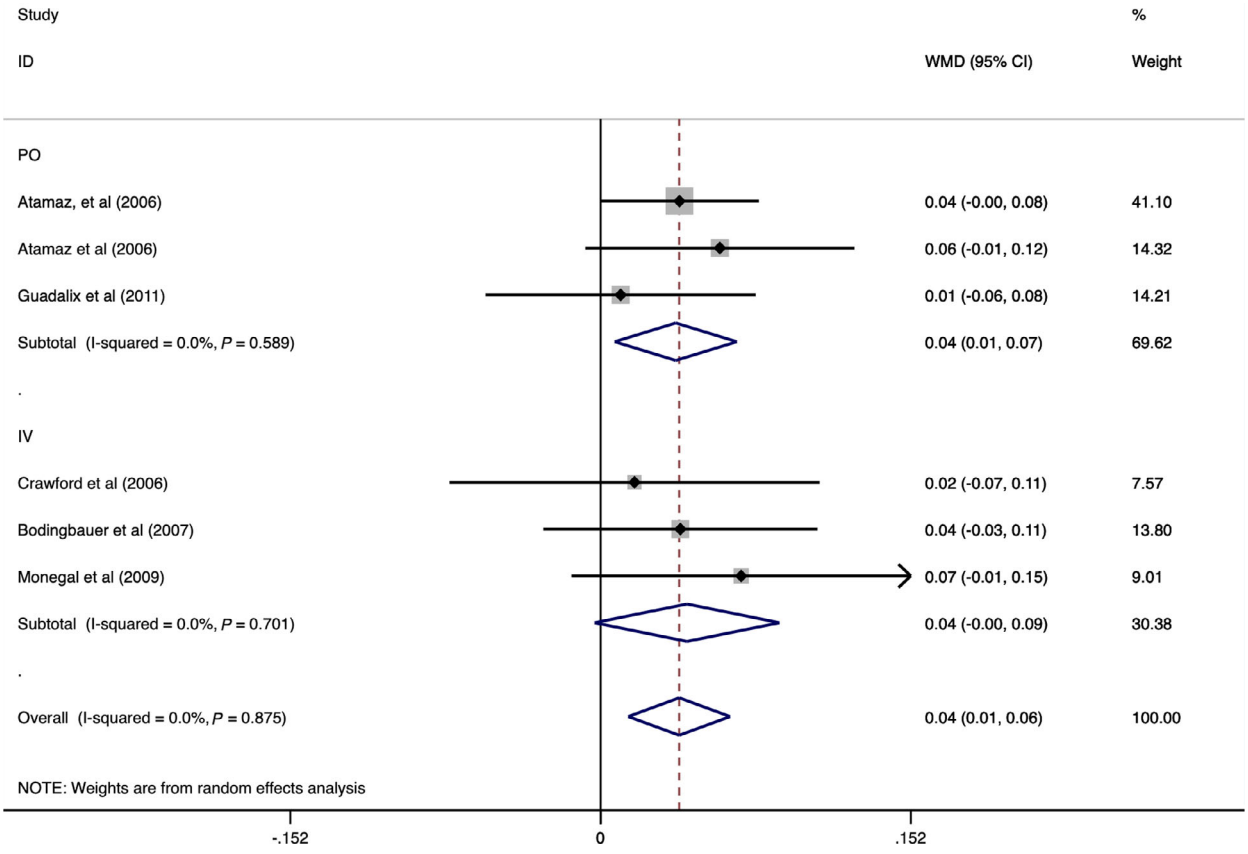

Figure 2 Change in lumbar spine BMD in g/cm^2.

pyrexia (n = 5). A total of three discontinuations were reported, of which two were because of persistent gastrointestinal distress [21] and one because of a severe acute phase reaction [16]. Musculoskeletal pain was reported in 3.1–38.8% of OLT patients [15,16,19,21], while gastrointestinal symptoms were reported in 17.8–28.6% of patients [15,18,21]. Hypocalcemia was also reported in 14.9–40.6% of patients [16,17]. Additionally, five patients (10.6%) developed pyrexia in the study by Bodingbauer *et al.* [16].

Oral versus intravenous treatment bisphosphonates

Subgroup analysis was performed for post-OLT patients on oral versus IV bisphosphonates or calcium and vitamin D treatment. Three articles used oral bisphosphonates [15,18,21], while six used IV [16,17,19,20,22,23]. The overall test for subgroup differences was insignificant; however, oral bisphosphonates did result in improved reduction of bone density loss and decreased fracture incidence for certain comparisons. A summary of the results can be found in Table 1.

There was a significant improvement in lumbar spine BMD with oral bisphosphonates, at 0.037 g/cm^2 (n = 263, CI: 0.007–0.067; P = 0.016); however, there was no significant change in the IV bisphosphonate group 0.042 g/cm^2 (n = 189, CI: −0.003 to 0.087; P = 0.067). Similarly, there was a significant improvement in post-OLT NoF BMD with oral bisphosphonates (0.029 g/cm^2; n = 263, CI: 0.000–0.057; P = 0.050) but not with patients on IV treatment (0.015 g/cm^2; n = 243, CI: −0.017 to 0.047; P = 0.369).

The rate of overall fractures observed was significantly lower in the oral group (n = 263; OR = 0.26; CI: 0.08–0.85; P = 0.02) but not in the IV group (n = 328; OR = 0.45; CI: 0.16–1.26; P = 0.129). Similarly, vertebral fractures were reduced in the oral group (n = 263; OR = 0.28; CI: 0.08–1.00; P = 0.05) but not in the IV group (n = 328; OR = 0.54; CI: 0.17–1.71; P = 0.30).

Discussion

BMD loss and fractures are serious complications that many liver transplant patients face post-OLT. There remains no current consensus on the choice of

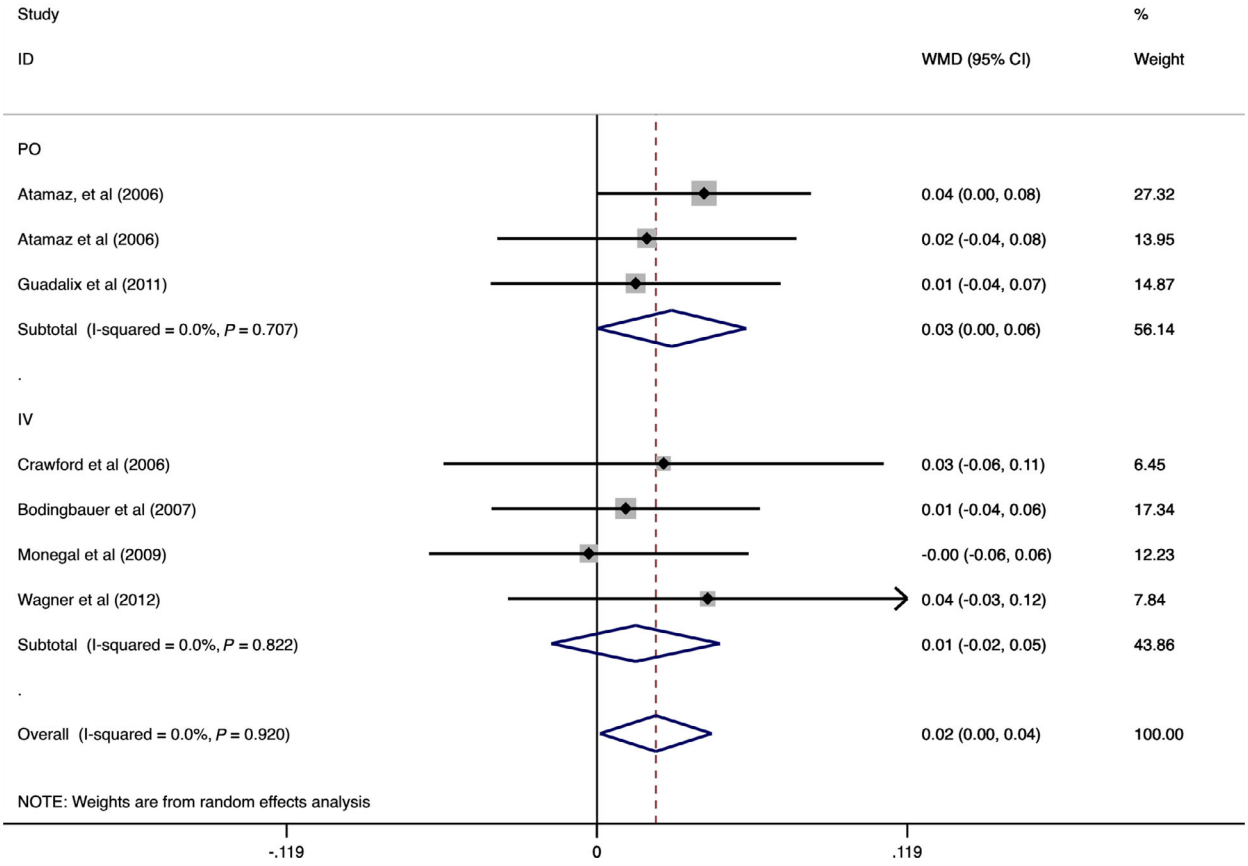

Figure 3 Change in neck of femur BMD in g/cm^2.

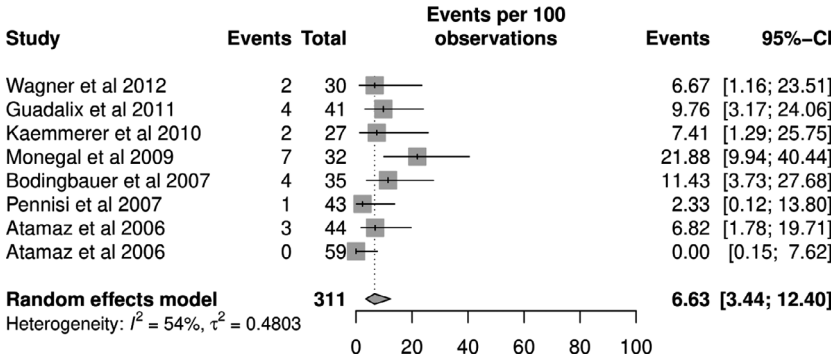

Figure 4 Total fracture incidence (bisphosphonates).

pharmacologic therapy in the prevention of post-OLT BMD loss and fracture incidence [36]. The previous meta-analysis, conducted a decade ago, compared the two most commonly prescribed treatment regimens for reducing bone loss and fracture incidence in post-OLT patients [13]. Since then, more cohort studies and RCTs have matured allowing for additional analysis. This current meta-analysis has twice the sample size and demonstrated significant reduction in fracture rates. Additionally, subgroup analysis, previously unreported, was performed in this meta-analysis to compare oral and IV routes of administration of bisphosphonate therapy.

The results show that bisphosphonate intervention is superior in preventing fractures as compared to calcium and vitamin D regimens (OR = 0.37; CI: 0.17–0.77;

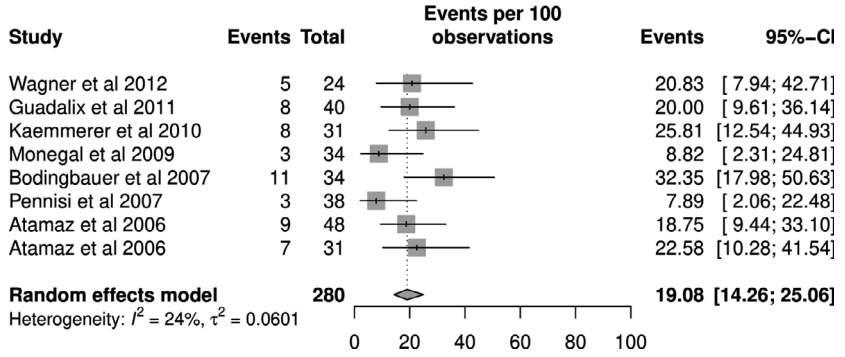

Figure 5 Total fracture incidence (calcium and vitamin D).

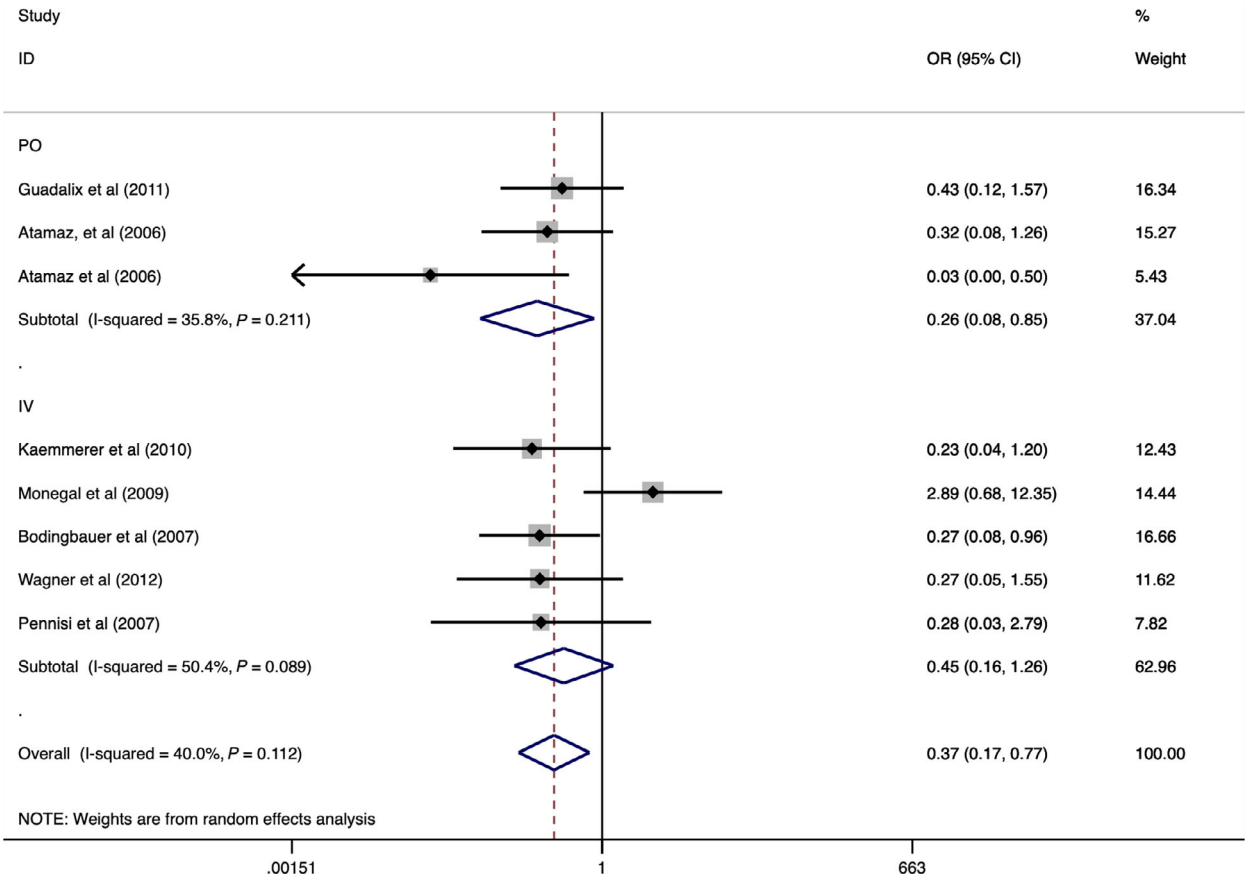

Figure 6 Total fracture incidence (bisphosphonate compared to calcium and vitamin D).

$P = 0.008$). Although sensitivity analysis at 12 months showed a nonsignificant decrease in fracture rates between both groups, this is likely because fractures require a longer duration for events to be significant as shown above. For overall incidence, while 19% of patients on calcium and vitamin D suffered fractures, only 7% of patients on bisphosphonate therapy experienced fractures. Similarly, vertebral fracture rates were lower in the bisphosphonate group at 5% compared to 14% in the calcium and vitamin D group. Importantly, bisphosphonates have an acceptable safety profile in post-OLT patients. None of the studies reported serious adverse reactions to bisphosphonate treatment. The most commonly reported adverse

Table 1. Summary of results.

	Effect size									
	Total fracture incidence		Nonvertebral fractures		Vertebral fractures		BMD lumbar spine 12 months		BMD neck of femur 12 months	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	WMD (95% CI)	*P*-value	WMD (95% CI)	*P*-value
Overall studies	0.0367 (0.176–0.766)	**0.008**	0.450 (0.154–1.316)	0.145	0.415 (0.190–0.904)	**0.027**	0.038 (0.014–0.063)	**0.002**	0.023 (0.001–0.044)	**0.039**
Oral regimens	0.263 (0.083–0.835)	**0.023**	0.458 (0.057–3.671)	0.462	0.289 (0.085–0.983)	**0.047**	0.037 (0.007–0.067)	**0.016**	0.029 (0.000–0.057)	**0.050**
Intravenous regimens	0.448 (0.159–1.263)	0.129	0.447 (0.128–1.563)	0.208	0.540 (0.171–1.710)	0.295	0.042 (−0.003 to 0.087)	0.067	0.015 (−0.017 to 0.047)	0.369

BMD, bone mineral density; OR, odds ratio; WMD, weighted mean differences.
Bold values show significant for p-value < 0.05.

reactions were musculoskeletal pain (3.1–38.8%), gastrointestinal discomfort (17.8–28.6%), hypocalcaemia (14.9–40.6%), and pyrexia (10.6%). Most of the adverse reactions were mild, with only three discontinuations.

Unexpectedly, the use of oral bisphosphonates over IV regimens was associated with improved patient outcomes. The use of oral bisphosphonates significantly improved the BMD in both lumbar spine and NoF regions in post-OLT patients with a lower incidence of both vertebral and total fractures in post-OLT patients, whereas this was not observed in the IV bisphosphonate group. This unanticipated result is in contrast to what was observed in several studies. In a study by Shane *et al.* [12] involving adults undergoing heart or liver transplant, the analyses suggested that IV zoledronic acid prevented bone loss at the femoral neck and total hip and improved spinal BMD in both heart and liver transplant recipients. However, while alendronate prevented bone loss at the total hip and femoral neck, it was associated with significant spinal bone loss in heart transplant patients. In a randomized controlled trial by Roux *et al.* [37] studying IV zoledronic acid versus oral risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis, zoledronic acid was reported to be more efficacious than risedronate in increasing the lumbar spine BMD at 12 months. A recent network meta-analysis concluded that oral alendronate was the most efficacious among five commonly used bisphosphonates (alendronate, risedronate, ibandronate, zoledronate, and etidronate) in preventing vertebral and hip fractures, while zoledronic acid was most efficacious in preventing nonvertebral nonhip fractures [38].

The superior efficacy of oral over IV regimens in this study may be partly attributable to the large variance in IV dosage regimens (2 mg/day to 30 mg/week) among the included articles. Of the six included articles on IV bisphosphonates, two used IV zoledronic acid, two used IV ibandronate, and two used IV pamidronate. The dosing of IV zoledronic acid and IV ibandronate in four of the six included trials differed from the current recommended regime of IV zoledronic acid 5 mg every 12 months and IV ibandronate 3 mg every three months in patients with osteoporosis [39]. On the other hand, the dosage of oral alendronate and risedronate in the included articles is in line with current recommendations for the treatment of both postmenopausal and glucocorticoid-induced osteoporosis. Furthermore, in postmenopausal osteoporosis, although ibandronate showed reduction in vertebral fracture risk, there has been no evidence for its efficacy in lowering hip or

nonvertebral fracture risk [40]; thus, it is generally not preferred for this indication [41]. Similarly, while IV pamidronate has been shown to prevent glucocorticoid-induced bone loss, it lacks fracture efficacy data and thus is currently not FDA-approved for use in post-menopausal osteoporosis [42].

However, there are several advantages to the IV formulation. Patients receiving IV bisphosphonate therapy do not usually experience gastroesophageal reflux disease and gastrointestinal discomfort, commonly associated with oral bisphosphonate therapy [43]. Moreover, patients are given about one to eight IV bisphosphonate infusions in their duration of treatment, while patients taking oral bisphosphonates have to comply to a weekly oral medication regimen for up to a year [43,44]. A previous study also reported an increased risk of fractures when oral bisphosphonates are taken together with acid-suppressing medications, particularly proton pump inhibitors [45]. Thus, patients may be more adherent to IV bisphosphonate regimens because of fewer side effects and an easier medication regimen. Despite these advantages, it is important to consider other risks of IV bisphosphonates such as transient acute phase reactions, including arthralgia, myalgia, fever, and lethargy [46], and adverse events associated with any IV infusions such as phlebitis, hematoma, and line infection [47]. Additionally, the use of IV bisphosphonates exposes patients to high doses of the drug in a short amount of time. This increases the risk of acute kidney injuries and exacerbation of pre-existing renal impairment in patients with co-morbid chronic kidney disease [48]. Drugs such as immunosuppressive agents can further aggravate renal damage caused by IV bisphosphonates [45,49].

Clinical implications

In accordance with guidelines on clinical management of OLT patients, although the OLT population most likely to benefit from bisphosphonate therapy has yet to be defined, bisphosphonate therapy should be considered in OLT recipients with osteoporosis or recent fractures [50,51], based on the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL). Oral alendronate at 70 mg weekly is an appropriate starting dose, although other oral agents may be equally efficacious [51]. As this study has demonstrated, oral bisphosphonates are efficacious in the treatment of osteoporosis. In addition, OLT patients with risk factors for incident fractures such as older age or lower pre-OLT BMD may also benefit from protective and perioperative bisphosphonate therapy.

Strength and limitations

This updated meta-analysis boosts a larger sample size and reports post-OLT fracture incidence while comparing bisphosphonates formulations, which was previously unreported. However, the results of this study must be interpreted in view of several limitations. To maintain homogeneity, BMD change was only analyzed at 12 months of follow-up from administration of bisphosphonates and long-term effects of post-OLT bisphosphonates on BMD change are yet to be answered. There was lack of granularity of data on severity of bone disease prior to treatment and cumulative steroid dosage in the included studies, preventing regression and further analysis for BMD change and fracture rates. However, it is important to note that glucocorticoid in the maintenance immunosuppression of OLT recipients has decreased over the years [52], and all included studies tapered steroids within 1st year post-OLT. Additionally, meta-analysis was not performed for adverse reaction data because of the sparsity in reporting and hence only systematically reported. Similarly, the effects of newer drugs such as denosumab and teriparatide could not be analyzed because of lack of studies in post-OLT patients.

Conclusion

In summary, both oral and IV bisphosphonates have been shown to be effective in reducing BMD loss in the L-spine and NoF, as well as fracture incidence. Evidence further suggests that oral bisphosphonates are efficacious and safe in reducing bone loss and fracture incidence in post-OLT patients. More studies are needed to assess the long-term efficacy and adverse events of current anti-resorptive therapy used for the treatment of skeletal complications in post-OLT patients.

Authorship

OT, WH, WCAN, ZGWO, YJH, WHL, JNY, RSW and CHN: contributed to the acquisition of data and analysis and interpretation of data and drafted the article. KLW, MDM and CM-LT: aided in revising the article critically for important intellectual content. All authors read and gave final approval of the version to be submitted.

Transplant International 2021; 34: 1386–1396

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Search strategy for medline.
Table S1. Summary of included studies.
Table S2. Quality assessment for included articles.

REFERENCES

1. Kovvuru K, Kanduri SR, Vaitla P, *et al*. Risk factors and management of osteoporosis post-transplant. *Medicina* 2020; **56**: 302.
2. Chauhan V, Ranganna KM, Chauhan N, *et al*. Bone disease in organ transplant patients: pathogenesis and management. *Postgrad Med* 2012; **124**: 80.
3. Hay JE. Osteoporosis in liver diseases and after liver transplantation. *J Hepatol* 2003; **38**: 856.
4. Krol CG, Dekkers OM, Kroon HM, *et al*. Longitudinal changes in BMD and fracture risk in orthotopic liver transplant recipients not using bone-modifying treatment. *J Bone Miner Res* 2014; **29**: 1763.
5. Schreiber PW, Bischoff-Ferrari HA, Boggian K, *et al*. Bone metabolism dynamics in the early post-transplant period following kidney and liver transplantation. *PLoS One* 2018; **13**: e0191167.
6. Premaor MO, Das TK, Debiram I, *et al*. Fracture incidence after liver transplantation: results of a 10-year audit. *QJM* 2011; **104**: 599.
7. Rodino MA, Shane E. Osteoporosis after organ transplantation. *Am J Med* 1998; **104**: 459.
8. Navasa M, Monegal A, Guañabens N, *et al*. Bone fractures in liver transplant patients. *Br J Rheumatol* 1994; **33**: 52.
9. Cohen A, Shane E. Osteoporosis after solid organ and bone marrow transplantation. *Osteoporos Int* 2003; **14**: 617.
10. Lim WH, Ng CH, Ow ZGW, *et al*. A systematic review and meta-analysis on the incidence of osteoporosis and fractures after liver transplant. *Transplant Int* 2021; **34**: 603.
11. Stein EM, Ortiz D, Jin Z, *et al*. Prevention of fractures after solid organ transplantation: a meta-analysis. *J Clin Endocrinol Metab* 2011; **96**: 3457.
12. Shane E, Cohen A, Stein EM, *et al*. Zoledronic acid versus alendronate for the prevention of bone loss after heart or liver transplantation. *J Clin Endocrinol Metab* 2012; **97**: 4481.
13. Kasturi KS, Chennareddygari S, Mummadi RR. Effect of bisphosphonates on bone mineral density in liver transplant patients: a meta-analysis and systematic review of randomized controlled trials. *Transpl Int* 2010; **23**: 200.
14. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700.
15. Atamaz F, Hepguler S, Karasu Z, *et al*. The prevention of bone fractures after liver transplantation: experience with alendronate treatment. *Transplant Proc* 2006; **38**: 1448.
16. Bodingbauer M, Wekerle T, Pakrah B, *et al*. Prophylactic bisphosphonate treatment prevents bone fractures after liver transplantation. *Am J Transplant* 2007; **7**: 1763.
17. Crawford BAL, 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.
18. Guadalix S, Martínez-Díaz-Guerra G, Lora D, *et al*. Effect of early risedronate treatment on bone mineral density and bone turnover markers after liver transplantation: a prospective single-center study. *Transpl Int* 2011; **24**: 657.
19. Monegal A, Guañabens N, Suárez MJ, *et al*. Pamidronate in the prevention of bone loss after liver transplantation: a randomized controlled trial. *Transpl Int* 2009; **22**: 198.
20. Pennisi P, Trombetti A, Giostra E, *et al*. Pamidronate and osteoporosis prevention in liver transplant recipients. *Rheumatol Int* 2007; **27**: 251.
21. Atamaz F, Hepguler S, Akyildiz M, *et al*. Effects of alendronate on bone mineral density and bone metabolic markers in patients with liver transplantation. *Osteoporos Int* 2006; **17**: 942.
22. Kaemmerer D, Lehmann G, Wolf G, *et al*. Treatment of osteoporosis after liver transplantation with ibandronate. *Transpl Int* 2010; **23**: 753.
23. Wagner D, Amrein K, Dimai HP, *et al*. Ibandronate and calcitriol reduces fracture risk, reverses bone loss, and normalizes bone turnover after LTX. *Transplantation* 2012; **93**: 331.
24. Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and:or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135
25. RStudio. *RStudio: Integrated Development Environment for R*. Boston, MA: RStudio; 2020.
26. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, *et al*. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods* 2019; **10**: 476.
27. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; **26**: 404.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177.
29. Harris RJ, Deeks JJ, Altman DG, *et al*. Metan: fixed- and random-effects meta-analysis. *Stata J* 2008; **8**: 3.
30. Ren Y, Lin L, Lian Q, *et al*. Real-world performance of meta-analysis methods for double-zero-event studies with dichotomous outcomes using the Cochrane database of systematic reviews. *J Gen Intern Med* 2019; **34**: 960.
31. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. *Cochrane Handbook Syst Rev Intervent* 2019; **10**: 241.
32. Bell A, Fairbrother M, Jones K. Fixed and random effects models: making an informed choice. *Qual Quant* 2019; **53**: 1051.

33. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006; **25**: 3443.
34. Wells G, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2014. Accessed February 01, 2021. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
35. Halpern, S, Douglas, M, & Jadad, AR, *et al*. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. *Controlled Clinical Trials*, **17**: 1.
36. Hay JE. How effective is bisphosphonate treatment for preventing bone fractures after liver transplantation? *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 190.
37. Roux C, Reid DM, Devogelaer J-P, *et al*. Post hoc analysis of a single IV infusion of zoledronic acid versus daily oral risedronate on lumbar spine bone mineral density in different subgroups with glucocorticoid-induced osteoporosis. *Osteoporos Int* 2012; **23**: 1083.
38. Shi L, Min N, Wang F, *et al*. Bisphosphonates for secondary prevention of osteoporotic fractures: a Bayesian network meta-analysis of randomized controlled trials. *Biomed Res Int* 2019; **2019**: 2594149.
39. Administration USFaD. *Prescribing Information for BONIVA(ibandronate) Injection, for Intravenous Use*. Maryland, Silver Spring, MD: Administration USFaD, 2003.
40. Barrionuevo P, Kapoor E, Asi N, *et al*. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab* 2019; **104**: 1623.
41. Eastell R, Rosen CJ, Black DM, *et al*. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society* clinical practice guideline. *J Clin Endocrinol Metab* 2019; **104**: 1595.
42. Bousten Y, Jamart J, Esselinckx W, *et al*. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001; **16**: 104.
43. Horikawa A, Miyakoshi N, Shimada Y, *et al*. A comparative study between intravenous and oral alendronate administration for the treatment of osteoporosis. *Springerplus* 2015; **4**: 675.
44. Sunyecz J. Optimizing dosing frequencies for bisphosphonates in the management of postmenopausal osteoporosis: patient considerations. *Clin Interv Aging* 2008.**3**: 611.
45. Rizzoli R, Reginster J-Y, Boonen S, *et al*. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. *Calcif Tissue Int* 2011; **89**: 91.
46. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. *Oncologist* 2004; **9**(Suppl 4): 28.
47. Miliani K, Taravella R, Thillard D, *et al*. Peripheral venous catheter-related adverse events: evaluation from a multicentre epidemiological study in France (the CATHEVAL Project). *PLoS One* 2017; **12**: e0168637.
48. Pazianas M, Cooper C, Ebetino F, *et al*. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. *Ther Clin Risk Manag* 2010; **21**: 325.
49. Olyaei AJ, de Mattos AM, Bennett WM, *et al*. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. *Curr Opin Crit Care* 2001; **7**: 384.
50. EASL. *EASL Clinical Practice Guidelines: Liver Transplantation*. Journal of Hepatology. Geneva, Switzerland: European Association for the Study of the Liver, 2015.
51. AASLD. *Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by AASLD and the American Society of Transplantation*. Alexandria, Virginia: American Association for the Study of Liver Disease, 2012.
52. Wiesner RH, Fung JJ. Present state of immunosuppressive therapy in liver transplant recipients. *Liver Transpl* 2011; **17**(Suppl 3): S1.