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

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CRD summary
The authors concluded that bisphosphonate therapy during the first year in liver transplant recipients appeared to reduce accelerated bone loss and improve bone mineral density at the lumbar spine. The authors' conclusion reflected the evidence presented, but the absence of detail on the review process made the reliability of the conclusion unclear.

Authors' objectives
To evaluate the effect of bisphosphonates on bone mineral density in patients following liver transplantation.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched from inception to February 2009. Search terms were reported. Reference lists of included articles were scanned for further studies. Conference meeting abstracts (Digestive Disease Week, American Association for the Study of Liver Diseases, American College of Gastroenterology, and European Association for the Study of the Liver annual scientific meetings) were accessed for unpublished data.

Study selection
Randomised controlled trials (RCTs) of liver transplant patients who received bisphosphonates alone or in conjunction with calcium and vitamin D supplementation compared with a control group who received placebo/no treatment alone or with calcium and vitamin D were eligible for inclusion. Patients with a history of organ transplantation, chronic kidney disease or those who received treatment that might influence bone metabolism were excluded. The outcome of interest was the change in bone mineral density 12 months after successful transplantation.

The included treatments were oral alendronate and etidronate and intravenous zoledronate and pamidronate. Doses and treatment durations varied. All except one study included patients who received calcium and vitamin D supplementation. Immunosuppressive treatments did not vary across the studies. Control groups received various doses and combinations of saline, calcium, calcitonin, calcitriol, calcium carbonate, ergocalciferol, glucose and vitamin D. Most patients were male. Mean patient age ranged from 40 to 54 years. The outcomes measured were bone mineral density change at lumbar spine and femoral neck, incident fractures and adverse events related to bisphosphonates.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Trial quality was assessed with the Jadad scale of covering randomisation, allocation concealment, blinding, withdrawals and follow-up. Maximum possible score was 5.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Baseline and 12-month means and standard deviations (SD) were extracted for bone mineral density values in the lumbar spine and femoral neck. Data were extracted for incident fractures. Authors were contacted for individual patient data where it was not possible to extract bone mineral density data (g/cm²) before and after transplantation from the published paper.

The authors did not state how many reviewers carried out the data extraction.
Methods of synthesis
Weighted mean differences (WMD) and 95% confidence intervals (CI) were pooled in a meta-analysis; a fixed-effect model was used where studies were homogeneous. Statistical heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic. Funnel plots were used to assess publication bias. Sensitivity analysis was carried out by removal of studies with low quality scores.

Results of the review
Six RCTs (n=364) were included in the meta-analysis. Jadad scores were 5 (one trial), 3 (three trials), 2 (one trial) and 1 (one trial). Results from the assessment of publication bias were not reported.

The pooled result for bone mineral density change at lumbar spine showed that bisphosphonate treatment significantly improved bone mineral density by $0.03\, \text{g/cm}^2$ (95% CI 0.01 to 0.05; six RCTs, n=364). Sensitivity analysis did not materially alter the result. An improvement was also noted at the femoral neck, but this change was not statistically significant at the end of 12 months (four trials, n=268). There was no statistically significant heterogeneity in either analysis.

Five trials provided data on incident fractures, but this could not be pooled (reported in the paper). None of the included trials reported any serious adverse events associated with bisphosphonate treatment.

Authors' conclusions
Bisphosphonate therapy in liver transplant recipients during the first year appeared to reduce accelerated bone loss and improve bone mineral density at the lumbar spine. The indications, optimum duration and dosage of treatment needed to be determined.

CRD commentary
The research question was clear. Inclusion criteria were adequately specified to enable replication. Several relevant sources were accessed to identify included trials and attempts were made to minimise publication bias, although results of the formal assessment were not presented. An appropriate tool was used to assess trial quality; interpretation of results shows that half of the included studies were moderate to high quality. The review process was poorly reported, which made it difficult to determine the extent to which efforts were made to minimise error and bias. Study details were provided and the chosen methods of synthesis appeared to be appropriate in relation to levels of heterogeneity.

The authors’ conclusion reflected the evidence presented, but the absence of detail on the review process means made the reliability of conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated that at the time of the review there was no justified role for bisphosphonates in fracture prevention following liver transplantation, despite the positive effect on mean bone mineral density.

Research: The authors stated that future studies should consider a precise estimation of incident fracture and identify interventions to reduce them. Researchers should also develop an appropriate surrogate to identify risk of post-transplant fracture. Longer-term follow-up of bisphosphonate treatment in liver transplant recipients was needed.

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Bibliographic details

PubMedID
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.