Prevention of fractures after solid organ transplantation: a meta-analysis

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CRD summary
This review concluded that treatment with bisphosphonates or active vitamin D analogues during the first year after solid organ transplantation was associated with a reduction in bone fractures. The authors’ conclusions reflect the review results, but it should be noted that there were only two trials of vitamin D analogues included and data were not reported separately for these trials.

Authors’ objectives
To determine whether treatment with bisphosphonates or active vitamin D analogues during the first year after organ transplantation reduced fracture risk and to estimate the effect of these interventions on bone loss

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Key words and search terms were reported. Reference lists of included trials were scanned for additional studies. Unpublished articles presented from 2003 to 2010 at the annual meetings of six relevant societies were searched and authors were contacted to obtain unpublished data.

Study selection
To be eligible for the review, studies had to be randomised controlled trials (RCTs) that followed patients from the time of transplantation and compared treatment with control group. Transplants could be liver, heart, lung or kidney. Eligible trials had to assess fractures as an outcome, include participants over 18 years old, and could be of any sample size. Eligible treatments were oral or IV bisphosphonates (alendronate, risedronate, pamidronate, ibandronate, zoledronic acid) or active vitamin D analogues (calcitriol, calcidiol, 1alpha-hydroxyvitamin D). There were no dose restrictions. Trials of bone marrow transplantation or historical control studies were excluded.

The primary outcome was vertebral or non-vertebral fracture during the first year after transplantation. Change in areal bone mineral density was assessed in all trials as a secondary outcome.

Most included trials compared a bisphosphonate with placebo or no treatment; most trials administered treatment intravenously at various doses and timings. Trials of active vitamin D analogues were compared with no treatment. In all but one trial, participants received calcium supplements with or without vitamin D. Immunosuppressant regimen varied by type of organ transplanted but all included prednisone steroid treatment. In most trials there were no bone mineral density inclusion criteria. All trials assessed fractures using spine x-ray.

More than one researcher was involved in the process of selecting studies for the review.

Assessment of study quality
Trial quality was assessed using the Jadad scale with scores from 0 to 5 points based on randomisation, blinding, and drop-outs and withdrawals.

Data extraction
Two reviewers independently extracted data on the proportion of patients with fractures and the total number of fractures. The log odds ratio of fracture between the two groups was estimated along with its standard error. For studies with no specific assessment of fractures at one year, the number of fractures and the number of patients with fracture were estimated using standard statistical techniques. Absolute change and percentage change in areal bone mineral density were also extracted. If only one of these changes was described in the publication, the other was calculated from the data provided. Authors were asked to provide raw data if possible.

Methods of synthesis
Statistical heterogeneity was assessed using the $X^2$ test. Fixed-effect and random-effects models were used to pool percentage difference in bone density and log odds ratios of fracture.
Analyses were presented for bisphosphonate and vitamin D trials combined and for bisphosphonate trials only.

Publication bias was assessed using funnel plots and linear regression.

**Results of the review**

Eleven RCTs (780 participants, 134 fractures) were included in the review. Transplant operations included were liver (four trials), kidney (four trials), heart (two trials), and heart and lung (one trial). The median quality of the included trials was 3 (range 2 to 5). Only two of the trials were powered to detect differences in fracture. There was no statistically significant publication bias for any outcome.

**Bisphosphonate and vitamin D trials combined** (11 trials): Significant differences in fracture were reported by four of the trials. The overall incidence of fracture in patients who were not treated was 24.7% over one year (659 patients were followed up). Treatment with either bisphosphonates or vitamin D analogues was associated with a reduction in participants with fractures (OR 0.50, 95% CI 0.29 to 0.83; fixed-effect model); there was no statistically significant heterogeneity. Treatment was also associated with a reduction in the number of all fractures (vertebral and nonvertebral) (OR 0.37, 95% CI 0.22 to 0.60; random-effects model); there was statistically significant heterogeneity. A reduction in the number of vertebral fractures was also observed with treatment (OR 0.24, 95% CI 0.07 to 0.78; random-effects model); there was statistically significant heterogeneity. The results did not change with sensitivity analysis. An increase in bone mineral density was found with treatment at the lumbar spine (2.98%, 95% CI 1.31 to 4.64; random-effects model; significant heterogeneity) and femoral neck (3.05%, 95% CI 2.16 to 3.93; fixed-effect model; no significant heterogeneity).

**Bisphosphonate trials only** (none trial, 625 participants): There was a reduction in the number of participants with fractures (OR 0.53, 95% CI: 0.30 to 0.91; fixed-effect model); there was no significant heterogeneity. There was no significant reduction in total number of all fractures or vertebral fractures; there was significant heterogeneity for both these outcomes. Bisphosphonate treatment was associated with improvement in lumbar spine (3.34%, 95% CI 1.10 to 5.58) and femoral neck (3.04%, 95% CI 1.42 to 5.65) bone mineral density; there was significant heterogeneity for both outcomes (random-effects models were used).

**Authors' conclusions**

Treatment with bisphosphonates or active vitamin D analogues during the first year after solid organ transplantation was associated with a reduction in the number of patients with fractures, fewer vertebral fractures and an increase in femoral neck and lumbar spine bone density.

**CRD commentary**

This review was based on defined inclusion criteria. Two databases were searched but this was supplemented by a range of other sources. Attempts were made to identify unpublished material and publication bias was tested. Two reviewers appeared to be involved in all the review processes, which helped to minimise reviewer bias and error.

Trial quality was assessed, although results of this were not presented in detail. A meta-analysis appeared to be appropriate, despite the differences in organs being transplanted across the trials.

The authors’ conclusions reflect the results of the review, but it should be noted that there were only two trials of vitamin D analogues included in the review and data were not reported separately for these trials.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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**Bibliographic details**

Record Status
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.