Effects of bisphosphonates on bone loss in the first year after renal transplantation: a meta-analysis of randomized controlled trials

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CRD summary
This review assessed the efficacy of bisphosphonates on preventing bone loss within the first year after kidney transplantation. The small number of included studies and associated small data-sets and the overall low quality of the included trials meant the reliability of the authors’ conclusion that treatment with bisphosphonates may be beneficial in countering the bone loss that occurs within the first year after engraftment is not clear.

Authors' objectives
To determine the efficacy of bisphosphonate on preventing bone loss in the first year after kidney transplantation.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched from inception to December 2004 without language restriction. Search terms were reported. Reference lists of relevant articles and abstracts from conference proceedings, including the American Society of Nephrology, the International Transplant Society and the European Dialysis and Transplantation Association were also checked. Authors of the included studies and experts in the field were contacted in order to locate unpublished studies.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion in the review. Studies that compared the use of bisphosphonates alone or in combination with calcium and/or vitamin D, with no treatment or placebo alone or in combination with calcium and/or vitamin D were eligible for inclusion in the review. Three studies used bisphosphonate pamidronate, one study used zoledronate and one study ibandronate. Most studies applied intravenous bisphosphonates in a cyclic fashion. All participants received daily calcium. One trial allowed supplementation with dairy products. Vitamin D was administered in three trials. Immunosuppressants administered included ciclosporin, azathioprine, mycophenolate mofetil (MMF) steroids and calcineurin inhibited steroids. Studies of adults (over 18) receiving their first or subsequent cadaver or living renal allograft were eligible for inclusion in the review. The percentage of female participants, by group, ranged from zero to 67 per cent. Studies reporting change in bone mineral density (BMD) within the first year after successful kidney transplant were eligible for inclusion the review. BMD at the lumbar spine and femoral neck were reported, as well as incidence of new fractures, graft function and adverse effects.

The authors stated neither how studies were selected for inclusion in the review nor how many reviewers performed the selection.

Assessment of study quality
The quality of the included studies was evaluated without blinding to journal or authorship using the Jadad scale, which assesses reported randomisation, allocation, blinding and completeness of follow-up. Possible scores range from 0 (lowest) to 5 (highest). The authors’ did not state how many reviewers assessed methodological quality.

Data extraction
Authors were contacted for individual bone densitometry results (expressed in g/cm²) for all randomised patients, determined at lumbar spine and femoral neck at baseline and after treatment. Individual absolute changes in BMD during the study period were calculated for each study using these data.

The authors stated neither how data were extracted nor how many reviewers performed the data extraction.

Methods of synthesis
Studies were pooled in a meta-analysis using a fixed-effects method grouped by site (femoral neck or lumbar spine). If
significant statistical heterogeneity was found a random-effects method was used. Summary estimates were reported as weighted mean differences (WMD) with their corresponding 95% confidence intervals (CI). Statistical heterogeneity was assessed using the $\chi^2$ test. Linear regression analysis of covariance (ANCOVA) was used to analyse post-treatment BMD results, accounting for pre-treatment BMD, at the lumbar spine and femoral neck with individual patient data.

**Results of the review**

Five RCTs were included in the review (n=180). Two trials received a Jadad score of 3, two trials received a Jadad score of 2 and one trial received a Jadad score of 1. None of the included trials were blinded.

**Lumbar spine and femoral neck BMD**

Lumbar spine: treatment with bisphosphonates was found to reduce BMD decline at the lumbar spine compared to control group at 6-12 months after renal transplantation. WMD 0.06 g/cm$^2$ (95% CI: 0.05, 0.08, p<0.001) based on five RCTs (n=180). No evidence of significant statistical heterogeneity was found. ANCOVA analysis showed an estimated BMD difference of 0.059 g/cm$^2$ (p<0.001) between the control and intervention group at the lumbar spine. Most variability of post-treatment BMD was explained by pre-transplant BMD.

Femoral neck: treatment with bisphosphonates at the femoral neck reduced loss of BMD. WMD 0.05 g/cm$^2$ (95% CI: 0.0, 0.11) based on five RCTs (n=180). However, significant statistical heterogeneity was found. When using a random-effects model no statistically significant difference between groups was found. ANCOVA analysis showed an estimated BMD difference of 0.048 g/cm$^2$ between treated and non-treated patients (P<0.001) when adjusted for absolute levels at baseline and trial site.

**Bone fractures and adverse effects**

Three studies reported the number of participants with new fractures. Results were mixed: one trial found a higher number of fractures in the control group (two versus one); one trial found an equivalent number of fractures in each group (two each); no fractures were reported in one trial. None of the included trials reported withdrawals due to side effects. Transient hypocalcaemia, bone pain and flatulence were reported as being temporally related to bisphosphonate administration.

**Graft function and immunosuppression**

Five studies used calcineurin inhibitor-based immunosuppressive regimes. No trial reported deterioration of kidney transplant function due to bisphosphonate treatment with comparable renal graft outcome at the end of the follow-up period. One study found significantly more acute graft rejections in the control group. Three studies reported equivalent numbers of rejections in both groups. No data were reported in one study.

**Authors' conclusions**

That bisphosphonate therapy in the first few months after renal transplantation may be beneficial in countering the bone loss that occurs within the first year after engraftment.

**CRD commentary**

The review question was supported by clear inclusion criteria. A number of sources were searched without language restriction and the authors made some attempt to locate unpublished studies, minimising the likelihood of language and publication bias. Review methods undertaken to select studies, extract data and assess quality were not reported, so the possibility of reviewer error or bias at these stages cannot be assessed. Although the methodological quality of the trials was assessed and a total score was reported, results for individual criteria were not provided, limiting the reader's evaluation of the included studies. The studies were pooled using appropriate meta-analytic methods. Statistical heterogeneity was assessed. The authors highlighted that BMD is a generally accepted surrogate endpoint for fracture rate. Overall, the reliability of the authors' conclusion is unclear due to lack of reported methods undertaken for study selection and data extraction, low overall quality of the included studies and the small number of studies and data-sets.

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

Practice: the authors suggested that the potential for induction of adynamic or low-turnover bone disease should be
considered in the decision to use bisphosphonates on an individual basis.

Research: the authors did not state any implications for research.

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