Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty: a meta-analysis

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CRD summary
This review assessed the effects of bisphosphonates on bone mineral density following total joint arthroplasty. The authors concluded that studies suggest that bisphosphonates maintain periprosthetic bone better than a control, but further research is required to assess clinical outcomes. This was a well-conducted review and the authors' cautious conclusions reflect the evidence.

Authors' objectives
To assess the effects of bisphosphonates on bone mineral density (BMD) following total joint arthroplasty.

Searching
EMBASE (1980 to 2003), MEDLINE (via OVID) and MEDLINE (via PubMed) (1966 to August 2003) were searched; the search terms were reported. The Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register, the website of the UK National Research Register and the archives of the American Academy of Orthopaedic Surgeons were also searched (1989 to 2003). Bibliographies of selected studies were checked, and corresponding authors and experts in the field suggested additional studies. No language restrictions were reported. Published and unpublished studies and studies reported as abstracts were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Oral or intravenous bisphosphonates used after joint arthroplasty were eligible for inclusion. The included studies compared oral alendronate (10 mg/day) and pamidronate (a one time infusion of 90 mg on the fifth post-operative day) with control (calcium carbonate or no medication).

Participants included in the review
Patients with hip or knee arthritis undergoing total joint arthroplasty were eligible for inclusion. The included studies were in patients receiving cemented, uncemented and hybrid hip arthroplasties and cemented knee components.

Outcomes assessed in the review
Studies that assessed BMD using dual-energy X-ray absorptiometry were eligible for inclusion. The review assessed BMD at 3, 6 and 12 months for the total proximal femoral metaphysis in patients undergoing hip arthroplasty, and the total distal femoral and proximal tibial metaphyseal bone density in patients undergoing knee arthroplasty.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies. The reviewers were blinded to the author, institution, journal and results. Inter-reviewer agreement was assessed using the kappa statistic.

Assessment of study quality
Studies were assessed using the 21-point scale described by Detsky. This assesses the reporting of eligibility criteria, adequacy of randomisation, description of treatments, assessment of outcomes and statistical analysis. The studies were also assessed for randomisation (present and concealed), blinding of the patients, clinicians and outcome assessors, and losses to follow-up. The maximum possible validity score was not reported. Two reviewers independently assessed...
validity and resolved any disagreements through discussion. The assessment of validity was sent to each corresponding author for verification. Inter-reviewer agreement was assessed using the kappa statistic.

**Data extraction**
One reviewer extracted the data and checked the accuracy. The data extraction was sent to each corresponding author for verification. The data extracted included the number of patients in each treatment group, the baseline BMD, and study outcomes extracted as the difference between treatments in the BMD at 3, 6 and 12 months. Values for BMD were extrapolated from graphs where required. For each study, the mean difference in BMD between treatments was calculated with the 95% confidence intervals (CIs).

**Methods of synthesis**
How were the studies combined?
Pooled weighted mean differences (WMDs) with 95% CIs between treatments were calculated. A funnel plot was used to assess publication bias.

How were differences between studies investigated?
Statistical heterogeneity was assessed using methods described by Hedges and Olkin (with a significance level of P<0.1). The influence of the following predefined factors was examined: type of arthroplasty (with or without cement); region (knee or hip); type of bisphosphonate; and study quality (less than 70 or 70 or more points). WMDs in BMD were calculated for all these subgroups.

**Results of the review**
Six RCTs (n=264) were included. The sample size ranged from 13 to 96 patients.

Inter-rater agreement was good for both study selection (kappa 0.85) and study quality (kappa 0.88).

In terms of study quality, 2 studies were blinded. There was complete follow-up in 4 studies.

Three studies assessed BMD at 3 months after surgery and all showed a decrease in both treatment groups.

There was significantly less periprosthetic bone loss at 3 months with bisphosphonates compared with the control; the WMD (n=152) was 3.3% (95% CI: 1.9, 4.7, P<0.01). The difference remained statistically significant at 6 and 12 months; the WMDs were 4.5% (5 studies, n=248; 95% CI: 1.6, 7.4, P<0.001) and 4.2% (4 studies, n=197; 95% CI: 1.5, 6.9, P=0.02), respectively.

Neither the type of bisphosphonate nor the quality score significantly altered the results.

The difference between bisphosphonate and control was significantly greater at 12 months (P<0.001) for cemented hip arthroplasties (WMD 7.5%, 95% CI: 4.3, 10.7) compared with uncemented hip arthroplasties (WMD 2.1%, 95% CI: 0.61, 3.6), but the results might have been confounded by the greater age of patients undergoing cemented arthroplasties (68 years for cemented versus 55 years for uncemented).

The difference between bisphosphonate and control was significantly greater at 6 months (P<0.001) for total knee arthroplasties (WMD 14.0%, 95% CI: 6.3, 21.7) compared with total hip arthroplasties (WMD 2.5%, 95% CI: 0.96, 4.1), but the difference was not statistically significant at one year.

The funnel plots showed no evidence of publication bias at 3, 6 or 12 months.

**Authors’ conclusions**
The studies suggested that bisphosphonates maintain periprosthetic bone better than a control, but further research is required to assess clinical outcomes.
CRD commentary
The review addressed a clear question defined in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. Appropriate methods were used to assess the presence of publication bias, but no evidence of it was found. Including studies published in more than one language reduced the possibility of language bias. Methods were used to minimise bias and error in the study selection, validity assessment and data extraction processes. Validity was assessed using established criteria. The data were appropriately combined using meta-analysis, meta-analysis graphs were presented, and subgroup analyses were used to examine the influence of predefined factors. This was a well-conducted review and the authors' cautious conclusions reflect the evidence.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that adequately powered methodologically sound studies are required to assess the effects of bisphosphonates on clinically relevant outcomes.

Bibliographic details

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Subject indexing assigned by NLM

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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.