Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis
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Authors' objectives
To summarise the literature concerning the use of bisphosphonates in the prevention and treatment of corticosteroid-induced osteoporosis, and to make recommendations concerning the proper use of these agents.

Searching
The literature searches were conducted independently by two authors, who searched MEDLINE, Current Contents and HealthSTAR using the following medical subject headings and search terms: 'bisphosphonates', 'diphosphonates', 'glucocorticoids', 'steroids' and 'osteoporosis'. In addition, bibliographies of selected citations and review articles were examined. Unpublished information was obtained by handsearching abstracts from recent meetings (1998) of the American Society for Bone and Mineral Research and the American College of Rheumatology.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were included.

Specific interventions included in the review
Studies were included if they evaluated the use of oral bisphosphonates in adults. The oral bisphosphonates studied included risedronate (2.5, 5 or 15 mg/day), etidronate (400 mg/day), alendronate (5 or 10 mg/day), and clodronate (800, 1600 or 2400 mg/day). The controls included placebo alone, placebo followed by calcium and/or vitamin D, and calcium alone.

Participants included in the review
The quality of the reporting of the participants' characteristics varied across the included studies. From the data reported in the review, the participants appeared to be mainly (50 to 75%) female, postmenopausal, and aged over 50 years.

Outcomes assessed in the review
The primary outcomes were differences between the treatment and placebo groups, in terms of the percentage change from baseline in the bone mineral density (BMD) at the lumbar spine, femoral neck, and femoral trochanter. The secondary outcomes included fracture risk and adverse effects.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The methodological quality was assessed using the scale of Jadad et al. (see Other Publications of Related Interest). Two authors assessed the methodological quality of the included trials. It was not reported whether this assessment was independent or how, if necessary, discrepancies were resolved.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on the treatment, e.g. agent and dose, study duration, and the participants' characteristics.
Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
The authors did not investigate specifically any potential sources of heterogeneity within the included studies. However, they did state that the results varied on the basis of the population, the bisphosphonate investigated, the dosing regimen, and other distinctions in the study design, although they failed to provide data in this regard.

Results of the review
Thirteen randomised controlled trials (n=1,711) were included. There were 8 studies of etidronate (n=522), 3 of risedronate (n=638), 1 of alendronate (n=477), and 1 of clodronate (n=74).

Methodological quality.
The quality scores ranged from 1 to 4 with 1 trial scoring 1, 2 trials scoring 2, 2 trials scoring 3, and 8 trials scoring 4. Although all studies were reported as randomised, only 1 trial described the randomisation process. Three trials did not report whether they used double-blind methodology.

Primary outcomes.

Lumbar spine.
The mean changes in BMD at the lumbar spine ranged from -0.137 to 4.9% in the treatment groups, and from 0.98 to 3.7% in the control groups. Three of the 13 studies (23%) did not show a significant benefit at the lumbar spine when compared with the control group, although 2 of these studies used unusual doses of bisphosphonate.

Femoral neck.
The changes in BMD at the femoral neck ranged from 1.28 to 3.6% in the treatment groups, and from 3.6 to 3.64% in the control groups. Nine of the 13 studies (69%) did not show a statistically-significant difference between the treatment and control groups at the femoral neck.

Femoral trochanter.
The changes in BMD at the femoral trochanter ranged from -1.35 to 2.7% in the treatment groups, and from 1.5 to 3.06% in the control groups. Six of the 10 studies reporting data at the femoral trochanter showed that the treatment group was not significantly better than the control group.

Secondary outcomes. Fracture risk.
In one study, a 10.1% reduction in vertebral fractures was found in patients receiving risedronate (2.5 or 5 mg) at 12 months (P=0.021). When these results were pooled with another trial, it was found that 5.0 mg risedronate statistically decreased the incidence of vertebral fractures at 1 year (16.2 versus 5.4%, P=0.01). Two studies found borderline significance in the fracture rate when postmenopausal women were analysed separately. The use of etidronate and alendronate led to an absolute risk reduction of 18.7% (P=0.05) and 8.6% (P=0.05), respectively.

Adverse effects.
In terms of the drop-out rates, no significant difference was reported between the treatment and control groups. In most of the studies, no statistical significance was found when comparing the treatment and control groups with regards to adverse effects. Nine studies discussed the subgroup of gastrointestinal (GI) adverse events. Eight studies found no difference in overall GI effects, whereas one study reported a statistical trend for increased GI side-effects with an increased dose of alendronate. In one study, diarrhoea was more common in patients receiving 5 mg risedronate than those taking placebo (the number-needed-to-harm was 15), although significance was not reported.
Authors' conclusions
The use of bisphosphonates significantly increased BMD in those patients at risk of corticosteroid-induced bone loss. However, there were little data concerning the ability of these agents to affect the clinically important outcome of fracture rate reduction, especially among premenopausal women in whom fractures are rare within the first few years of exposure to corticosteroids. Long-term studies powered to detect fracture risk reduction, and comparative trials with bisphosphonates and other agents, are needed.

CRD commentary
The review question was stated clearly and was supported by the study inclusion criteria. The literature search was adequate, although only English language publications appear to have been included, and no search dates were provided. A formal quality assessment of the included studies was undertaken using a published instrument. Details of the included studies were adequately presented in tabular format and were discussed in the text. However, some potentially important data were not reported, such as the baseline BMD of the participants. It is unclear why the studies were not combined statistically.

Some details of the review process were not reported, such as how the data were extracted, or how many of the reviewers performed the data extraction. The extent to which bias played a role in the review is, therefore, unknown.

The authors' conclusion that 'bisphosphonates significantly increased BMD in patients at risk for corticosteroid-induced bone loss' appears unjustified. Specifically, whilst there appeared to be evidence that bisphosphonates significantly increased BMD in the lumbar spine, there was little evidence for this effect in the femoral trochanter, and even less for the femoral neck.

Implications of the review for practice and research
Practice: The authors stated three main implications for practice.

1. All patients beginning high-dose (greater than 7.5 mg/day prednisone), long-term (greater than 6 months) glucocorticoid therapy should be evaluated for pharmacologic prophylaxis against osteoporosis. Since the majority of bone loss occurs within the first 6 months of therapy, clinicians must develop a preventive plan in advance, preferably before the glucocorticoid prescription is given to the patient.

2. If BMD has decreased by more than 5% from baseline at 6 to 12 months, the initial choice of therapy should be changed or expanded.

3. Once osteoporosis is established (regardless of the pathogenesis) in postmenopausal patients, treatment should be aggressive to prevent further loss of bone density. In this population bisphosphonates are an appropriate therapeutic option.

Research: The authors stated four main implications for research:

1. Large studies are required to assess vertebral and nonvertebral fractures.

2. Head-to-head comparative trials of bisphosphonates with other pharmacological options, such as hormonal therapy or calcitonin, are essential to establish evidence-based clinical guidelines.

3. Studies addressing combination therapy with bisphosphonates and hormone replacement therapy in postmenopausal women would be useful.

4. Comparative studies of the various bisphosphonates in relation to one another are needed.

Bibliographic details
Blair M M, Carson D S, Barrington R. Bisphosphonates in the prevention and treatment of glucocorticoid-induced...
osteoporosis. Journal of Family Practice 2000; 49(9): 839-848

**PubMedID**
11032210

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Bone Density /drug effects; Diphosphonates /adverse effects /pharmacology /therapeutic use; Evidence-Based Medicine; Female; Fractures, Bone /etiology /prevention & control; Glucocorticoids /adverse effects; Humans; Male; Middle Aged; Osteoporosis /chemically induced /complications /drug therapy /prevention & control; Randomized Controlled Trials as Topic; Risk Factors

**AccessionNumber**
12000001982

**Date bibliographic record published**
30/04/2002

**Date abstract record published**
30/04/2002

**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.