Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs

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Authors' objectives
To analyse the relationship between improvement in spine bone mineral density (BMD) and treatment with antiresorptive drugs.

Searching
MEDLINE was searched from 1966 to July 2000 using the keywords 'osteoporosis' and 'trial', or 'estrogen' and 'trial'. In addition, the authors manually searched all abstracts from major meetings of bone research societies from 1995 to July 2000.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) including a placebo treatment group were eligible. The authors chose to limit inclusion to those studies reporting more than five vertebral fractures per treatment group.

Specific interventions included in the review
Studies investigating antiresportive drugs (oestrogens, bisphosphates, raloxifene, or calcitonin) versus placebo were eligible. The included interventions were alendronate, calcitonin, etidronate, tiludronate, risedronate, estradiol and raloxifene. Studies investigating anabolic agents, nutritional supplements or vitamin D metabolites were excluded. Studies that compared different doses of a drug were included; each dose was included as a separate observation in comparison with placebo.

Participants included in the review
Studies in postmenopausal women in community- or medical practice-based cohorts were eligible. Studies in women with secondary causes of osteoporosis were excluded.

Outcomes assessed in the review
Studies reporting spine BMD or bone mineral content at the end of treatment, as well as incident vertebral fractures by radiographs, were eligible. Outcomes at three years were included when available.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened all potential articles and abstracts for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The data from eligible studies were extracted by one reviewer and checked for accuracy by a second reviewer.

To measure the improvement in spine BMD, the authors subtracted the percentage in the placebo group from the corresponding change in the active group to calculate the percentage difference for each study. The study authors were contacted for missing data relating to spine BMD and vertebral fractures.

Methods of synthesis
How were the studies combined?
The authors developed regression models to analyse the association between the improvement in BMD and the relative risk (RR). The improvement in spine BMD (versus placebo) was plotted against the RR of vertebral fracture in the trial. Further regression models were developed to estimate how much of an improvement in bone mass would be predicted to reduce the risk of vertebral fractures, and by how much this improvement would reduce the risk. Full details of the methods used were reported in the paper. Publication bias was tested through a funnel plot and Kendall tau rank correlation.

How were differences between studies investigated?
The authors carried out a sensitivity analysis to investigate the impact of excluding small studies from the meta-analysis.

Results of the review
Twelve RCTs (n=21,404) were included.

Improvements in BMD were associated with decreases in the risk of vertebral fracture during treatment. Compared with placebo, a 1% improvement in spine BMD was associated with a 0.03 decrease in the RR of spine fracture (95% confidence interval, CI: 0.02, 0.05, p=0.002). The sensitivity analysis showed that the exclusion of the small studies did not change the findings.

The authors found no evidence of publication bias.

The authors applied logistic regression models to data from the Fracture Intervention Trial, to estimate the proportion of the reduction in risk of vertebral fracture that could be explained by the effects of treatment on spine BMD. The authors noted that the improvement in spine BMD explained 16% (95% CI: 11, 27) of the reduction in risk. Therefore, the authors found that the reductions in risk were greater than those predicted from improvements in BMD.

Authors' conclusions
The improvement in spine BMD during treatment with antiresorptive drugs accounts for a small part of the observed reduction in the risk of vertebral fracture.

CRD commentary
The methodology of this review was generally adequate. The authors described the inclusion and exclusion criteria for the review, but the search was limited to one database (MEDLINE) and conference abstracts. The authors may, therefore, have missed important studies. The validity of the included studies was not assessed, and only the numbers of reviewers who carried out the study selection and data extraction processes were reported. Details of the studies were presented clearly, and the authors described the development of the regression models in detail. A number of sensitivity analyses were also undertaken. The authors' conclusions follow from the data presented.

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

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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.