Authors’ objectives
To determine the incidence of vertebral and non-vertebral fractures in published randomised clinical trials using calcitonin by parenteral injection or intra nasal spray.

Searching
Searches were conducted of MEDLINE from 1988 to 1996, conference proceedings to the end of 1997, and reference lists of various review articles and books. Studies were accepted in English, German, Spanish, Italian, and French. Where necessary, senior authors were contacted for specific information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 6 months duration that compared calcitonin therapy with placebo, no therapy or calcium supplements with or without vitamin D were included. Duration of trials ranged from 6 months to 3 years. Reasons were given for the exclusion of identified studies.

Specific interventions included in the review
Calcitonin (synthetic salmon or human calcitonin) given intramuscularly (100 IU for 10 days in each month to 400 IU daily), sub-cutaneously (dose ranging from 0.25 mg four times weekly for 4 weeks out of each 10 weeks to 400 IU daily) or intra nasally (dose ranging from 50 IU to 400 IU) was compared to placebo, no therapy or calcium (1000 mg calcium ) with or without 400 IU vitamin D.

Participants included in the review
The following groups of patients were included: postmenopausal women including those with one or more crush fractures, low bone mass, or established osteoporosis; perimenopausal women; patients starting steroids for temporal arteritis or polymyalgia; men and women taking glucocorticoids; and men with established osteoporosis. The mean age of subjects (where stated) ranged from 49 to 70 years and the age (where stated) ranged from 27 to 80 years.

Outcomes assessed in the review
The number of patients experiencing fractures and the number of fractures was assessed.

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 authors do not state that they assessed validity.

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.

Methods of synthesis
How were the studies combined?
The relative risk (RR) and 95% confidence interval (CI) of a patient experiencing a fracture (where data allowed) or the RR of fracture were calculated.
How were differences between studies investigated?
The fracture risk was re-calculated after omitting men and excluding any secondary cause of osteoporosis.

Results of the review
Fourteen RCTs were included (2,452 patients).

Fewer vertebral and non-vertebral fractures were reported in the group receiving calcitonin: Pooled number of fractures (vertebral + non-vertebral) RR = 0.43 (95% CI: 0.38, 0.50). 237 vertebral fractures in 1309 calcitonin treated patients compared to 271 vertebral fractures in 678 placebo treated patients. RR = 0.45 (95%CI: 0.39, 0.55). Fracture burden adjusted for duration of follow-up was reduced in calcitonin group (6.94 vs 16.56 fractures per 100 patient years). For non vertebral fractures RR = 0.34 (95% CI: 0.17, 0.68). The exclusion of men and any secondary cause of osteoporosis did not alter these results RR = 0.53 (95%CI: 0.43, 0.64).

Fewer patients reported vertebral fractures in the calcitonin treated group though this did not reach statistical significance (1744 patients): 166 patients with a vertebral fracture in 1190 patients treated with calcitonin compared to 96 patients out of 554 treated with placebo. RR = 0.80 (95%CI: 0.64, 1.01). A non significant decrease in patients with a non-vertebral fracture was reported in the calcitonin group RR = 0.48 (95%CI: 0.20, 1.15). Pooled number of patients with vertebral and non-vertebral fractures favoured calcitonin treatment with RR = 0.74 (95%CI: 0.60, 0.93).

Authors' conclusions
On the balance of probabilities it was concluded that calcitonin decreases osteoporotic fracture rate but that it remains to be determined whether this can be shown 'beyond a reasonable doubt'.

CRD commentary
The aims and inclusion criteria were stated. Studies in several languages were sought. Some relevant details of the primary studies was clearly presented in tabular format. Some investigation of the influence of patient characteristics on results was undertaken. The author correctly stated that formal meta-analysis was not appropriate given the variability among studies in length of treatment and measures used and methods used to assess vertebral fractures. The following potential limitations of the review were discussed: lack of reporting of the occurrence of fractures; publication bias; several studies were single rather than double blinded; and the relatively short duration of most studies with only two exceeding two years.

By limiting the literature search to one database, some relevant studies may have been omitted. No details were given of methods used to select studies or extract data. No assessment of validity or heterogeneity was undertaken. In the calculation of fracture rates no mention was made of the problems in analysing event rates that are dependent. There was no mention of adverse reactions, drop-out rates (though some appear high) or reasons for withdrawal. The analysis was not conducted by intention to treat.

In view of the above, caution is required in interpreting the results.

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

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