Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials


CRD summary
This well-conducted systematic review concluded that 700 to 800 IU/day oral vitamin D supplementation appears to reduce the risk of hip and nonvertebral fractures in older persons, whereas 400 IU/day is insufficient for fracture prevention. However, the trials’ concurrent administration of calcium means that the independent effect of vitamin D cannot be determined.

Authors' objectives
To assess the effectiveness of oral vitamin D supplementation in preventing hip and nonvertebral fractures in older people.

Searching
MEDLINE (1960 to January 2005), EMBASE (1991 to January 2005) and the Cochrane Controlled Trials Register (1960 to January 2005) were searched for English and non-English articles; the search terms were reported. Reference lists and abstracts presented at the American Society for Bone and Mineral Research (1995 to 2004) were handsearched. The authors also contacted experts for additional publications. Only published trials were eligible for inclusion in the review.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) with a minimum follow-up of one year were eligible for inclusion.

Specific interventions included in the review
Studies that compared oral vitamin D supplementation (cholecalciferol or ergocalciferol), with or without calcium supplementation, versus calcium supplementation or placebo were eligible for inclusion. Studies that used active vitamin D metabolites were not eligible for inclusion. All studies used cholecalciferol; the doses used were 400 IU/day (2 studies) and 700 to 800 IU/day (5 studies). Four trials also gave calcium supplementation (500 to 1,200 mg/day), whilst one trial asked participants to consume three dairy products daily to increase calcium intake to at least 800 mg/day. Five trials had placebo control groups, in one trial the control group were given calcium supplementation, and in another trial the control group were given cod liver oil.

Participants included in the review
Studies that included participants with a mean age of at least 60 years were eligible for inclusion. Studies of patients who had recently had organ transplantation or a stroke, who were receiving steroid therapy or care for Parkinson's disease, or who had unstable health states (e.g. recent acute hospitalisation), were not eligible for inclusion. The trial participants were in stable health states and had a mean age of approximately 79 years. Sixty-eight per cent of the participants were female.

Outcomes assessed in the review
Studies that examined hip or nonvertebral fractures were eligible for inclusion, as long as more than one fracture had occurred in each study. The studies also had to state how fractures were ascertained and that 25-hydroxyvitamin D levels were measured during follow-up in the treatment group (or a subset thereof). All of the included studies had hip or nonvertebral fractures as the primary or secondary outcome.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors assessed the following aspects of study quality: randomisation, random allocation concealment, masking of treatment allocation, blinding and withdrawals. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two independent reviewers extracted the data; consensus was achieved for all data. Data on the relative risk (RR) of a first hip or nonvertebral fracture, as well as associated 95% confidence intervals (CIs), were extracted in an intention-to-treat format.

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects meta-analysis. Where there was no heterogeneity among studies, a fixed-effect models was also used. The risk difference for preventing a fracture was calculated in order to determine the number of patients who would need to be treated to prevent one fracture (i.e. number-needed-to-treat, NNT).

The authors assessed publication bias using the Begg and Egger test, a funnel plot and a trim-and-fill analysis.

How were differences between studies investigated?
Heterogeneity was assessed using the Cochran Q test. Heterogeneity by vitamin D dose was explored by pooling studies that used a dose of more than 400 IU/day separately from those that used a dose of 400 IU/day or less. In order to visually explore heterogeneity by vitamin D dose, 25-hydroxyvitamin D levels in the treatment group of each trial were plotted against the effect size of each trial. A random-effects meta-regression analysis was also performed to assess whether higher 25-hydroxyvitamin D level in the treatment group was a significant predictor of antifracture efficacy.

Two trials that reported only one hip fracture each were included in a sensitivity analysis. Three trials that did not meet the inclusion criteria for the review (one was an unblinded pragmatic trial and two were unpublished trials) were included in a sensitivity analysis. The authors also performed subgroup analyses based on additional calcium supplementation, gender and length of follow-up, where possible.

Results of the review
Seven RCTs (n=9,820) were included in the review.

The authors stated that there was no evidence of publication bias when using the Begg and Egger test. The funnel plot suggested a possible absence of negative studies involving small sample sizes; however, the trim-and-fill analysis did not confirm this suggestion.

Hip fractures.
When studies with high and low dosages of oral vitamin D supplementation were pooled together, there was no statistically significant reduction in the RR of hip fracture (5 trials; RR 0.88, 95% CI: 0.69, 1.13) but significant heterogeneity between studies (P=0.09). When 2 trials reporting one hip fracture each were included in a sensitivity analysis, there was still no statistically significant reduction in the RR of hip fracture (7 trials; RR 0.87, 95% CI: 0.70, 1.09).

There was a statistically significant reduction in the RR of hip fracture (3 trials; RR 0.74, 95% CI: 0.61, 0.88) for patients receiving 700 to 800 IU/day oral vitamin D supplementation, with no significant heterogeneity between studies (P=0.74). The pooled risk difference was 2% (95% CI: 1, 4, P<0.001), therefore the NNT was 45 (95% CI: 28, 114) for a treatment duration of 24 to 60 months. When 2 trials that only reported one hip fracture each were included in a sensitivity analysis, there was still a statistically significant reduction in the RR of hip fracture (RR 0.73, 95% CI: 0.61, 0.88).

There was no reduction in the RR of hip fracture (2 trials; RR 1.15, 95% CI: 0.88, 1.50) for patients receiving 400
IU/day oral vitamin D supplementation, with no significant heterogeneity between studies (P=0.68). A greater reduction in hip fractures (meta-regression P=0.02) and any nonvertebral fracture (meta-regression P=0.03) was observed with higher achieved 25-hydroxyvitamin D levels in the treatment group. The results were unchanged in a sensitivity analysis that included 3 additional studies that did not meet the inclusion criteria for the review.

Nonvertebral fractures.

When studies with high and low dosages of oral vitamin D supplementation were pooled together, there was a statistically significant reduction in the RR of any nonvertebral fracture (7 trials; RR 0.83, 95% CI: 0.70, 0.98) but significant heterogeneity between studies (P=0.07). There was a statistically significant reduction in the RR of any nonvertebral fracture (5 trials; RR 0.77, 95% CI: 0.68, 0.87) for patients receiving 700 to 800 IU/day oral vitamin D supplementation, with no significant heterogeneity between studies (P=0.41). The pooled risk difference was 4% (95% CI: 2, 5, P=0.02), therefore the NNT was 27 (95% CI: 19, 49) for a treatment duration of 12 to 60 months. There was no reduction in the RR of any nonvertebral fracture (2 trials; RR 1.03, 95% CI: 0.86, 1.24) for patients receiving 400 IU/day oral vitamin D supplementation, with no significant heterogeneity between studies (P=0.36).

In a subgroup analysis by gender, there was a statistically significant reduction in the RR of hip fracture (3 trials; RR 0.73, 95% CI: 0.61, 0.89) and any nonvertebral fracture (4 trials; RR 0.80, 95% CI: 0.70, 0.91) for women taking oral vitamin D supplementation. However, there was no statistically significant reduction in the RR of hip fracture (1 trial; RR 0.76, 95% CI: 0.35, 1.67) or any nonvertebral fracture (1 trial; RR 0.70, 95% CI: 0.40, 1.20) for men taking oral vitamin D supplementation.

**Authors’ conclusions**

Oral vitamin D supplementation between 700 and 800 IU/day appears to reduce the risk of hip and nonvertebral fractures in ambulatory or institutionalised elderly people. However, a dose of 400 IU/day is insufficient for fracture prevention.

**CRD commentary**

The review question was clear in terms of the study design, participants, intervention and outcomes of interest. Three relevant electronic databases were searched without language restrictions, thus reducing the potential for language bias. Unpublished data were sought, but these were only included in a sensitivity analysis. The authors reported that there was no evidence of publication bias when using the Begg and Egger test or trim-and-fill analysis. The data extraction was carried out in duplicate, thus reducing the potential for errors and reviewer bias. However, the study selection and quality assessment procedures were not reported, and so cannot be assessed. The quality of the included studies was assessed using appropriate criteria.

Adequate details of the included studies were presented. The authors assessed and investigated sources of heterogeneity, and the methods used to combine the studies were appropriate. This was a well-conducted systematic review and, although the authors’ conclusion that dietary supplements reduce fractures is likely to be reliable, it should be noted that all but one of the higher dose vitamin D trials also administered calcium; therefore, the independent effect of vitamin D could not be determined.

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

Practice: The authors stated that their results are compelling for general vitamin D supplementation in the range of 700 to 800 IU/day in elderly people, and for increasing the suggested dose in the current vitamin D intake recommendations (currently 400 to 600 IU/day) for middle-aged and older adults.

Research: The authors stated that future research should focus on testing higher doses of vitamin D and assessing whether, and in what dose, calcium is adding value to the efficacy of vitamin D.

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**Other publications of related interest**
This additional published commentary may also be of interest. Bogaisky M, Leipzig RM. Review: 700 to 800 IU/d of vitamin D reduces hip and nonvertebral fractures in older persons. ACP J Club 2005;143:72-4.

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