Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials

CRD summary
This well-conducted review found that high-dose (at least 400 IU/day) vitamin D supplementation reduced fractures in people aged 65 or older but lower doses were not effective. The authors' conclusions follow from the high quality evidence presented and are likely to be reliable.

Authors' objectives
To determine the efficacy of oral vitamin D supplementation for preventing fractures in people aged 65 years or older.

Searching
The authors searched MEDLINE and the Cochrane Central Register of Controlled Trials from 1960 to August 2008, and EMBASE from 1991 to August 2008. Search terms were reported. No language restrictions were imposed. Additional studies were identified by screening reference lists and abstracts presented at the American Society for Bone and Mineral Research (1995-2007), and by contact with experts in the field.

Study selection
Randomised controlled trials (RCTs) with a minimum follow-up of one year that compared oral vitamin D (cholecalciferol or ergocalciferol) supplementation (with or without calcium) with placebo or calcium alone were eligible for the review. Mean age of study participants was required to be 65 years or more. To be included in the main analysis, trials had to have a double-blind study design and report treatment adherence and how fractures were ascertained. Trials with an open design were included in sensitivity analyses.

The primary review outcome was the relative risk (RR) of nonvertebral or hip fracture.

Mean age of participants in included trials was 78 years; 89% were women. Treatment duration ranged from 12 to 84 months. Participants included people living in the community and residents of nursing homes and other sheltered accommodation. Vitamin D and calcium regimens varied between studies.

The authors did not state how the studies were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity beyond the requirement for a double-blind trial design for inclusion in the main analysis.

Data extraction
Data on numbers of participants and events in each group were extracted to calculate the relative risk (RR) of fracture. Data on vitamin D dose and adherence were used to calculate the received dose of supplemental vitamin D (the product of dose and percentage adherence).

Three reviewers independently extracted data for the review.

Methods of synthesis
Trials were pooled by meta-analysis using random-effects models. Pooled relative risks, with confidence intervals (CIs), and numbers needed to treat were calculated. Heterogeneity was assessed using the Q-statistic (p < 0.1 being considered significant). Heterogeneity in received dose and achieved 25-hydroxyvitamin D level was explored visually and using random-effects meta-regression analysis. Predefined subgroup analyses were performed by age, type of dwelling and additional calcium supplementation. Publication bias was assessed using funnel plots.
Results of the review
Twelve double-blind RCTs (n=42,279) were included in the main analysis; an additional four open trials (n=14,180) were included in sensitivity analyses.

In the primary analysis, vitamin D supplementation significantly reduced nonvertebral fractures (RR 0.86, 95% confidence interval CI 0.77, 0.96, 12 RCTs) but not hip fractures (RR 0.91, 95% CI 0.78, 1.05; eight RCTs; n=40,886). Heterogeneity was significant for both outcomes.

In trials with a received dose of 400 IU/day or more (range 482-770 IU/day), vitamin D supplementation significantly reduced both types of fracture without significant heterogeneity; for nonvertebral fracture relative risk 0.80 (95% CI: 0.72, 0.89, 9 RCTs, n=33,265), and for hip fracture relative risk 0.82 (95% CI 0.69, 0.97; five RCTs, n=31,872). Lower doses did not significantly reduce fractures. The higher dose significantly reduced nonvertebral fractures in people living in the community and in institutions and the effect was independent of calcium supplementation.

Other analyses were reported. Inspection of the Begg funnel plot suggested possible publication bias but this was not confirmed by trim-and-fill analysis.

Authors’ conclusions
Nonvertebral fracture prevention with vitamin D was dose dependent and higher doses (482-770 IU/day) should reduce fractures in individuals aged 65 years or older by at least 20%.

CRD commentary
Inclusion criteria were clear. The authors searched a number of databases without language restrictions and made some attempt to locate unpublished studies. Risk of publication bias was assessed.

Validity was not assessed, but some quality features were used as inclusion criteria for the main analysis. Relevant details of included trials were presented. Appropriate methods were used to minimise errors and bias in data extraction, although it was unclear whether similar methods were used in study selection. Trials were pooled by meta-analysis; sources of heterogeneity were extensively analysed.

The authors’ conclusions follow from the evidence presented and are likely to be reliable for the population included in the trials (mainly elderly women).

Implications of the review for practice and research
Practice: The authors stated that low-dose vitamin D should not be used for fracture prevention in older people.

Research: The authors stated that the effects of higher doses of vitamin D, earlier initiation of treatment and longer duration of treatment should be explored in future research.

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