Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials

CRD summary
This review concluded that supplemental vitamin D at doses between 700 and 1000 IU per day reduced the risk of falling among older individuals by 19%. This primary conclusion is probably reliable despite the poor reporting of some aspects of the review. However, concerns with the appropriateness of the synthesis make other conclusions less reliable.

Authors’ objectives
To assess the efficacy of supplemental vitamin D and active forms of vitamin D with or without calcium for the prevention of falls among older individuals.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials, BIOSIS Previews and EMBASE were searched without language restrictions. Dates ranged from 1960 up to August 2008. Abstracts presented at the American Society for Bone and Mineral Research were searched from 1995 to 2008. References of identified studies were checked and experts were contacted. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of a defined oral dose of supplemental vitamin D (vitamin D₃ or vitamin D₂) or oral active vitamin D (1α-hydroxyvitamin D₃ or 1,25-dihydroxyvitamin D₃) for fall prevention in individuals aged 65 years or older were eligible for inclusion. Trials were required to have a minimum of three months follow up and to define and assess fall incidence as a primary or secondary endpoint over the entire trial period. Studies that focused on patients with Parkinson’s disease, organ transplant recipients or patients with stroke were excluded from the review. Also excluded were studies that employed intramuscular injection of vitamin D. Studies in which patients were recruited during acute inpatient care were included in the review, but excluded from the primary analysis.

Included studies used a range of doses and types of vitamin D supplementation with or without supplemental calcium. Most (81%) participants in studies that were included in the primary analysis were women, all were in stable health and with an average age of approximately 80 years. Participants lived either in the community or in nursing homes. Serum levels of 25-hydroxyvitamin D₃ were assessed using competitive protein binding assays or radioimmunoassays, where reported.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The criteria of randomisation, allocation concealment, blinding, adherence and withdrawals were assessed. Only RCTs that were double-blinded were eligible for inclusion in the primary analysis. The authors did not state how many reviewers performed the assessment.

Data extraction
Two reviewers independently extracted intention-to-treat data to permit the calculation of relative risks with 95% confidence intervals (CI). Authors were contacted for additional data where necessary.

Methods of synthesis
Double-blind RCTs were combined in a random-effects model meta-analysis to calculate pooled relative risks with 95% CI. Risk differences and numbers needed to treat (NNT) were calculated where significant differences were detected. Statistical heterogeneity was assessed using the Q statistic. Where significant statistical heterogeneity was detected, visual inspection and random-effect meta-regression analysis were used to assess the impact of dose of vitamin D and...
concentration of serum 25-hydroxyvitamin D₃. Subgroup analyses based on the type of vitamin D (D2 or D3), gender, age (less than 80 years or 80-plus years), duration (less than 12 months versus at least 12 months), level of independence (institutionalised or not) and additional calcium supplementation. A sensitivity analysis that included trials which were not double-blind was conducted. The ratio of effect sizes for supplemental vitamin D and active forms of vitamin D was calculated. Publication bias was assessed using Begg's test and Egger's test.

Results of the review
Fifteen RCTs were included in the review (n=17,786), of which eight double-blind RCTs were included in the primary analysis (n=2,426). Adherence ranged between 68% and 100%; seven of eight trials reported rates above 80%.

The overall pooled relative risk (RR) for vitamin D's effect on fall prevention was statistically significant at 0.87 (95% CI: 0.77 to 0.99; eight RCTs). But, statistically significant heterogeneity was detected (Q test, p = 0.05). Stratification of trials by dose of vitamin D (200 to 600 IU versus 700 to 1000 IU) resolved the heterogeneity.

There was a statistically significant benefit in trials that used higher doses of vitamin D (RR 0.81, 95% CI: 0.71 to 0.92; seven RCTs; NNT 11, 95% CI: 7 to 20), but no such effect was found in trials that used lower doses. A statistically significant benefit was found for active forms of vitamin D (RR 0.78, 95% CI: 0.64 to 0.94; two RCTs, n=624).

The ratio of the two effect sizes (high dose supplemental vitamin D: active forms of vitamin D) was 1.04 (95% CI: 0.84 to 1.31). There was a statistically significant benefit in trials in which serum 25-hydroxyvitamin D₃ levels above 60 nmol/L were achieved (RR 0.77, 95% CI: 0.65 to 0.90); there was no statistically significant benefit in trials that achieved concentrations below this level.

There were no other statistically significant results of subgroup analyses. A sensitivity analysis that included seven trials which did not meet the criteria for inclusion in the primary analysis found a non-significant benefit in fall reduction; adding these seven to the analysis of high-dose trials gave a statistically significant result (RR 0.92, 95% CI: 0.85 to 0.99) with highly significant statistical heterogeneity (p=0.006).

There was no consistent evidence of publication bias.

Authors' conclusions
Supplemental vitamin D at doses between 700 and 1000 IU per day reduced the risk of falling among older individuals by 19%, a similar impact to active forms of vitamin D. Doses of vitamin D under 700 IU per day, or those that result in serum 25-hydroxyvitamin concentrations under 60 nmol/L may not reduce the risk of falling among older individuals.

CRD commentary
The review question and inclusion criteria were clear. The authors searched relevant databases and other sources and made some attempts to identify unpublished studies. The authors reported using methods designed to reduce reviewer bias and error in the extraction of data, but not in the selection of studies and in the assessment of validity. The validity assessment used appropriate criteria but was not fully reported or used to inform the synthesis beyond the use of double-blinding as a criterion for inclusion in the primary analysis. The decision to use meta-analysis appeared appropriate. Subgroup and sensitivity analyses were specified prospectively. The analysis of high-dose studies on which the main conclusion rested was conducted appropriately. However, the analysis of low-dose studies treated three arms of one study as independent trials, which was inappropriate as it ignored the high degree of correlation that would exist between them. Despite this concern and the poor reporting of some aspects of the review, the overall conclusion is probably reliable.

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

Research: The authors stated that the benefits of doses of vitamin D above 1000 IU per day should be investigated.

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