Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men (Review)

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[Intervention Review]

Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men

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Editorial group: Cochrane Bone, Joint and Muscle Trauma Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 4, 2014.
Review content assessed as up-to-date: 1 June 2013.

Citation: Avenell A, Mak JCS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD000227. DOI: 10.1002/14651858.CD000227.pub4.

ABSTRACT

Background

Vitamin D and related compounds have been used to prevent osteoporotic fractures in older people. This is the third update of a Cochrane review first published in 1996.

Objectives

To determine the effects of vitamin D or related compounds, with or without calcium, for preventing fractures in post-menopausal women and older men.

Search methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (to December 2012), the Cochrane Central Register of Controlled Trials (2012, Issue 12), MEDLINE (1966 to November Week 3 2012), EMBASE (1980 to 2012 Week 50), CINAHL (1982 to December 2012), BIOSIS (1985 to 3 January 2013), Current Controlled Trials (December 2012) and reference lists of articles.

Selection criteria

Randomised or quasi-randomised trials that compared vitamin D or related compounds, alone or with calcium, against placebo, no intervention or calcium alone, and that reported fracture outcomes in older people. The primary outcome was hip fracture.

Data collection and analysis

Two authors independently assessed trial risk of selection bias and aspects of methodological quality, and extracted data. Data were pooled, where possible, using the fixed-effect model, or the random-effects model when heterogeneity between studies appeared substantial.

Main results

We included 53 trials with a total of 91,791 participants. Thirty-one trials, with sample sizes ranging from 70 to 36,282 participants, examined vitamin D (including 25-hydroxy vitamin D) with or without calcium in the prevention of fractures in community, nursing home or hospital inpatient populations. Twelve of these 31 trials had participants with a mean or median age of 80 years or over.

Another group of 22 smaller trials examined calcitriol or alfacalcidol (1-alphahydroxyvitamin D3), mostly with participants who had established osteoporosis. These trials were carried out in the setting of institutional referral clinics or hospitals.

In the assessment of risk of bias for random sequence generation, 21 trials (40%) were deemed to be at low risk, 28 trials (53%) at unclear risk and four trials at high risk (8%). For allocation concealment, 22 trials were at low risk (42%), 29 trials were at unclear risk (55%) and two trials were at high risk (4%).

There is high quality evidence that vitamin D alone, in the formats and doses tested, is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; risk ratio (RR) 1.12, 95% confidence intervals (CI) 0.98 to 1.29) or any new fracture (15 trials, 28,271 participants; RR 1.03, 95% CI 0.96 to 1.11).

There is high quality evidence that vitamin D plus calcium results in a small reduction in hip fracture risk (nine trials, 49,853 participants; RR 0.84, 95% confidence interval (CI) 0.74 to 0.96; P value 0.01). In low-risk populations (residents in the community: with an estimated eight hip fractures per 1000 per year), this equates to one fewer hip fracture per 1000 older adults per year (95% CI 0 to 2). In high risk populations (residents in institutions: with an estimated 54 hip fractures per 1000 per year), this equates to nine fewer hip fractures per 1000 older adults per year (95% CI 2 to 14).

There is high quality evidence that vitamin D plus calcium is associated with a statistically significant reduction in incidence of new non-vertebral fractures. However, there is only moderate quality evidence of an absence of a statistically significant preventive effect on clinical vertebral fractures. There is high quality evidence that vitamin D plus calcium reduces the risk of any type of fracture (10 trials, 49,976 participants; RR 0.95, 95% CI 0.90 to 0.99).

In terms of the results for adverse effects: mortality was not adversely affected by either vitamin D or vitamin D plus calcium supplementation (29 trials, 71,032 participants, RR 0.97, 95% CI 0.93 to 1.01). Hypercalcaemia, which was usually mild (2.6 to 2.8 mmol/L), was more common in people receiving vitamin D or an analogue, with or without calcium (21 trials, 17,124 participants, RR 2.28, 95% CI 1.57 to 3.31), especially for calcitriol (four trials, 988 participants, RR 4.41, 95% CI 2.14 to 9.09), than in people receiving placebo or control. There was also a small increased risk of gastrointestinal symptoms (15 trials, 47,761 participants, RR 1.04, 95% CI 1.00 to 1.08), especially for calcium plus vitamin D (four trials, 40,524 participants, RR 1.05, 95% CI 1.01 to 1.09), and a significant increase in renal disease (11 trials, 46,548 participants, RR 1.16, 95% CI 1.02 to 1.33). Other systematic reviews have found an increased association of myocardial infarction with supplemental calcium; and evidence of increased myocardial infarction and stroke, but decreased cancer, with supplemental calcium plus vitamin D, without an overall effect on mortality.

Authors' conclusions

Vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people. Supplements of vitamin D and calcium may prevent hip or any type of fracture. There was a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium. This review found that there was no increased risk of death from taking calcium and vitamin D.

PLAIN LANGUAGE SUMMARY

Vitamin D and related vitamin D compounds for preventing fractures resulting from osteoporosis in older people

Why do older people suffer bone fractures?

Hip fractures and several other types of fractures are very common in post-menopausal women and older men due to age-related weakening of their bones (osteoporosis).

What is the impact of bone fractures in older people?

Fractures due to osteoporosis often occur in the hip, wrist or spine and can lead to considerable disability or even death. Those who survive often have reduced mobility and may require greater social and nursing care.

Why might vitamin D help?

Vitamin D is necessary for building strong bone. Older people often have low vitamin D levels because of lack of exposure to sunlight and low consumption of vitamin D in their diet. Therefore, it has been suggested that taking additional vitamin D in the form of supplements may help to reduce the risk of fractures of the hip and other bones.

Purpose of this review

To investigate the effects of vitamin D or vitamin D-related supplements, taken with or without calcium supplements, for preventing fractures in post-menopausal women and older men.

Conduct of this review

The review authors searched the medical literature up to December 2012, and identified 53 relevant medical trials, with a total of 91,791 people taking part. The trials reported fracture outcomes in postmenopausal women or men aged over 65 years from community, hospital and nursing-home settings. These trials compared vitamin D or related supplements with - or without - calcium supplements, against fake supplements (placebo), no supplement or calcium supplements alone.

Findings of this review

The review found reliable evidence that taking vitamin D only, in the forms tested in the trials, is unlikely to prevent fractures. However, reliable evidence showed that vitamin D taken with additional calcium supplements slightly reduces the likelihood of hip fractures and other types of fracture. The review found that there was no increased risk of death from taking vitamin D and calcium.

Although the risk of harmful effects (such as gastrointestinal (stomach) symptoms and kidney disease) from taking vitamin D and calcium is small, some people, particularly with kidney stones, kidney disease, high blood calcium levels, gastrointestinal disease or who are at risk of heart disease should seek medical advice before taking these supplements.