

# Review: Vitamin D plus calcium, but not vitamin D alone, prevents osteoporotic fractures in older persons

Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev.* 2005;(3):CD000227.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆☆☆ Endocrinology ★★★★★☆☆☆ Geriatrics ★★★★★☆☆☆

**QUESTION**

In older persons, does supplementation with vitamin D or a vitamin D analogue, alone or in combination with calcium, reduce the incidence of fractures?

**METHODS**

**Data sources:** 10 databases, lists of conference abstracts, bibliographies of relevant studies, and contact with researchers in the field.

**Study selection and assessment:** Randomized and quasi-randomized controlled trials (RCTs) that compared vitamin D or a vitamin D analogue (alone or in combination with calcium) with placebo, no intervention, or calcium alone in postmenopausal women or men > 65 years of age. Studies involving corticosteroid therapy were excluded.

**Outcomes:** New vertebral, hip, and other nonvertebral fractures and adverse events.

**MAIN RESULTS**

38 RCTs met the selection criteria. Vitamin D plus calcium prevented hip and nonvertebral fractures more than placebo or no treatment, but not more than calcium alone (Table). The benefit was greater in persons who lived in institutions (i.e., frail elderly). No difference in treatment effect was observed between persons with or without a history of osteoporotic fracture. Only a few trials, most with small sample size, assessed the efficacy of vitamin D analogues. Vitamin D or its analogues increased risk for hyper-

calcemia, especially the analogue calcitriol (relative risk 15, 95% CI 3 to 76, 3 trials). Risk for gastrointestinal events or renal disease was not increased.

**CONCLUSIONS**

In postmenopausal women and older men, vitamin D alone does not reduce risk for fracture more than placebo or no treatment. Vitamin D plus calcium reduces risk for hip and nonvertebral fractures more than placebo or no treatment, especially in older, frail per-

sons living in institutions; however, vitamin D plus calcium is not more effective than calcium alone.

*Sources of funding:* Australian Institute of Health and Welfare; Scottish Executive Health Department; Health Research Council of New Zealand; Medical Research Council UK.

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**Vitamin D, alone or in combination with calcium, vs placebo or no treatment (control) or calcium alone for prevention of osteoporotic fractures in older persons at 1 to 5 years\***

| Comparisons                          | Types of fracture | Number of trials (n) | Weighted event rates |         | RRI (95% CI)    | NNH (CI)        |
|--------------------------------------|-------------------|----------------------|----------------------|---------|-----------------|-----------------|
|                                      |                   |                      | Treatment            | Control |                 |                 |
| Vitamin D vs control                 | Hip               | 7 (18 668)           | 2.6%                 | 2.2%    | 17% (-2 to 41)  | Not significant |
|                                      | Any               | 8 (18 935)           | 9.0%                 | 8.9%    | 2% (-7 to 11)   | Not significant |
| Vitamin D + calcium vs control       | Hip               | 7 (10 376)           | 3.9%                 | 4.8%    | 19% (4 to 32)   | 110 (66 to 522) |
|                                      | Nonvertebral      | 7 (10 376)           | 10%                  | 12%     | 13% (3 to 22)   | 65 (39 to 280)  |
| Vitamin D + calcium vs calcium alone | Hip               | 3 (6866)             | 2.1%                 | 2.6%    | 19% (-10 to 40) | Not significant |
|                                      | Nonvertebral      | 4 (3061)             | 12%                  | 12%     | 4% (-16 to 21)  | Not significant |

\*Abbreviations defined in Glossary; weighted event rates, RRI, RRR, NNH, NNT, and CI calculated from data in article using a fixed-effects model.

**COMMENTARY**

It has long been known that calcium and vitamin D are important to bone, but it is uncertain whether vitamin D alone is enough. Interestingly, calcium or vitamin D is recommended in all guidelines, either alone, combined, or in addition to a bone-active drug.

Avenell and colleagues reviewed 38 trials assessing vitamin D and vitamin D analogues for prevention of fractures associated with postmenopausal osteoporosis. The main finding was that vitamin D alone showed no statistically significant reduction in hip fractures. A combination of vitamin D and calcium marginally reduced hip fractures by 19%. However, this effect seems to be mainly restricted to persons living in institutional care. Lack of compliance was a major issue in some of the studies, which may partially explain the negative findings. The risk for hypercalcemia was elevated with the use of the more potent vitamin D analogue calcitriol, but not with vitamin D or  $\alpha$ -calcidol.

The conclusion is that frail older persons confined to institutions may sustain fewer hip fractures and other nonvertebral fractures if given vitamin D with calcium supplements. The evidence strongly supports

calcium plus vitamin D for fracture prevention in nursing homes or long-term care, in agreement with the recent meta-analysis by Bischoff-Ferrari and colleagues (1), which concluded that an oral dose of vitamin D  $\geq$  700 IU/d is needed. The effect of vitamin D alone in fracture prevention is still unclear, and no evidence exists of an advantage of vitamin D analogues compared with vitamin D.

How should we interpret these data, since most guidelines recommend vitamin D and calcium? We should still advise our patients to take vitamin D and calcium, until the reasons for negative findings in recent studies have been explored. At least we know from the meta-analysis by Avenell and colleagues that the combination is valuable in institutionalized patients, perhaps because of vitamin D deficiency, an issue that requires more study.

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**Reference**

1. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. *JAMA.* 2005;293:2257-64.