



## Q/ Does vitamin D without calcium reduce fracture risk?

### EVIDENCE-BASED ANSWER

**A/** No. Supplemental vitamin D without calcium—in doses averaging as much as 800 IU per day—doesn't reduce the risk of hip, vertebral, or non-vertebral fractures in postmenopausal women and older men (strength of recommendation [SOR]: **A**, large, high-quality meta-analysis of randomized or quasi-randomized placebo-controlled trials).

The vitamin D analogs alfacalcidol and calcitriol also don't reduce hip or nonvertebral fractures (SOR: **A**, multiple randomized, controlled trials [RCTs]), although

alfacalcidol (but not calcitriol) does reduce vertebral fractures by 43% (SOR: **B**, one RCT and one quasi-randomized trial with potential for bias)

Vitamin D supplementation, with or without calcium, doesn't affect mortality. It does double the risk of mild hypercalcemia (about 2.7 mmol/L increase), raise the risk of renal calculi or mild renal insufficiency by 16%, and slightly increase (4%) gastrointestinal adverse effects (SOR: **A**, meta-analysis of RCTs or quasi-randomized trials).

### Evidence summary

A 2014 meta-analysis of 15 trials (quasi-random and RCT) with a total of 28,271 patients that compared the effect of vitamin D on fracture risk with placebo or no treatment, found no benefit for vitamin D supplementation (TABLE).<sup>1</sup> Patients lived in community and nursing home settings and ranged in age from 50 to 85 years; 24% to 100% were female.

Only 3 trials required patients to have had a previous fracture. Exclusions included: diseases affecting bone metabolism, cognitive impairment, drugs affecting bone metabolism (bisphosphonates, selective estrogen receptor modulators, and corticosteroids), renal failure, hypercalcemia, nephrolithiasis, and decreased mobility (recent stroke recovery and Parkinson's disease).

Formulations of vitamin D included cholecalciferol (D<sub>3</sub>) 400 to 2000 IU/d for 4 months to 5 years or 100,000 to 500,000 IU every 3 to 12 months for 1 to 5 years; calcifediol (25(OH) D<sub>3</sub>) 600 IU/d for 4 years; and ergocalciferol (D<sub>2</sub>) 400 IU/d for 2 years or 3000 to 300,000 IU every 3 to 12 months for 10 months to 3 years.

### Vitamin D analogs generally have no benefit either

The same meta-analysis compared vitamin D analogs to placebo or no treatment (8 trials, quasi-random and RCT, 1743 patients) on the risk of fracture, again finding no benefit in all but one case. Included patients were mostly by referral to tertiary or university hospitals and outpatient community settings.

Most of the studies included only a small number of patients (about 200), with the largest study having 740 patients. The age range was 50 to 77 years, and 50% to 100% were female. Most of the trials required patients to have osteoporosis or vitamin D deficiency with a previous vertebral deformity on imaging. Study exclusions included osteomalacia, malabsorption, hyperparathyroidism, active kidney stones, history of hypercalcemia, cancer, incurable disease, dementia, severe chronic illness (renal or liver failure), recent stroke or fracture, and drugs that affect bone metabolism.

Vitamin D analogs were given as alfacalcidol (1-alpha-hydroxyvitamin D<sub>3</sub>)

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TABLE

How vitamin D and vitamin D analog supplementation affects fracture risk compared with placebo or no treatment<sup>1</sup>

Supplement	Number of trials (total patients)	Outcome	Fracture RR	95% CI	Comments
Vitamin D	12 (22,930)	Nonvertebral fracture	1.05	0.96-1.14	Nonsignificant
	11 (27,693)	Hip fracture	1.12	0.98-1.29	Nonsignificant
	6 (11,396)	Vertebral fracture or deformity	1.03	0.76-1.39	Nonsignificant
	15 (28,271)	Any new fracture	1.03	0.96-1.11	Nonsignificant
Alfacalcidol	4 (658)	Nonvertebral fracture	0.70	0.22-2.18	Nonsignificant
	1 (132)	Hip fracture	0.33	0.01-8.04	Nonsignificant
	2 (872)	Vertebral fracture	0.57	0.49-0.65	Significant*
Calcitriol	1 (246)	Nonvertebral fracture	0.42	0.15-1.15	Nonsignificant
	1 (246)	Hip fracture	0.33	0.01-8.10	Nonsignificant
	3 (327)	New vertebral fracture or deformity	0.75	0.40-1.41	Nonsignificant

CI, confidence interval; RR, relative risk.

\*Result subject to bias.

0.5 mcg twice daily or 1 mcg/d for 36 weeks to 2 years or calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) 0.25 to 1 mcg once or twice daily for one to 3 years. Researchers found a significant reduction in vertebral (but not nonvertebral or hip) fractures with alfacalcidol, but the finding occurred in a single trial that was assessed by the authors of the meta-analysis as subject to bias.

**Supplementation doesn't affect mortality, but does have some side effects**

Patients taking vitamin D or an analog with or without calcium showed no difference in risk of death compared with patients taking placebo (29 trials, 71,032 patients; relative risk [RR]=0.97; 95% confidence interval [CI], 0.93-1.01).

Patients taking vitamin D or an analog were more likely than controls to have mild hypercalcemia, with an average increase of 2.7 mmol/L (21 trials, 17,124 patients;

RR=2.28; 95% CI, 1.57-3.31). Patients taking calcitriol had the highest risk (4 trials, 988 patients; RR=4.41; 95% CI, 2.14-9.09).

Gastrointestinal adverse effects (4% increase) and renal calculi or mild renal insufficiency (16% increase) were more common with vitamin D and analogs than placebo (GI adverse effects: 15 trials, 47,761 patients; RR=1.04; 95% CI, 1.00-1.08; renal calculi or mild renal insufficiency: 11 trials, 46,548 patients; RR=1.16; 95% CI, 1.02-1.33).

**Recommendations**

There are no guidelines recommending vitamin D supplementation without calcium to prevent fracture. JFP

**Reference**

1. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev*. 2014;4:CD000227.