Note: This is a three-article spread with a shared commentary. Please scroll down for the second and third articles.

Review: 700 to 800 IU/d of vitamin D reduces hip and nonvertebral fractures in older persons

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. **Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials.** JAMA. 2005;293:2257-64.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Geriatrics ★★★★★★☆ Rheumatology ★★★★★★☆

QUESTION

Does oral vitamin D supplementation prevent hip and any nonvertebral fractures in older persons?

METHODS

Data sources: MEDLINE and the Cochrane Controlled Trials Register (January 1960 to January 2005), EMBASE/Excerpta Medica (January 1991 to January 2005), experts in the field, reference lists of relevant studies, and abstracts presented at the American Society for Bone and Mineral Research (1995 to 2004).

Study selection and assessment: Blinded randomized controlled trials (RCTs) of oral vitamin D supplementation (cholecalciferol or ergocalciferol) alone or combined with calcium supplementation compared with placebo or calcium supplementation alone in participants ≥ 60 years of age, ≥ 1 fracture occurred in each trial, and follow-up was ≥ 1 year. Individual studies were assessed for randomization procedure, concealment, blinding, and withdrawals.

Outcomes: First hip or nonvertebral fracture.

MAIN RESULTS

7 RCTs (n = 9820, mean age 79 y, 68% women) met the selection criteria. 2 RCTs evaluated 400 IU/d of vitamin D, and 5 RCTs evaluated 700 to 800 IU/d. 4 RCTs included 500 to 1200 mg/d of calcium in the vitamin D intervention; in 2 RCTs the mean calcium intake was 450 to 742 mg/d, and 1 RCT recommended a calcium intake of 800 mg/d through dairy products. Treatment duration ranged from 12 to 60 months. When random effects were used, pooling 3 RCTs of vitamin D at higher doses showed reduced hip fracture, while pooling 2 RCTs using lower doses did not (Table). Pooling of 5 RCTs with high doses of vitamin D showed a reduction in any nonvertebral fracture, but not for 2 RCTs with low doses (Table).

CONCLUSIONS

Vitamin D at doses of 700 to 800 IU/d reduces hip and nonvertebral fractures in older persons. 400 IU/d of vitamin D does not reduce fractures.

Sources of funding: Medical Foundation (Charles H. Farnsworth Trust; U.S. Trust Company; Trustee and Charles A. King Trust; Fleet National Bank) and James Knox Memorial Foundation.

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Vitamin D supplementation alone or with calcium vs placebo or calcium alone (control) to prevent fracture in older persons at 12 to 60 months*

Outcomes	Vitamin D dose (IU/d)	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
			Vitamin D	Control		
Hip fracture	700 to 800	3 (5572)	6.0%	8.4%	26% (12 to 39)	46 (31 to 100)†
					RRI (CI)	NNH
	400	2 (3722)	4.2%	3.5%	14% (–13 to 49)	Not significant
					RRR (CI)	NNT (CI)
Any nonvertebral fracture	700 to 800	5 (6098)	11%	16%	25% (11 to 37)	24 (14 to 80)
					RRI (CI)	NNH
	400	2 (3722)	11%	10.6%	3% (–14 to 24)	Not significant

*Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a random-effects model.
†Calculated using relative risk and control event rate.

COMMENTARY

The review by Bischoff-Ferrari and colleagues, the study by Porthouse and colleagues, and the RECORD trial examined calcium and vitamin D supplementation for the prevention of fractures in older persons. The systematic review by Bischoff-Ferrari and colleagues found that high-dose vitamin D (700 to 800 IU/d) combined with calcium (500 to 1200 mg/d) reduced the risk for hip fractures by 26% (CI 12 to 39) and all nonvertebral fractures by 23% (CI 13 to 32). However, the RECORD and Porthouse studies (which were not included in the Bischoff-Ferrari review) reported no benefit of high-dose vitamin D and calcium for either secondary prevention of fractures or prevention of fractures in high-risk patients of whom over half had previous fractures. Could differences in patient populations, study power, or adherence to study drugs explain these seemingly discordant results?

The effect of vitamin D with or without calcium on fracture prevention may vary in different populations. Frail, elderly persons and nursing home patients are at greater risk for falls and fractures than community-dwelling elderly persons. This difference may in part be explained by vitamin D deficiency in persons who are often sunlight-deprived. Many of the patients in the Bischoff-Ferrari meta-analysis were nursing-home residents. A Cochrane review that included 4 recent studies (including the RECORD and Porthouse studies) found that vitamin D alone did not reduce fractures (1). However, when vitamin D was given in combination with calcium, reductions occurred in hip and nonvertebral fractures but not in vertebral fractures. Subgroup analysis suggested that this effect was restricted to elderly patients living in institutions, with a reduction in fractures of 13% (CI 5 to 28). In both the RECORD and Porthouse studies, patients were community-dwelling.

In the Porthouse and RECORD studies, power may not have been sufficient to show a clinically important difference, especially between the vitamin D plus calcium and placebo groups. The RECORD trial was designed to have 80% power to detect an absolute difference in fracture rates of 3% between treatment groups. The intervention

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Calcium and vitamin D supplementation did not reduce fractures in women ≥ 70 years of age

Porthouse J, Cockayne S, King C, et al. **Randomised controlled trial of calcium and suplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care.** BMJ. 2005;330:1003.

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

QUESTION

Do calcium and vitamin D reduce the risk for fracture in at-risk community-dwelling older women?

METHODS

Design: Randomized controlled trial.
Allocation: Concealed.*
Blinding: Unblinded.*
Follow-up period: Median 25 months.
Setting: Nurse-led clinics in England, UK.
Patients: 3454 women ≥ 70 years of age (mean age 77 y) with ≥ 1 risk factor for hip fracture (body weight < 58 kg, previous fracture, maternal history of hip fracture, smoking, and poor to fair health). Exclusion criteria were calcium supplementation > 500 mg/d, history of kidney or bladder stones, renal failure, hypercalcemia, cognitive impairment, or life expectancy < 6 months.
Intervention: Information leaflet alone (n = 1993) or 6-month supply of calcium, 1000 mg, and cholecalciferol (vitamin D), 800 IU daily, taken as 2 tablets (Calcichew D, Forte, Hampshire, UK); lifestyle advice on how to reduce fracture risk; and an information leaflet on prevention of falls and calcium and vitamin D intake (n = 1321).
Outcomes: Any fracture (excluding ribs, digits, face, and skull). Secondary outcomes were hip fracture, quality of life (12-item Short Form Health Survey), death, hospital admissions and doctor visits, falls, and fear of falling. The study had 80% power to detect a 34% reduction in fracture.
Patient follow-up: 140 patients were excluded directly after randomization. 3314 patients (96%) were included in the intention-to-treat analysis.

MAIN RESULTS

During follow-up, 149 fractures were reported. Calcium and vitamin D supplementation did not reduce fractures (Table). Groups did not differ for quality of life, death, hospital admissions and doctor visits, and falls. The adjusted odds ratio for falling was 0.99 (95% CI 0.8 to 1.20) at 6 months and 0.93 (CI 0.79 to 1.20) at 12 months.

CONCLUSION

Supplementation with calcium and vitamin D for 2 years did not reduce the risk for fracture in at-risk community-dwelling older women.

Sources of funding: Northern and Yorkshire NHS Research and Development; Healthy Ageing Programme; Shire; Nycomed.

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*See Glossary.

Calcium and vitamin D supplementation vs no supplementation in older women at risk for fracture at median 25 months†

Outcomes	Supplementation	No supplementation	RRR (CI)	NNT
Any fracture	4.4%	4.6%	3.8% (–32 to 30)	Not significant
Hip fracture	0.6%	0.9%	29% (–60 to 69)	Not significant

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

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groups were formed by collapsing the 2 groups that received the specific intervention (calcium or vitamin D), and the control groups were formed from the 2 groups that did not receive the intervention. The groups that received calcium with vitamin D only or placebo were smaller and had only about 62% power to detect a 3% difference in fracture rate between these 2 groups. Insufficient power was also an issue in the study by Porthouse and colleagues. The authors could not exclude a reduction in risk < 30% for fractures with vitamin D plus calcium. Meta-analyses in a Cochrane review (1) and the review by Bischoff-Ferrari and colleagues both found reductions in risk for fractures < 30%.

Adherence to therapy and consequent vitamin D levels may have varied in these trials, resulting in differences in biological effects. A meta-regression analysis in the review by Bischoff-Ferrari and colleagues showed a greater reduction in hip and nonvertebral fractures with higher serum levels of 25-hydroxyvitamin D. 2 hip fracture studies that were included in Bischoff-Ferrari (Decalyos II 2 and Decalyos I 3) reported exceptionally high rates of compliance with treatment and placebo (95% in Decalyos II and 83% in Decalyos I). In contrast, compliance rates were 60% in the RECORD trial and 56.6% in the study by Porthouse and colleagues. For a subset of patients in the RECORD and Decalyos I studies, baseline 25-hydroxyvitamin D levels were similar (15.2 ng/mL and 16 ng/mL, respectively). However, after 1 year of treatment, the mean 25-hydroxyvitamin D levels in the Decalyos I treatment group increased to 42 ng/mL (3), while levels in the RECORD study only increased to 24.8 ng/mL.

The review by Bischoff-Ferrari and colleagues and the Porthouse and RECORD studies suggest that calcium plus high-dose vitamin D is effective for the prevention of hip and nonvertebral fractures in older

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Vitamin D_3, calcium, or both did not prevent secondary fractures in older persons

The RECORD Trial Group. **Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial.** Lancet. 2005;365:1621–8.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Emergency Med ★★★☆☆☆☆ Geriatrics ★★★★★★★
Phys Med & Rehab ★★★★★★☆ Rheumatology ★★★★★☆☆

QUESTION

In older persons with a previous low-trauma fracture, how do vitamin D_3, calcium, or both compare for preventing secondary fractures?

METHODS

Design: Randomized placebo-controlled trial (Randomized Evaluation of Calcium Or Vitamin D [RECORD]).

Allocation: Concealed.*

Blinding: Blinded ({patients, clinicians, data collectors}†, and outcome assessors).*

Follow-up period: 24 to 62 months.

Setting: 21 hospitals in the United Kingdom.

Patients: 5292 patients ≥ 70 years of age (mean age 77 y, 85% women) who had a low-trauma, osteoporotic fracture (a fracture due to a fall from no more than standing height, or radiologist-confirmed vertebral fracture) in the previous 10 years. Exclusion criteria included bed or chair-bound before the fracture; cognitive impairment; cancer in the past 10 years that could metastasize to bone; fracture associated with preexisting local bone abnormality; hypercalcemia; renal stone in the past 10 years; life expectancy < 6 months; daily intake of > 200 IU vitamin D or > 500 mg calcium; intake in the previous 5 years of fluoride, bisphosphonates, calcitonin, tibolone, hormone replacement therapy, selective estrogen-receptor modulators, or any vitamin D_3 metabolite; and vitamin D_3 by injection in the past year.

Intervention: Vitamin D_3, 800 IU taken as 2 tablets with meals (n = 1343); calcium, 1000 mg given as a carbonate (n = 1311); vitamin D_3 plus calcium (COMBO) (n = 1306); or placebo (n = 1332). Groups were combined to allow comparisons between calcium and non–calcium-containing regimens (COMBO + calcium vs vitamin D_3 + placebo), vitamin D_3 and non–vitamin D_3-containing regimens (COMBO + vitamin D_3 vs calcium + placebo), or COMBO and placebo.

Outcomes: All new low-trauma fractures. Secondary outcomes were all new fractures, radiographically confirmed fractures, hip fractures, death, number of falls, and quality of life.

Patient follow-up: 90% (intention-to-treat analysis).

MAIN RESULTS

Of 698 patients (13%) who had a new low-trauma fracture, 183 (4%) had a hip fracture. New low-trauma fractures did not differ between calcium and non–calcium-containing regimens (Table). Results were similar between vitamin D_3 and non–vitamin D_3-containing regimens (Table). COMBO and placebo groups did not differ for new low-trauma fractures (Table). Secondary outcomes did not differ among any group comparisons.

CONCLUSION

In older persons with a previous low-trauma fracture, calcium, vitamin D_3, or both did not prevent secondary fractures.

Sources of funding: Chief Scientist Office, Scottish Executive Health Department; Medical Research Council; Shire Pharmaceuticals; Nycomed.

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*See Glossary.

†Information provided by author.

Calcium (Ca) and vitamin D_3 (VitD3) regimens to prevent new low-trauma fracture at 24 to 62 months‡

Comparisons	Event rates	RRR (95% CI)	NNT
Ca regimen (COMBO + Ca) vs no Ca regimen (VitD3 + placebo)	13% vs 14%	8% (–6 to 20)	Not significant
VitD3 regimen (COMBO + VitD3) vs no VitD3 regimen (Ca + placebo)	13% vs 13%	2% (–11 to 17)	Not significant
COMBO vs placebo	13% vs 13%	6% (–14 to 23)	Not significant

‡COMBO = VitD3 + Ca. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

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persons, particularly those in institutions. It is important to note that in the secondary prevention trials, which showed the effectiveness of bisphosphonates, calcium and vitamin D were given to all participants (4-6). For patients with a previous low-impact fracture, prevention should include a bisphosphonate in addition to calcium and vitamin D.

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