

VITAMIN D & CALCIUM

KEY POINTS

- The combination of vitamin D and calcium is minimally effective for non-vertebral fracture reduction.
 - one fewer hip fracture per 1000 older adults per year in low risk patients
 - nine fewer hip fractures per 1000 older adults in high risk patients (e.g. institutionalised, elderly, postmenopausal women).
- The combination of vitamin D and calcium is NOT effective for vertebral fracture reduction.
- The combination of vitamin D plus calcium reduces falls more effectively than vitamin D alone or placebo.
- Caution is advised with use of intermittent high doses of vitamin D, as doses of 60000iu per month seem to be associated with increased risk of falls.
- Vitamin D with calcium supplementation optimises the efficacy of other osteoporosis treatment strategies such as bisphosphonates, denosumab and raloxifene.
- There is debate about whether calcium supplementation increases the risk of myocardial infarction, if there is an effect, it is likely to be small.
- Currently, there is no evidence for the benefit of vitamin D supplementation alone for any health outcome.

CONTEXT

This guide considers the use of vitamin D and/or calcium supplementation for musculoskeletal health.

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients taking vitamin D (without calcium) to prevent fractures and/or falls should be considered for either the addition of calcium to their regimen, or cessation of the vitamin D if their fracture/falls risk is low.
- Patients taking vitamin D (without calcium) for indications other than fracture or falls risk reduction should be considered for cessation.
- Patients who are low falls risk (especially those that are immobile) are unlikely to obtain significant benefit in terms of falls risk or fracture risk from vitamin D and calcium supplementation and cessation should be considered.
- Postmenopausal patients taking calcium (without vitamin D) who have an adequate dietary intake of calcium should be considered for calcium cessation.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
<p>Main Benefits</p> <ul style="list-style-type: none"> ➢ Reduction in fractures and/or falls 	<p>Increased Benefit</p> <ul style="list-style-type: none"> ➢ Established osteoporosis receiving antiresorptive therapy ➢ Frail institutionalised elderly people with a high fracture risk with low dietary calcium intake and low serum vitamin D 	<p>Decreased Benefits</p> <ul style="list-style-type: none"> ➢ Low falls risk due to complete immobility ➢ Low falls risk due to independence ➢ Normal bone mineral density ➢ Adequate dietary calcium intake and adequate vitamin D levels ➢ Limited life expectancy due to comorbidities (dementia, heart failure, airways disease, malignancy)
<p>Main Harms</p> <ul style="list-style-type: none"> ➢ Increased falls, hypercalcaemia 	<p>Reduced Harms</p> <ul style="list-style-type: none"> ➢ Maintenance vs Treatment dose of PPI 	<p>Increased Harms</p> <ul style="list-style-type: none"> ➢ High intermittent doses of vitamin D (less frequent than monthly) ➢ Presence of primary hyperparathyroidism ➢ Presence of, or potential for, hypercalcaemia from malignancy

 BACKGROUND

VITAMIN D

Vitamin D is a hormone with numerous effects in the body. Of these, the facilitation of calcium absorption and maintenance of musculoskeletal health has been most studied. Plasma concentration of vitamin D (in the form of 25(OH) vitamin D) is considered a reliable biomarker of vitamin D. Vitamin D adequacy is considered a serum level of ≥ 50 nmol/L at the end of winter (the level may need to be 10–20 nmol/L higher at the end of summer, to allow for seasonal decrease).

Current recommended classification of vitamin D levels are:

- Mild vitamin D deficiency: 30–49 nmol/L
- Moderate vitamin D deficiency: 12.5–29 nmol/L
- Severe vitamin D deficiency: < 12.5 nmol/L

Determining whether optimal vitamin D concentrations are present can be established through several criteria. Low levels of vitamin D lead to an elevation in serum parathyroid hormone (PTH) and some authors establish the upper level of vitamin D as that required to suppress PTH (above 70nmol/L).¹ Other criteria include sufficient vitamin D to ensure adequate intestinal calcium absorption (above 11 nmol/L) or levels thought to be associated with fracture reduction (above 70 nmol/L).

Thus, in addition to the classifications listed above, some laboratories routinely report a classification of “vitamin D insufficiency” at 50-75nmol/L.

While severe vitamin D deficiency may cause hypocalcaemia, hypophosphatemia and Ricketts, there is debate about whether treatment of subclinical vitamin D deficiency impacts on health outcomes in otherwise healthy community-dwelling individuals.

CALCIUM

Older men and women are recommended to take 1300mg of calcium daily for bone health. Dietary intake provides the majority of this for most Australians. Each dietary calcium “serve” (~ 30g cheese or 250ml milk or yoghurt) is approximately 300mg of calcium. Estimating deficiency of calcium is difficult, as serum calcium does not reflect bone density.

 EFFICACY

A summary of the findings for the impact of vitamin D or vitamin D/Calcium supplementation on the frequency of falls, and the frequency of hip, vertebral or any fractures is shown in the table below.^{3,4}

	FALLS	ANY FRACTURE	VERTEBRAL FRACTURE	HIP FRACTURE
Calcium	Not studied	7 Studies 421/3376 (12.47%) vs 480/3411 (14.07%) Not significant	9 Studies 111/3235 (23.43%) vs 137/3282 (4.17%) Not significant	6 Studies 79/3334 (2.37%) vs 55/3369 (1.63%) Not significant
Vitamin D	37 Studies 7117/17488 (40.7%) vs 7022/16656 (42.2%) Not significant	36 Studies 1775/22601 (7.85%) vs 1759/22189 (7.93%) Not significant	6 Studies 82/5711 (1.44%) vs 80/5685 (1.41%) Not significant	11 Studies 405/13809 (2.93%) vs 362/13884 (2.61%) Not significant
Vitamin D plus Calcium	8 Studies 1858/6206 (29.9%) vs 1766/5673 (31.9%) ARR= 1.2% NNT= 82	10 Studies 2741/24771 (11.06%) vs 2889/25205 (11.46%) ARR= 0.4% NNT= 250	4 Studies 191/21103 (0.90%) vs 212/21082 (1.01%) Not significant	2 Studies (nursing home) 164/2023 (8.12%) vs 199/1830 (10.87%) ARR= 2.77% NNT= 36 7 Studies (community) 235/22686 (1.03%) vs 262/23314 (1.12%) ARR= 0.9% NNT= 108

Figure 1: Summary of impact of calcium, vitamin D and combined calcium/vitamin D supplementation on falls and fracture risk (all NNT annual)^{1,3,4}

FRACTURE RISK REDUCTION

Although calcium and vitamin D are essential for bone health, there is no evidence that supplementation of these is required in patients without patent deficiency.

The relative benefit of calcium, vitamin D or the combination in terms of fracture risk reduction is minimal, and the absolute benefit is greatest in patients with the highest fracture risk. The US preventative services task force recently reviewed 11 studies of supplementation of vitamin D, calcium or the combination in low fracture risk patients (community based) and found no impact on fracture risk.¹

Calcium without Vitamin D

The Auckland calcium study was a 5-year randomised controlled trial of 1g/day calcium citrate in 1,471 postmenopausal women. Calcium did not reduce total, vertebral or forearm fracture incidence, did not decrease hip fracture incidence even though it had some beneficial effects on bone mineral density (BMD).⁵ Other studies have failed to demonstrate consistent effects of calcium supplements alone for the primary prevention of fractures

in low risk patients.¹⁶ A systematic review of calcium intake (dietary or with supplements) showed slight overall benefit of calcium supplementation, but could not confirm the benefit from dietary calcium.¹ The small benefit shown for calcium was confounded by publication bias and the authors conclude that the evidence for calcium supplements preventing fractures is weak and inconsistent. There is debate about whether dietary calcium is an alternative to supplemental calcium and the possible benefits of increasing calcium from dietary sources. Two recent publications (a systematic review⁴ and a meta-analysis⁷) of calcium dietary intake and bone health concluded that increased dietary calcium intake is associated with a 1-2% increase in bone mineral density over 5 years, but this does not translate into any reduction in risk of fracture. This has been confirmed by a more recent systematic review and meta analysis.⁸

Vitamin D with/without Calcium

A recent Cochrane systematic review of vitamin D and vitamin D analogues for fracture prevention included 31 trials, with sample sizes ranging from 70 to 36,282 participants. The trials 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. Of these 31 trials, 12 had participants with a mean or median age of 80 years or over.⁹

The authors made two key conclusions. Firstly, **vitamin D alone did not change fracture risk.** "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).⁹

Secondly, the combination of vitamin D and calcium was **only effective for non-vertebral fracture reduction** (hip fractures as opposed to vertebral fractures) and the effect size was moderate. In low risk patients (residents in the community: with an estimated eight hip fractures per 1000 per year), the effect equated 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), the effect equated to nine fewer hip fractures per 1000 older adults per year (95% CI 2 to 14).⁹

Thus, Vitamin D supplementation (with adequate calcium intake or appropriate supplementation), may remain an option to reduce hip fracture risk in high risk patients with moderate or severe vitamin D deficiency (<30nmol/L).

REDUCTION OF FALLS

Calcium supplements alone have not been shown to decrease the rate of falls. Multiple randomised controlled studies of various vitamin D formulations and doses have been undertaken to assess the impact of vitamin D on fall frequency. A recent analysis of 12 studies showed that both vitamin D2 and vitamin D3 supplementation did not have an impact on frequency of falls.¹⁰

These authors also analysed eight studies of calcium combined with vitamin D and found a slight overall reduction in the number of falls from 31.1% in the control arms to 29.9% in the supplemental calcium/vitamin D arms (ARR 1.22%, NNT= 82).

In a recent editorial Cummings et al stated **"It is uncertain whether any dose of vitamin D supplementation reduces the risk of falls or fractures in community dwelling older adults."** He suggested that the use of vitamin D supplements should be limited to combination with calcium for patients dwelling in institutions.¹¹

OTHER INDICATIONS

Vitamin D has been studied extensively in relation to multiple health outcomes. In 2014, authors from Edinburgh sought to undertake an umbrella review of all systematic reviews, meta-analyses, observational studies and randomised trials undertaken with vitamin D. They found 107 systematic reviews, 74 meta-analyses of observational studies, and 87 meta-analyses of randomised trials.¹²

The outcomes covered a range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic and other diseases. Of these 137 outcomes, the authors identified only four with a probable association with vitamin D concentrations, being:

- Increased risk of low birth weight with low maternal vitamin D concentrations
- Supplementation of vitamin D is probably linked to a decrease in dental caries in children
- Low levels of vitamin D were associated with increased parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis.

Their major conclusion was "Despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable".¹²

In December 2017, a review of all available metaanalyses and trials of vitamin D published from 2013 to May 2017 was undertaken.¹³ They analysed 202 randomised trials and 32 meta-analyses and found no new evidence that supplementation had any effect on cardiovascular disease, adiposity, glucose metabolism, mood disorders, muscular function, tuberculosis, colorectal adenomas or maternal and perinatal conditions. A Cochrane review of vitamin D supplementation and mortality concluded that there was a small effect of vitamin D3 supplementation on overall mortality (11% vs 11.4 %; ARR 0.4%, NNT= 250).¹⁴

This information, taken together with the plethora of epidemiological and observational studies that link low vitamin D levels with increased risk of cancer and infectious diseases, autoimmune diseases and cardiovascular disease, supports the hypothesis that low vitamin D status may be a consequence of ill health rather than its cause.

 **ADVERSE EFFECTS**

CALCIUM

Cardiovascular Risk

Concern has been raised about the possibility of an increased incidence of myocardial infarction and stroke in patients taking supplemental calcium.^{15,16} Multiple meta-analyses and randomised trials have been published and these were recently summarised by Reid et al.¹⁶ They identified that the increased risk of myocardial infarction seemed to occur within a year of commencing treatment, whereas the increased risk of stroke took three to four years to become apparent. The magnitude of the elevated risk for myocardial infarction was ~30% and for stroke was ~20%. These relative increases translate to absolute increases of ~6 per 1000 patient years (NNH 166).

Not all systematic reviews, however, come to the same conclusion regarding risks of calcium. A review of 17 studies found no significant increase in incidence of myocardial infarction,¹⁷ and a meta-analysis published in 2015 concluded: “current evidence does not support the hypothesis that calcium supplementation with or without vitamin D increases coronary heart disease or all cause mortality risk in elderly women.”¹⁸

It should be noted that these analyses are all based on studies where the trial was not designed to assess cardiovascular outcomes. These meta-analyses represent post-hoc analyses of secondary or unplanned outcomes that could possibly be inadequately reported. Of importance, trials of vitamin D alone do not suggest any cardiovascular harm.

Other Adverse Effects of Calcium

Calcium supplementation may be associated with a range of other adverse effects. Up to 10% of patients report one or more of abdominal pain, anorexia, constipation, flatulence, hyperacidity, nausea, vomiting or xerostomia.

Occasional endocrine & metabolic effects (hypercalcemia and/or hypophosphatemia) have been reported.

VITAMIN D

Safety of vitamin D was assessed in a Cochrane review of 31 studies.⁹ They found no increase in mortality, but moderate increases in the following adverse events.

- Hypercalcaemia: 74/8526 (0.867%) vs 35/8598 (0.407%); RRI 2.28 [1.57, 3.31]; **ARI 0.46% (NNH=217)**
- Gastrointestinal adverse effects: 4023/24034(16.74%) vs 3833/23727 (16.15%); 1.04 [1.00, 1.08]; **ARI 0.58% (NNH=172)**
- Renal Calculi or renal insufficiency: 461/23244 (1.98%) vs 395/23304 (1.69%); RRI 1.16 [1.02, 1.33]; **ARI 0.29% (NNH=345)**

Caution with High Dose Intermittent Vitamin D Therapy

Various dose schedules for vitamin D are used and there has been some concern in the past regarding the use of very high dose vitamin D. An annual dose of 500,000 units of cholecalciiferol was associated with an increased risk of falls.¹⁹ More recently, a study of monthly doses of vitamin D of 60,000 units (equating 2,000 units daily) found that this dose resulted in more falls than a control group taking 24,000 units monthly (equating to 800 units daily).²⁰ After one year, the mean number of falls in the 60,000 unit group was 1.47, compared to the 24,000 unit group mean of 0.94.

A proposed mechanism relating to the rapidity of vitamin D level rise is suggested by Winzenberg et al.²¹ They found that hip flexion strength increased with a less than 100% rise in vitamin D levels, but decreased with a greater than 100% rise in vitamin D levels.²¹

 **FACTORS TO CONSIDER**

It remains unclear whether a moderately low vitamin D level alone is sufficient cause to undertake replacement and then supplementation of vitamin D. It seems clear that very low vitamin D is associated with significant bone metabolic changes and in such cases appropriate replacement and supplementation may be required.

IN FAVOUR OF DEPRESCRIBING

- ✓ Patients with a low risk of falls and/or fractures are unlikely to achieve a significant benefit in terms of reduction of fall/fracture frequency from vitamin D and calcium supplementation.

AGAINST DEPRESCRIBING

- ✘ Severe vitamin D deficiency may contribute to osteomalacia and calcium/vitamin D supplementation was a component of the majority of studies of osteoporosis treatment regimens (e.g. bisphosphonates, raloxifene, denosumab). If patients are receiving active osteoporosis treatment, then calcium and vitamin D supplementation is likely to be required.

 **DISCONTINUATION SYNDROMES**

None described

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was updated by Dr Peter Tenni and Dr David Dunbabin from a document developed in consultation with the Deprescribing Reference Group.

REFERENCES

1. Kahwati LC. et al Vitamin D, calcium or combined supplementation for the primary prevention of fractures in community-dwelling adults: Evidence report and systematic review for the US Preventative Services Task Force. JAMA 2018; 319(15): 1600-1612.
2. Osteoporosis Australia. Calcium Consumer guide 2017 available at [https://www.osteoporosis.org.au/sites/default/files/files/OA%20Calcium%20Ed4\(1\).pdf](https://www.osteoporosis.org.au/sites/default/files/files/OA%20Calcium%20Ed4(1).pdf) accessed 23rd Aug 2018.
3. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diab Endocrinol 2018; Nov; 6(11):847-858.
4. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ 2015; 351: H4183
5. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006 Sep;119(9):777-85.
6. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006 Apr 24;166(8):869-75.
7. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ 2015; 351: H4183.
8. Zhao JG et al. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: A systematic review and meta analysis. JAMA 2017; 318(24): 2466-2482.
9. Avenell A, Mak JCS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in postmenopausal women and older men. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD000227. DOI: 10.1002/14651858.CD000227.pub4.
10. Wu H, Pang Q. The effect of vitamin D and calcium supplementation on falls in older adults: A systematic review and meta-analysis. Der Othopade 2017; 9: 729-736.
11. Cummings SR, Keil DP, Black DM. Vitamin D supplementation and increased risk of falling. A cautionary tale of vitamin supplements retold. JAMA Intern Med. 2016 Feb;176(2):171-172.
12. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014 Apr 1; 348:g2035. doi: 10.1136/bmj.g2035.
13. Autier P et al. Effect of vitamin D supplementation on non-skeletal disorders: A systematic review of meta-analyses and randomised trials. Lancet Diab Endocrinol 2017; 5(12): 986-1004.
14. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 2014; :CD007470.
15. Boland M, et al. Calcium and cardiovascular risks Aust Prescr 2013;36:5-8
16. Ian R. Reid, Sarah M. Bristow, Mark J. Bolland. Cardiovascular Complications of Calcium Supplements. Journal of Cellular Biochemistry 116:494-501 (2015).
17. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med. 2010;152(5):315-23.
18. Joshua R Lewis et al. The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta Analysis of Randomized Controlled Trials. Journal of Bone and Mineral Research, Vol. 30, No. 1, January 2015, pp 165-175
19. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial [published correction appears in JAMA. 2010;303(23):2357]. JAMA. 2010;303(18):1815-1822.
20. Bischoff-Ferrari HA, Dawson-Hughes B, Orave JE, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline [published online January 4, 2016]. JAMA Intern Med. doi:10.1001/jamainternmed.2015.7148.
21. Winzenberg T, van der Mei I, Mason RS, Nowson C, Jones G. Vitamin D and the musculoskeletal health of older adults. Aust Fam Physician 2012;41(3):92-99.

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