A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

VITAMIN D AND CALCIUM

KEY POINTS

Whilst the combination of vitamin D and calcium is effective for non-vertebral fracture reduction, the absolute benefit is small.

- 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 (eg 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 may result in a small reduction in falls compared to vitamin D alone or placebo.

Caution is advised with use of high doses of vitamin D (≥ 2000units/day or equivalent) , as research raises safety signals regarding increased risk of falls and reduced BMD.

Vitamin D and/or calcium supplementation is likely to be required for many patients receiving osteoporosis therapies such as bisphosphonates, denosumab or raloxifene.

There is debate about whether calcium supplementation increases the risk of myocardial infarction and stroke. If there is an effect, it is likely to be small.

Currently, there is no unequivocal evidence for the benefit of vitamin D supplementation alone for any health outcome in the general population.

deprescribing
FOR BETTER HEALTH OUTCOMES

CONTEXT

This guide considers the use of vitamin D and/or calcium supplementation for musculoskeletal health In the absence of antiresorptive osteoporosis treatment.

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients taking vitamin D (without calcium) to prevent fractures or falls should be considered for either the addition of calcium to their regimen (if dietary intake is inadequate), 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
Main Benefits Reduction in fractures and/or falls	**Increased Benefit** • Established osteoporosis receiving antiresorptive therapy • Frail institutionalised elderly people with a high fracture risk with low dietary calcium intake and very low serum vitamin D	**Decreased Benefits** • 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)
Main Harms Increased falls, hypercalcaemia	**Reduced Harms** • Taking lower doses (<400IU) of vitamin D	**Increased Harms** • High intermittent doses of vitamin D (monthly or less frequently) • 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 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 boundary of vitamin D levels as that required to suppress PTH vitamin D levels (above 70nmol/L). Other criteria include sufficient vitamin D to ensure adequate intestinal calcium absorption (above 11 nmol/L) or levels 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.[1]

CALCIUM

Older men and women are recommended to consume 1300mg of calcium daily for bone health.[2] Dietary intake provides the majority of this for most Australians. Each dietary "serve" (~ 30g cheese or 250ml milk or yoghurt) is approximately 300mg of calcium. Estimating deficiency of calcium is difficult, as serum calcium levels do not reflect bone density.

EFFICACY

Multiple associations of low vitamin D levels with a range of health conditions have been published. However, when randomised controlled studies of vitamin D supplementation are considered, there appears to be no clear benefit in patients with moderate vitamin D deficiency.[3] It is likely that the many associations between vitamin D deficiency and adverse health outcomes are driven by confounding factors or reverse causality.

The majority of the interest in vitamin D has been in the area of bone health (osteoporosis and fractures) and falls (musculoskeletal health). The absolute benefit of any pharmacological preventative intervention is related to the underlying risk of the event being prevented, with those patients at highest risk of the event obtaining the highest absolute benefit. As such the underlying risk of the population included in vitamin D/Calcium studies is highly relevant (e.g. community dwelling vs institutionalised patients).

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 in randomised trials is shown in **Table 1**.[4,5]

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. There is a degree of discordance amongst systematic reviews and meta-analyses of supplementation and fracture risk. This is likely due to inclusion of different studies, different search periods and different eligibility criteria. Fundamentally, the small fracture risk reduction of vitamin D and/or calcium supplementation is likely driven by the inclusion of institutionalised patients in some of the reviews. No fracture risk reduction has been clearly demonstrated in studies evaluating community dwelling patients or those receiving vitamin D supplements without concurrent calcium supplements.

	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**	**9 Studies** 399/24709 (1.60%) vs 461/25144 (1.83%) **ARR= 0.23%** **NNT= 435**	**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= 0.09%** **NNT= 1080**

Table 1: Summary of impact of Calcium, Vitamin D and combined calcium/vitamin supplementation on falls and fracture risk (all NNT annual) (From Refs[1,3,4])

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.[6] A 2022 umbrella review of vitamin D supplementation and fractures found similar results.

Calcium Supplementation without vitamin D Supplementation

The Auckland calcium study was a 5-year randomised controlled trial of 1 g/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).[7]

Other studies have failed to demonstrate consistent effects of calcium supplements alone for the primary prevention of fractures in low risk patients.[1,8] 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. 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-analysis[9]) of dietary calcium intake and bone health concluded that increased dietary calcium 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 more recent systematic reviews and meta analyses.[1,10]

Vitamin D supplementation with and without Calcium

A 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.[11]

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).*

Secondly, the combination of vitamin D and calcium was only effective for non-vertebral fracture reduction 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; Annualised Number Needed to Treat= 1000.
- 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; Annualised Number Needed to Treat= 111).[11]

Vitamin D supplementation (with adequate intake of calcium from diet or supplementation), may remain an option to reduce fracture risk in patients at very high risk (over 5% per year) with severe vitamin D deficiency (<12.5nmol/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. An analysis of 12 studies showed that both vitamin D2 and vitamin D3 supplementation did not have an impact on frequency of falls.[12]

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 an 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.[13]

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.[14,15] Multiple meta-analyses and randomised trials have been published and these were recently summarised by Reid et al.[15] 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,[16] 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."*

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.

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.[10] 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 often 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 cholecalciferol was associated with an *increased* risk of falls.[18] A study of monthly doses of vitamin D of 60,000 units (equating 2,000 units daily)[19] found that this dose resulted in more falls than a control group taking 24,000 units monthly (equating to 800 units daily). 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.[20] 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.[20]

Furthermore, a Canadian randomised controlled trial compared daily vitamin D does of 400 units, 4000 units and 10000units finding that higher doses resulted in lower BMD and the authors concluded that their results do not support a benefit of high-dose supplementation for bone health.[21]

FACTORS TO CONSIDER

It remains unclear whether mild or moderate vitamin D deficiency (12.5-49nmol/L) alone is sufficient reason to undertake replacement and then supplementation of vitamin D. It seems clear that severe vitamin D deficiency (<12.5nmol/L) is associated with significant bone metabolic changes (confirmed by changes in PTH) and in such cases appropriate replacement and supplementation may be required.

FACTORS FAVOURING DEPRESCRIBING

- Patients with a low risk of falls are unlikely to achieve a significant benefit in terms of reduction of fall frequency from vitamin D and calcium supplementation.
- Patients with vitamin D levels that significantly exceed the threshold for deficiency. Such patients may remain above this threshold without supplementation or with lower dose supplementation.
- Patients with a dietary calcium intake that meets their needs based on age/gender.

FACTORS 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, denusomab).
- If patients are receiving active osteoporosis treatment, calcium and vitamin D supplementation is likely to be required, unless dietary calcium intake is adequate and vitamin D levels are known to be sufficient.

DISCONTINUATION SYNDROMES

None described.

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AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Dr Peter Tenni and reviewed by the Deprescribing Project Advisory Group, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania and Dr David Dunbabin, Geriatrician.

DEPRESCRIBING PROJECT ADVISORY GROUP

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