A GUIDE TO

deprescribing

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 reduces falls more effectively than either calcium alone or placebo.**
- **Patients taking calcium supplements (without vitamin D) are unlikely to obtain benefit for bone health unless dietary calcium intake is very low.**
- **There is debate about whether calcium supplementation increases the risk of myocardial infarction; if there is an effect it is likely to be small.**
- **Vitamin D and calcium supplementation optimises the efficacy of other osteoporosis prevention strategies such as bisphosphonates, denosumab and raloxifene.**
- **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 calcium supplementation.

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients who are low falls risk (especially those who 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.
- Patients taking vitamin D (without calcium) to prevent fractures 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.

EFFICACY

FRACTURE RISK REDUCTION

Calcium without Vitamin D

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).[1]

Other studies have failed to demonstrate the effects of calcium supplements alone for the prevention of fractures.[2]

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 review[3] and a meta-analysis[4]) 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.

As more than half of Australians have less than their recommended daily intake, Osteoporosis Australia makes the following recommendations to increase calcium intake:[5]

- Dairy foods contain a high level of calcium which is easily absorbed – include 3 serves per day in your normal diet eg: glass of milk (250 ml), tub of yoghurt (200 g), slice of cheese (40 g). Low fat options contain similar levels of calcium.
- Try canned salmon or sardines which contain bones rich in calcium
- Use yoghurt in soups or salads
- Add milk or skim milk powder to soups or casseroles
- Try soy based products and tofu that contain calcium
- Include broccoli, mustard cabbage, Bok Choy, silverbeet, cucumber, celery and chick peas in your regular diet
- Eat more almonds, dried figs and dried apricots
- Products fortified with calcium (e.g. some breakfast cereals) can help improve your calcium intake

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.[6]

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 (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).[6]

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

REDUCTION OF FALLS

An investigation of the benefit of vitamin D supplementation in relation to vitamin D serum levels has been undertaken.[7] These authors reviewed multiple observational and randomised controlled studies and collated the data for serum level of vitamin D and faller status. There was an association between hypovitaminosis D (regardless of the definition used) and being a faller. This association remained significant after adjustment for a number of potential confounders including age, gender, body mass index, comorbidities, polypharmacy, depression, cognitive decline, muscular strength and visual acuity.

A meta-analysis of 26 randomised controlled trials of vitamin D against a control showed that overall, vitamin D supplementation was associated with a reduction in the risk of falls (OR 0.86 [95% CI 0.77-0.96]).[8] As there was substantial heterogeneity between studies, subgroup analysis was performed. The results of the analyses are shown in Table 1. As can be seen, the benefit of vitamin D supplementation was only evident when the oral dose was above 800IU daily and when given in combination with calcium supplements. The majority of the studies reviewed included elderly women and the magnitude of the effects was of the order of a 15% reduction in risk of suffering at least one fall.[7,9]

The benefit of vitamin D (not surprisingly) seemed greater (see **Table 1**) in patients that had established vitamin D deficiency.

Two further randomised, placebo-controlled studies, completed after the meta-analysis, have confirmed that vitamin D (without supplemental calcium) at a dose of 800IU daily does not reduce the incidence of falls or injurious falls in postmenopausal women 75 years old or younger.[9,10]

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]

SUBGROUP	OR (95% CI)	NO. OF STUDIES	*P* (INTERACTION TEST)[b]
Population's dwelling			0.51
Community dwelling	0.80 (0.69–0.93)	16	
Institutionalized	0.87 (0.71–1.07)	10	
Administration route			0.16
Intramuscular	0.52 (0.27–1.01)	2	
Oral	0.85 (0.76–0.95)	24	
Vitamin D deficiency status			0.00
Not deficient	0.90 (0.81–0.99)	20	
Deficient	0.53 (0.39–0.72)	6	
Documented increase in serum 25(OH) D level			0.86
Yes	0.82 (0.70–0.96)	16	
No/NR	0.84 (0.72–0.98)	10	
Vitamin D2 vs. D3			0.58
D2	0.79 (0.65–0.97)	8	
D3	0.85 (0.74–0.97)	18	
Adherence >80%			0.52
Yes	0.81 (0.69–0.94)	13	
No	0.87 (0.75–0.99)	13	
Vitamin D dose[a]			0.28
High dose	0.82 (0.73–0.93)	18	
Low dose	1.0 (0.72–1.37)	8	
Calcium coadministration status			0.01[b]
Vitamin D + calcium *vs.* placebo	0.83 (0.72–0.93)	10	
Vitamin D *vs.* placebo	0.97 (0.84–1.11)	10	
Vitamin D + calcium *vs.* placebo	0.63 (0.50–0.81)	6	
Study Quality			0.62
High	0.82 (0.72–0.93)	19	
Low	0.87 (0.72–1.05)	7	

[a] High dose is defined as greater than 800IU/d
[b] Changing the definition of high dose to at least 800 IU/d changes *P* value for interaction test to 0.85 and 0.92, respectively.

Table 1: Effect of Vitamin D on risk of falls, subgroup analysis from Murad et al.[8]

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.

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".[6,7]

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.[12,13] Multiple meta-analyses and randomised trials have been published and these were recently summarised by Reid et al.[13] 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,[14] 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."[15]

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.[6] 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 cholecalciiferol was associated with an increased risk of falls.[16] 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).[17] 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.[18] 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.[18]

FACTORS TO CONSIDER

It remains unclear whether a 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 are unlikely to achieve a significant benefit in terms of reduction of fall 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, denusomab). If patients are receiving active osteoporosis treatment, then calcium and vitamin D supplementation is likely to be required.

DISCONTINUATION SYNDROMES

None described

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was written by Dr Peter Tenni and Dr David Dunbabin in consultation with the Deprescribing Clinical Reference Group.

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