



Vitamin D and calcium supplementation in primary care: an update

KEY PRACTICE POINTS

- Most people can achieve adequate levels of vitamin D through exposure to sunlight
- Vitamin D supplementation should be reserved for frail older people or those at risk of deficiency; routine supplementation for the general population is not recommended
- There is no evidence of vitamin D toxicity at doses recommended to treat mild deficiency, although this practice may increase the risk of renal tract stones
- Testing vitamin D levels is rarely beneficial for patients, is expensive and often unreliable; in most cases deficiency is likely to be a consequence of poor health rather than a cause
- Encourage an increase in dietary calcium before considering calcium supplementation, i.e. two to three serves of dairy products a day

In 2011, bpac^{nz} produced guidance on vitamin D supplementation for primary care. In the past five years vitamin D use has risen substantially and it is now the 12th most frequently prescribed medicine in New Zealand. Previously, prescribing vitamin D on the basis of deficiency risk was recommended, without testing. This is still broadly considered best practice, however, it is now more evident which groups of patients are likely to benefit from supplementation. Dietary calcium should be optimised in people taking vitamin D supplements, but routine supplementation with calcium is not recommended. Despite the growing number of studies reporting associations between vitamin D deficiency and non-skeletal diseases, there remains no convincing evidence of a causal link from meta-analyses or randomised controlled trials.

 For further information on vitamin D, see: www.bpac.org.nz/BPJ/2011/june/vitamin-d.aspx

Sunlight is the preferred source of vitamin D

People derive approximately 80% of their circulating vitamin D from the ultraviolet B (UV-B) rays in sunlight.¹ Most healthy people can achieve adequate vitamin D levels by spending time outdoors during the day. Skin needs to be exposed to direct sunlight to allow the synthesis of vitamin D to occur as glass blocks UV-B rays.

How much sunlight is enough?

To prevent vitamin D deficiency, a daily walk in the early morning or late afternoon from September to April in the Southern hemisphere with face, arms and hands exposed is recommended.¹ At the height of summer as little as six to eight minutes of sun exposure may be sufficient to produce 1000 IU of vitamin D.² From May to August outdoor activity is best scheduled around noon as approximately 30 – 50 minutes of sun exposure is required to produce the same amount of vitamin D.^{1,2} Dark skin pigmentation is correlated with decreased rates of vitamin D production and people with darker skin may require three to six times more sun exposure to achieve equivalent levels of vitamin D production.² It is not possible to develop vitamin D toxicity due to exposure to sunlight.¹

The use of sun beds to boost vitamin D levels is not recommended as this practice is associated with an increased risk of melanoma which rises with greater use and earlier age of first use.¹

Diet is a secondary source of vitamin D

Diet contributes approximately 5 – 10% of a person's vitamin D requirement.² Diet can be an important source of vitamin D during winter months or when sun exposure is reduced. Cod liver oil is the best dietary source of vitamin D while oily fish, e.g. salmon, tuna, eel and warehou, are rich whole food sources.¹ Milk, yoghurt and margarine fortified with vitamin D are now available in New Zealand.

Prescribing of vitamin D is increasing

As in 2011, guidance continues to recommend prescribing vitamin D supplements based on risk of deficiency (see below).¹ However, the number of people prescribed vitamin D each year is increasing (Figure 1) and it is questionable whether all of those prescribed supplements are at risk of long-term deficiency. Colecalciferol (vitamin D₃) is the predominant formulation prescribed; in 2015 it was the 12th most frequently prescribed medicine in New Zealand.⁴

Benefits versus risks of vitamin D supplementation

Severe vitamin D deficiency reduces bone mineralisation which causes osteomalacia and increases fracture risk. This can be prevented by empiric supplementation of people who are at risk. Since 2011, evidence has accumulated that only a limited number of patients benefit from supplementation with vitamin D.

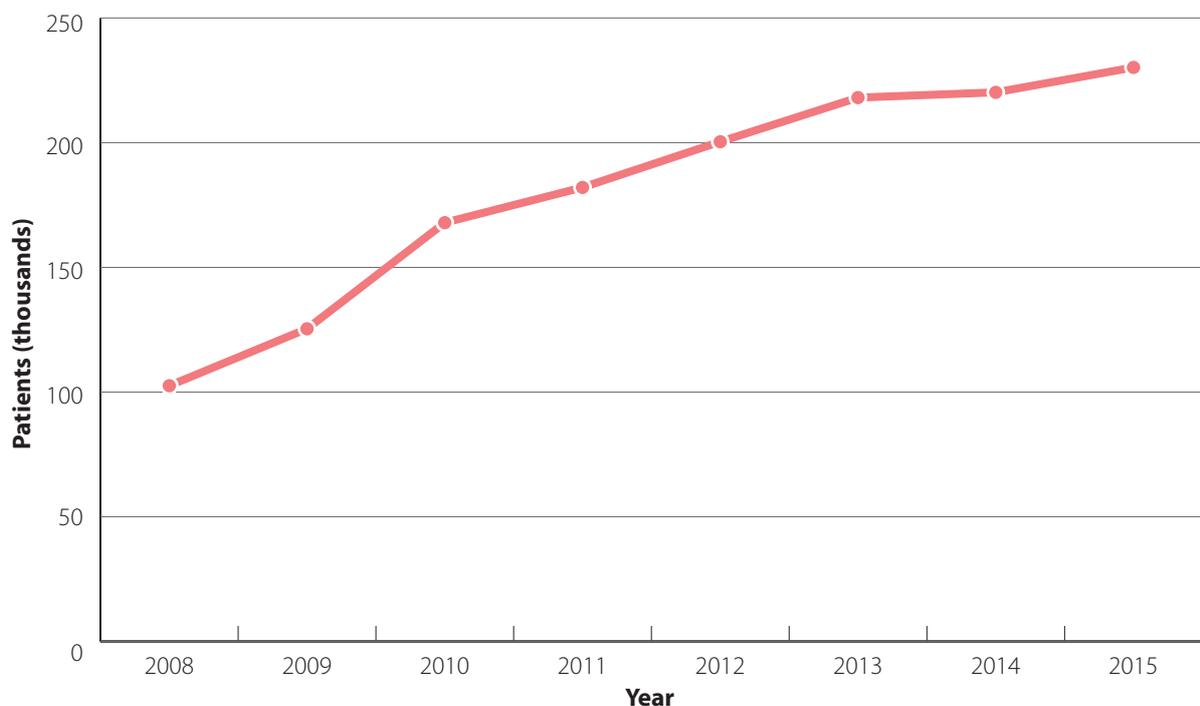


Figure 1: Number of patients dispensed subsidised vitamin D supplements in New Zealand (2008 – 2015).⁵

The benefits of supplementation on bone health and falls prevention have been overstated

More than 50 meta-analyses have examined the effects of vitamin D on falls or fractures.⁶ This research now confirms that vitamin D supplementation for the general population provides no benefit and is a waste of resources. Key findings from studies include:

- The United States Preventative Services Task Force concluded, in 2013, that daily supplementation with 400 IU (10 micrograms) of vitamin D₃ and 1000 mg of calcium has no effect on fracture incidence in post-menopausal women.⁷
- A meta-analysis involving more than 50 000 participants concluded that vitamin D taken without calcium has no effect on fracture incidence and that vitamin D taken in combination with calcium has weak and inconsistent effects on fracture risk; benefits were restricted to frail, older females living in institutions.⁸
- Analyses of randomised controlled trials involving almost 30 000 participants found that vitamin D with or without calcium has no effect on the risk of falls.⁸

Adverse effects associated with vitamin D supplementation have been reported

Vitamin D taken at recommended doses, i.e. 1.25 mg per month or 10 – 20 micrograms (400 – 800 IU) per day, is generally well tolerated and considered to be safe. There is no evidence of toxicity at doses of vitamin D₃ below 25 micrograms (1000 IU),

daily, however, hypercalcaemia and hyperphosphatemia can occur at substantially higher doses, e.g. 50 000 IU daily.¹⁰ Vitamin D supplementation in combination with calcium supplements is reported to increase the risk of renal tract stones.⁷

In a randomised controlled trial it was found that single high doses of colecalciferol, e.g. 12.5 mg (500 000 IU) given annually, were associated with an increased risk of falls and fractures in older women who were considered at high risk of fracture (see: "High and low levels of vitamin D can cause bone weakness").⁹

Inconclusive research has created confusion

In addition to preventing osteomalacia, there are a plethora of health claims associated with vitamin D supplementation. This has created confusion both for patients trying to make informed treatment decisions and for clinicians guiding their care.

Numerous studies have examined associations between vitamin D deficiency and a range of conditions including: cardiovascular disease, cancer, autoimmune and inflammatory diseases, neurodegeneration, cognitive impairment and mood disorders.¹⁰ Association does not equate to causation, however, and randomised controlled trials show that vitamin D supplementation has little or no effect on the non-skeletal illnesses studied; the meta-analyses reported also do not support the observational findings.¹¹ It is more likely that vitamin D deficiency is a marker of reduced health, rather than a cause of it.¹¹

High and low levels of vitamin D can cause bone weakness

Vitamin D is thought to affect bone mineralisation by regulating circulating calcium.¹² If levels of circulating calcium are low, this is rectified through the stimulation of osteoclasts which cause bone resorption via secondary hyperparathyroidism, thereby reducing bone mineralisation.¹² High levels of vitamin D can also cause bone weakness by stimulating osteoclasts directly.¹² These two mechanisms explain why high and low levels are both associated with bone weakness.



When to consider vitamin D supplementation

Vitamin D supplementation is only beneficial for people at risk of deficiency such as frail older people, those with dark skin and women who are veiled; supplementation of the general population is not recommended.¹ Vitamin D and calcium supplements are indicated for patients treated for osteoporosis if their dietary calcium intake is inadequate (see below).¹³

See: "Vitamin D supplementation during pregnancy and infancy" for guidance on prescribing vitamin D to women who are pregnant or breast feeding.

Risk factors for vitamin D deficiency

Groups considered to be at high risk of vitamin D deficiency and who may benefit from supplementation include people:¹

1. With very dark skin pigmentation
2. Who completely avoid the sun for medical reasons, e.g. they have had skin cancer or are using photosensitising medicines long-term
3. With reduced mobility who are frail or housebound and at risk of musculoskeletal pain and osteomalacia

People who completely cover their skin with clothing or veils will be at greater risk of vitamin D deficiency.¹ Living in southern regions means that transitory vitamin D deficiency is more likely to occur between the months of May and August.¹

The symptoms of vitamin D deficiency

In children, vitamin D deficiency is associated with delayed tooth eruption and rickets.¹⁴

In adults, severe vitamin D deficiency causes osteomalacia with symptoms of bone pain and muscle weakness.¹⁴

Physiological changes consistent with osteomalacia in adults who are vitamin D deficient include:¹⁴

- Elevated alkaline phosphatase levels; often the earliest finding
- Low calcium levels
- Elevated parathyroid hormone levels, i.e. secondary hyperparathyroidism
- Low phosphate levels

Vitamin D testing is only indicated if severe deficiency is suspected

Vitamin D supplementation can be initiated in people at risk of deficiency without the need for testing.¹ Testing of vitamin D levels is usually only indicated in patients with features of severe deficiency.¹ This includes patients who may have:^{15, 16}

- Metabolic bone disease or features such as unexplained fractures or bone pain

- Unexplained raised alkaline phosphatase, low calcium or phosphate levels
- Chronic kidney or liver disease
- Osteoporosis secondary to endocrine disorders, e.g. Cushing syndrome
- Malabsorption of dietary fat, due to conditions such as coeliac disease, previous intestinal surgery or gastric bypass

When vitamin D testing is requested serum 25-hydroxyvitamin D (vitamin D) is measured as it is a stable metabolite with a plasma half-life of three weeks.² The optimal serum vitamin D level is contentious: a serum level ≥ 50 nmol/L is generally considered to be sufficient to maintain adequate bone health,² and levels below 25 nmol/L are considered to be deficient.¹ Day-to-day variations in serum vitamin D are small (5%), although levels may decrease by as much as 20 nmol/L over winter compared to measurements taken during summer.² Where severe symptomatic vitamin D deficiency is suspected serum calcium, phosphate and alkaline phosphatase should also be tested.¹

There is limited clinical value in testing vitamin D levels in patients without symptoms of deficiency because the results of testing are difficult to interpret, as the optimum level of vitamin D is unknown and levels can vary substantially between seasons.

Prescribing vitamin D for those at risk of deficiency

Colecalciferol is the recommended form of vitamin D for patients at risk of deficiency,¹³ who are unlikely to meet sun exposure recommendations.¹

 Vitamin D undergoes hydroxylation in the kidney to its active form, therefore hydroxylated derivatives alfacalcidol or calcitriol should be prescribed for patients with renal failure.¹³

Contraindications for colecalciferol include patients with hypercalcaemia, hypervitaminosis, metastatic calcification, and renal osteodystrophy with uncontrolled hyperphosphatemia.¹³ The current subsidised brand of colecalciferol contains soya oil in the gel capsule and is contraindicated in patients with soy allergy.¹⁷ People with a history of peanut-induced anaphylaxis should also avoid this formulation as they may react to soya oil.

For mild to moderate vitamin D deficiency prescribe:¹³

- 1.25 mg (50 000 IU) colecalciferol, once a month

For moderate to severe vitamin D deficiency prescribe an initial loading dose of one capsule daily for up to ten days. Vitamin

Vitamin D supplementation during pregnancy and infancy

During pregnancy the same risk factors for vitamin D deficiency and recommendations for sun exposure apply as for the general population.

In general, testing vitamin D levels is not recommended in either asymptomatic women who are pregnant or infants.¹⁵ Supplements should be prescribed based on the risk of vitamin D deficiency.¹⁵

The same colecalciferol regimen subsidised for adults who are at risk of vitamin D deficiency, i.e. colecalciferol, 1.25 mg, monthly, may be beneficial for women who are pregnant and vitamin D deficient, or at high risk of deficiency; this is not recommended for all women who are pregnant due to a lack of safety data.¹⁵ Women who are pregnant who are at a lower risk of vitamin D deficiency may benefit from lower daily dosing, i.e. 10 micrograms per day of vitamin D, especially during the third trimester.¹⁵ There is no 10 microgram vitamin D supplement subsidised in New Zealand but this quantity of vitamin D is included in ante-natal multivitamin tablets that can be purchased over-the-counter.

Supplementation during infancy

Infants who are exclusively breastfed or who receive less than 500 mL of milk formula per day may benefit from vitamin D supplementation if they also have one or more

of the following risk factors:¹⁵

- Dark skin
- A mother who is vitamin D deficient or is at increased risk of becoming deficient
- A sibling diagnosed with rickets or hypocalcaemic seizures
- Being born preterm with a body weight less than 2.5 kg (see NZFC: www.nzfchildren.org.nz/nzf_5385)

Vitadol C, containing vitamins A, D and C is the recommended supplement in New Zealand for infants.¹⁵ This can be given as ten drops (0.3 mL, approximately 10 micrograms of colecalciferol) once per day.¹⁵ Due to the high vitamin A concentration in Vitadol C this formulation is not appropriate for infants who are not deficient.¹⁵ It is reasonable to wait until breastfeeding is well established in full-term babies before introducing vitamin D supplementation, e.g. at six weeks of age (See NZFC: www.nzfchildren.org.nz/nzf_70283).¹⁵

 Further information on vitamin supplementation during pregnancy or infancy is available from: www.health.govt.nz/system/files/documents/publications/companion-statement-vit-d-sun-exposure-pregnancy-infancy-v3.pdf

D taken at these doses is associated with few adverse effects, however, it may raise concentrations of calcium and phosphate in the plasma and urine,¹³ and increase the risk of renal tract stones and arterial deposits.

Patients with vitamin D deficiency due to malabsorption or liver disease often require higher maintenance doses and consultation with an endocrinologist is recommended.¹³ Hypervitaminosis D from excessive supplementation has non-specific symptoms resulting from hypercalcaemia, including: dehydration, vomiting, decreased appetite, irritability, constipation, fatigue and muscle weakness.¹

Optimising calcium intake

Increasing dietary calcium is preferred over oral calcium supplementation for patients prescribed vitamin D supplements; both are associated with increases in bone mineral density of 1 – 2%,¹⁸ although calcium supplementation is associated with some adverse effects (see below). It should be noted, however, that modest changes in bone mineral density of this magnitude are unlikely to result in a reduced fracture risk for most patients.¹⁸

Dietary sources of calcium

The recommended daily intake of calcium in New Zealand is:¹⁹

- 1000 mg for men and women aged 19 – 70 years
- 1300 mg for men and women aged over 70 years

Dairy products are the richest source of calcium and two to three serves, e.g. a cup of milk, a pottle of yoghurt or two slices of cheese, per day will maintain adequate calcium intake.¹⁹

Oral calcium supplements may be associated with adverse effects

Serum calcium levels are slightly elevated in the short term by taking oral calcium supplements.⁷ People who ingest an equivalent amount of calcium from their diet do not experience the same elevations in serum calcium.⁷ Since vascular calcification is an established risk factor for cardiovascular disease it has been suggested that calcium supplementation may increase cardiovascular risk.⁷

Calcium supplementation is known to be associated with increased rates of:²⁰

- Renal tract stone formation
- Constipation
- Gastrointestinal symptoms
- Cardiovascular events, including myocardial infarction

A 2015 meta-analysis concluded that due to the limited benefits of calcium supplementation and the increased risk of relatively serious adverse events, calcium supplements should not be recommended for individuals or at a population level.²⁰

The final word

It has become clearer since 2011 that the proportion of the population who are likely to benefit from vitamin D supplementation is relatively small and restricted to frail older patients and those at risk of deficiency. The prescribing of vitamin D to nearly one-quarter of a million people in New Zealand therefore may not be justified. When discussing new or ongoing supplementation with patients who do not have a clear indication for treatment, an evidence-based conversation about the likelihood of benefit may be helpful.

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