

# Vitamin D supplementation: Navigating the debate

## Key concepts

- There is no evidence to support blanket supplementation with vitamin D for the total population
- Severe vitamin D deficiency is a serious health concern, however, there is only weak evidence that mild deficiency is clinically significant
- Vitamin D testing is expensive and there is no consensus on the optimal vitamin D serum level. Monitoring vitamin D levels is also considered unnecessary.
- The best way to increase vitamin D levels for the general population is short (non-burning) bouts of sunlight exposure to 20% of the body (i.e. arms and legs)
- Supplementation can be recommended for asymptomatic people, who are at high-risk of vitamin D deficiency, without the need for serum testing
- Vitamin D toxicity is rare and requires excessive and prolonged supplementation, however, emerging data suggest possible adverse effects associated with sustained high levels

## **Vitamin D: why all the confusion?**

Vitamin D is required by everyone to regulate the body's calcium balance. This homeostasis is achieved by influencing calcium absorption, mainly in the small intestine. Vitamin D is important for bone mineralisation and general muscle and bone health. Severe deficiency can result in hypocalcaemic seizures and weak or misshapen bones – rickets in children, osteomalacia and osteoporosis in adults.<sup>1</sup> Normally, vitamin D is produced in the skin following exposure to UVB which then becomes metabolically active following reactions in the liver and kidney.

Despite vitamin D being essential for maintaining good health, there is disagreement as to what the optimal level of vitamin D is, as international recommendations vary. This has led to uncertainty in exactly how to interpret serum levels when individuals are tested. In recent years low vitamin D levels have been associated with a host of non-musculoskeletal conditions, such as cancer, autoimmune diseases, diabetes, multiple sclerosis and heart disease, although studies often produce mixed results.<sup>1, 2</sup> Consequently, a number of groups have begun advocating blanket supplementation as a form of catch-all prophylaxis. Requests by patients to have vitamin D levels assessed are also increasing despite a lack of evidence that vitamin D improves any non-musculoskeletal outcomes.<sup>3</sup>

With sufficient exposure to UVB in sunlight, a healthy person can synthesise all of their vitamin D requirements in their skin. However, the amount of sunlight a person is exposed to is determined by factors such as season, latitude, clothing, mobility, occupation and personal behaviour. Dark skin pigmentation also reduces the amount of vitamin D that can be produced, which can result in up to a six-fold slower production rate.<sup>4</sup> Individuals within communities may display wide variations in circulating levels of vitamin D. Therefore, unless severe deficiency is suspected, testing serum levels is not recommended and clinical decisions regarding supplementation can usually be made by assessing individual risk factors.

## **How much vitamin D are we getting in New Zealand?**

In New Zealand, vitamin D serum levels are lowest during winter. Studies have shown that females have lower vitamin D levels than males, Māori have lower levels than Europeans and levels in Pacific peoples are lower still. People with darker skin pigmentation, e.g., Africans and Indians, are likely to have even lower levels. Obese people also have lower levels of vitamin D than non-obese people.<sup>5, 6</sup>

Generally accepted guidelines for assessing vitamin D serum levels in New Zealand are shown in Table 1. There

is contention as to the significance of levels between 100 and 150 nmol/L. These levels have previously been considered to be in the normal range, however, recent studies are beginning to demonstrate adverse effects in people with vitamin D levels > 100 nmol/L.

**Table 1:** Recommended vitamin D levels<sup>7</sup>

Vitamin D serum concentration	Vitamin D status
<25 nmol/L	Moderate to severe deficiency
25–50 nmol/L	Mild deficiency/insufficiency
50–100 nmol/L	Optimal range
>100–150 nmol/L	Associations with adverse effects
>250 nmol/L	Vitamin D toxicity

It is estimated that almost half of the population in New Zealand have mean vitamin D levels below 50 nmol/L. However, only 3 – 4 % are thought to have levels lower than 17.5 nmol/L – classified as severe deficiency.<sup>8,9</sup>

### Vitamin D deficiency in a clinical setting

Severe vitamin D deficiency is associated with various diseases, such as osteomalacia and rickets. Deficiency is also associated with secondary hyperparathyroidism – low levels of vitamin D in turn cause low levels of calcium and the parathyroid hormone compensates for this calcium deficiency by stimulating renal conversion of active vitamin D.<sup>10</sup>

Vitamin D has been associated in the literature with several other diseases, such as multiple sclerosis, cardiovascular disease, diabetes and cancer, but there is no evidence of a causal role (see sidebar).

#### Bone disease

Moderate to severe vitamin D deficiency can cause inadequate bone mineralisation resulting in bone

softening. The most common examples of this are osteomalacia in adults and rickets in children.<sup>1</sup>

### Increased risk of falls in elderly people

Elderly people, particularly those in residential care, are exposed to less sunshine and have a reduced ability to synthesise vitamin D. Insufficiency decreases muscle strength and increases the risk of falls.<sup>3</sup> Some studies have shown that vitamin D supplementation decreases the number of falls experienced by elderly people in residential care who are vitamin D deficient, and decreases the number of hip fractures when combined with calcium supplementation.<sup>11,12</sup> However, supplementation should be combined with regular medicine review and a programme of exercise for maximum benefit.<sup>13</sup> All elderly people can be safely prescribed vitamin D supplementation, without prior testing, unless they are known to be hypercalcaemic, or taking other medicines which influence calcium levels such as alfacalcidol, calcitriol or calciptriol (which is applied topically to treat psoriasis).<sup>14</sup>

### Foetal development and infant bone growth

Maternal vitamin D is necessary for foetal development. Infants born to vitamin D deficient mothers are at risk of rickets, limb pain, bone fracture or hypocalcaemic seizures. The Australian and New Zealand College of Obstetricians has recommended supplementation for pregnant or breast-feeding women considered to be at risk of deficiency.<sup>15</sup>

### Kidney disease

Vitamin D undergoes several metabolic reactions, in the liver and kidney, in order to produce active forms of the molecule. In patients with chronic kidney disease, or in patients on dialysis or following kidney transplantation, reductions in the activity of renal enzymes magnify any vitamin D deficiency. Supplementation has been shown to reduce proteinuria,<sup>16</sup> and some studies have shown improved bone mineralisation and reduced fracture risk when combined with standard therapies.<sup>17</sup> Calcitriol rather

than cholecalciferol is the preferred treatment for vitamin D deficiency in chronic kidney disease, as it does not require renal metabolism to become active.

### Preventing vitamin D deficiency

The best way to prevent vitamin D deficiency in the general population is to increase exposure to direct sunlight. This can be further enhanced by increasing the amount of vitamin D rich food that is eaten.

### Sunlight is the primary source of vitamin D

Approximately 90% of the body's vitamin D requirements can be synthesised by way of the skin, with adequate exposure to sunlight.<sup>1, 18, 22</sup> Increasing a person's exposure to sunlight should therefore be first-line treatment of suspected deficiency. N.B. the exposure must be to be to direct sunlight, as UVB does not pass through glass.

Sunlight intensity varies with latitude and topography, therefore sunlight exposure requirements differ throughout the country and individual judgement is required. It is agreed that shorter, more frequent exposure periods are better than long periods of exposure and that the time spent in direct sunlight should be less than the time taken to redden and burn the skin.<sup>1</sup>

Some people may be concerned at apparent conflicting health messages regarding skin cancer and vitamin D. The amount of skin exposed to the sun should not be excessive – approximately 20% skin exposure is sufficient. Wearing shorts and a tee shirt equates to approximately 33% body exposure. There is evidence that sunscreen reduces rather than stops vitamin D production, therefore advising frequent, short (non-burning), bursts of direct sunlight with sunscreen application as required, is still consistent with the SunSmart “slip, slop, slap” message.<sup>1</sup>

Table 2 shows approximate sunshine exposure times for regions in New Zealand, however, sunshine levels vary greatly with seasons, across regions and even across the same region on consecutive days.

## Unsubstantiated claims for vitamin D

There is no evidence that vitamin D has a causal role in the following diseases and conditions:

- Cardiovascular disease - supplementation does not reduce prevalence or improve outcomes<sup>1, 18</sup>
- Cancer – no therapeutic effect demonstrated<sup>9</sup>
- Multiple sclerosis – no proven causal link
- Diabetes – no proven causal link<sup>1, 18</sup>
- Cystic fibrosis – No evidence supplementation improves disease state<sup>19</sup>
- Epilepsy – does not reduce seizures<sup>20</sup>
- Chronic pain – does not relieve symptoms<sup>21</sup>
- Immunity – no evidence that supplementation strengthens the immune system or reduces autoimmune responses<sup>9</sup>

Synthesised vitamin D is stored in body fat, however, this reserve is unable to prevent serum levels dropping over winter.<sup>1, 18, 23</sup> The clinical significance of this seasonal variation is unknown, but it is experienced in all temperate climates. During winter, sun exposure is more difficult, especially in colder regions of the country. Actions, such as rolling up sleeves when outside on warmer days, can assist in boosting vitamin D levels.

The Ministry of Health does not recommend the use of sunbeds to increase vitamin D levels due to the significantly increased risk of melanoma.<sup>8</sup>

**Table 2:** Recommended daily sun exposure for vitamin D production for people with fair skin\*<sup>7</sup>

Region	Dec–Jan (summer) at 10 am or 2 pm	July–Aug (winter) 10 am or 2 pm	July–Aug (winter) Midday
Auckland	6–8 min	30–47 min	24 min
Christchurch	6–9 min	49–97 min	40 min

\* Exposure times for highly pigmented skin are three to four times greater

### Diet can boost vitamin D levels

Diet is a minor source of vitamin D in comparison to sunlight. Supplementation through diet alone is unlikely to provide adequate vitamin D in order to satisfy daily requirements.<sup>18, 22</sup> Most people only derive 2.5 µg (100IU) of vitamin D per day from food, which is less than the New Zealand guidelines for vitamin D intake (Table 3).<sup>8, 18</sup>

However, during winter months, diet can be an important source of vitamin D and increased intake of vitamin D rich foods should be combined with sensible amounts of sun exposure.

The flesh of oily fish, e.g. salmon, and fish liver oils are the best dietary sources of vitamin D. Vitamin D content of

common vitamin D rich foods is as follows:<sup>25</sup>

- 1 Tablespoon of cod liver oil = 34 µg\*
- 100 g Salmon = 15 µg
- 100 g cooked mackerel = 11 µg
- 100 g canned tuna = 5 µg
- 250 mL fortified milk = 3 µg
- 100 g cooked beef or liver = 1.5 µg
- 1 tablespoon fortified margarine = 1.5 µg
- 1 cup fortified cereal = 1 µg
- 1 egg yolk = 1 µg

\* Limit ingestion to avoid excessive levels of vitamin D

There is no mandatory vitamin D fortification of food products in New Zealand. However, most margarines in New Zealand are sourced from Australia, where fortification with vitamin D is mandatory. In New Zealand, vitamin D may be added voluntarily to milk and milk-based products, formulated beverages and some legume and cereal products.

N.B. Sufficient dietary intake of calcium is also recommended in association with vitamin D intake.

**Table 3:** New Zealand guidelines for daily vitamin D intake\*

Age (years)	Vitamin D (µg per day)	Vitamin D (IU per day)
0–50	5	200
51–70	10	400
70+	15	600

\* The US Institute of Medicine has recently updated its guidelines and recommends greater daily intake of vitamin D, compared to New Zealand guidelines.<sup>24</sup>

**Table 4:** Groups at-risk of vitamin D deficiency where supplementation may be considered

Risk group	Rationale for supplementation
Elderly people (> 70 years)	Age related decline in vitamin D levels – possibly due to decreased skin thickness resulting in decreased ability to synthesise vitamin D. <sup>27</sup> Elderly people may be less mobile, have a reduced calorific intake and impaired kidney function. Consider supplementing on a case by case basis, depending on lifestyle and circumstances. Supplementation recommended for those in residential care or house-bound.
People with hip fracture – past or present	A marker for osteoporosis. Patients may benefit from supplementation. <sup>7</sup>
Dark-skinned people	Require up to six times more sunlight to synthesise the same amount of vitamin D as lighter-skinned people. <sup>4</sup> Supplementation recommended.
People who rarely go outdoors, e.g. night shift workers, or have their skin covered for long periods due to cultural or occupational reasons	Unable to synthesise vitamin D as skin is not exposed to UVB. Supplementation recommended for people who are veiled. For others consider on a case by case basis depending on circumstances.
Infants who are exclusively breast feeding, if their mothers are vitamin D deficient or at risk	An infant’s vitamin D status reflects that of the mother (see sidebar). Supplementation recommended.
People who are diet deficient, e.g. vegans	Most fruits and vegetables do not contain vitamin D. Risk is increased when sunshine exposure is low during winter. Consider supplementation only if other risk factors.
People who are obese	Generally have lower serum levels – possibly because vitamin D is held in adipose tissue (and therefore not in circulation) and less UVB exposure due to more time spent indoors. <sup>28</sup> Consider supplementation only if other risk factors.
People taking medicines that affect vitamin D levels, such as rifampicin and anticonvulsants	These medicines increase vitamin D metabolism. Consider supplementation only if other risk factors.
People with fat malabsorption conditions, e.g. coeliac disease	Vitamin D is present in the fat of food. Consider supplementation only if other risk factors.


N.B. People belonging to more than one risk group have an even higher risk of deficiency.

## What about Māori and Pacific peoples?

It is recognised that dark skin pigmentation correlates with decreased rates of vitamin D production.<sup>4</sup> The extent to which this affects the health of Māori and Pacific people is unknown. New Zealand based studies have shown that Māori and Pacific peoples have lower levels of vitamin D than European New Zealanders.<sup>5, 6</sup> However, Pacific adults have higher bone mineral content and lower fracture rates than European New Zealanders.<sup>5</sup>

A pragmatic approach to assessing the risk of vitamin D deficiency is best. It is likely that the darker the skin pigmentation of an individual, the more sunlight they will require to maintain an adequate level of vitamin D, particularly during winter.<sup>4</sup> Healthy people, regardless of their skin pigmentation, who regularly participate in outdoor activity and eat a balanced diet are unlikely to require vitamin D supplementation. However, people with darker skin that are also part of another at-risk group, e.g. shift workers, may benefit from vitamin D supplementation.

The issue of dietary compliance also needs to be considered. It is easier to take a pill once a month, than it is to cook fish several times a week. However, if an entire family can make a shift towards a healthier diet, then this is more beneficial to general health and wellbeing.

 **Best Practice Tip:** It is a good idea to find out about a person's eating habits when considering supplementation. How much oily fish are they eating, and do they even like fish? Some people will be able to increase their vitamin D intake by eating more fish and less red meat, while others do not have a preference for seafood.


## To supplement, or not to supplement?

There is no evidence to support blanket vitamin D supplementation of the New Zealand population.<sup>4</sup> Evidence is beginning to emerge that high levels of vitamin D, which may result from unnecessary supplementation of people with adequate levels to begin with, are associated with adverse effects.

Vitamin D supplements should be only prescribed to people at-risk of vitamin D deficiency (Table 4) and people with known low serum levels, when they are:

- Unable to increase their exposure to direct sunlight
- Unable to modify their diet to include more vitamin D rich foods

Serum testing of vitamin D levels is not required before prescribing supplementation, unless severe deficiency is suspected, e.g. clinical signs and symptoms. Testing is expensive and likely to return a sub-optimal vitamin D level (if deficiency already suspected). In comparison supplementation is inexpensive and highly unlikely to cause toxicity when used at recommended levels.<sup>26</sup>

 For further information see: "Vitamin D testing in primary care", *bpac<sup>nz</sup>* (Jan, 2007).

People at risk of becoming vitamin D deficient, where supplementation may be considered, are listed in Table 4 (Page 31). It is reasonable to routinely supplement:

- Elderly people who are institutionalised or house bound
- People who are veiled
- People with very dark skin who receive little direct sunlight
- Infants who are exclusively breastfed from mothers at risk of deficiency

### Supplementation with cholecalciferol

In New Zealand, for at risk people, the recommended vitamin D supplement is cholecalciferol (fully funded) – a form of vitamin D also known as vitamin D3. Supplementation begins with a loading dose of two 1.25 mg tablets taken immediately, then one tablet monthly thereafter.<sup>8</sup> In cases of severe deficiency (where serum levels have been tested) an increased loading dose of one 1.25 mg tablet, every day, for ten days may be prescribed.<sup>7</sup>

### Summary of supplementation regimen:

Month 1: One dose of 2 × 1.25 mg cholecalciferol

**Or** if severe deficiency, 1 × 1.25mg cholecalciferol daily for ten days

Month 2: Continue with 1 × 1.25 mg cholecalciferol every month

Patients with severe renal impairment, who require vitamin D supplementation, should be prescribed hydroxylated derivatives of vitamin D such as alfacalcidol and calcitriol. Doses of these medicines vary from patient to patient and require careful monitoring of serum calcium levels to prevent hypercalcaemia. These patients are most likely to be treated in secondary care.

### Monitoring vitamin D levels is unnecessary

The value of monitoring vitamin D levels is limited by the uncertainty surrounding the interpretation of results.

## Treating vitamin D deficiency in infants

Vitamin D is required for normal bone growth in infants and is present at low levels in breast milk. The World Health Organisation recommends exclusive breast feeding of infants until age six months (with mixed breastfeeding continuing until at least age one year). Since breast milk is initially an infant's sole source of nutrition, it is important that mothers receive adequate vitamin D through sunlight and vitamin D rich foods.

In New Zealand, infants born to mothers who are vitamin D deficient, or at risk of being deficient, are most vulnerable to vitamin D deficiency. The Australian and New Zealand College of Obstetricians recommends supplementation of these infants.<sup>15</sup> In other countries including Canada, the United Kingdom, the United States, France, the Netherlands and Germany, vitamin D supplementation in all exclusively breastfed infants is common practice.

GPs should prescribe supplements (10 µg/day, 400 IU), to all breast fed infants at high-risk of vitamin D deficiency, e.g. mothers who are dark skinned or veiled. Vitadol C liquid (fully funded) contains 400 IU vitamin D per ten drops (along with vitamins A and C), therefore prescribe 10 drops per day with feeds.

Infant milk formula is fortified with 5 mcg/L vitamin D, therefore deficiency is less likely to be a problem in infants fed milk formula, who are unable to breast feed.

For infants with symptoms of vitamin D deficiency, such as bone pain or deformation, tetany, delayed motor development and dental development issues, refer immediately for specialist assessment and treatment.

In addition, vitamin D assays are significantly more expensive than vitamin D supplements, which are safe at recommended doses. Some laboratories in New Zealand are now restricting testing to people with symptoms of vitamin D deficiency and this practice is likely to become more widespread.

## Vitamin D toxicity

Vitamin D toxicity cannot occur as a result of excessive sun exposure, as sunlight limits the body's production, causing vitamin D to break-down before it reaches toxic levels.<sup>29</sup> However, vitamin D obtained from foods and supplements is not naturally regulated. Vitamin D toxicity can occur following several months of excessive and prolonged supplementation.<sup>24</sup> Monthly supplementation with 1.25 mg cholecalciferol is safe. However, as some over-the-counter products contain significant levels of vitamin D, e.g. cod liver oil, vitamin D and multi-vitamin supplements, it is possible people may unknowingly be taking too much.

Vitamin D toxicity is mainly due to the effects of hypercalcaemia and is associated with headaches and gastrointestinal disturbance. Kidney stones, kidney failure and cardiac arrhythmias have also been reported. Growth restriction in children can occur when toxic levels are reached.<sup>8, 13</sup>

People who are particularly sensitive to changes in calcium balance due to vitamin D include individuals with:

- Hyperparathyroidism
- Chronic kidney failure

Vitamin D toxicity is treated by ceasing supplementation immediately and reducing calcium intake. If severe hypercalcaemia (>3.0 mmol/L) is present then IV saline with calcitonin and a bisphosphonate may be administered in a hospital setting.

Most reports in the literature focus on acute toxicity and few studies have been conducted assessing long-term elevated exposure to vitamin D. However, preliminary evidence suggests there may be adverse effects from long-term supplementation at levels lower than that which causes acute toxicity. For example, a recent study found that single annual, high-dose supplementation (500 000 IU) resulted in an increased risk of falls and fractures in elderly people.<sup>30</sup> Further studies are required to confirm this effect, however, there is a growing body of evidence contradicting the "more is better" view promoted by some groups. Vitamin D supplementation should only be prescribed to those who require it.

**ACKNOWLEDGEMENT** Thank you to **Dr Lisa Houghton**, Lecturer, Department of Human Nutrition, University of Otago, **Associate Professor Andrew Grey**, Auckland Medical School, University of Auckland and Consultant Endocrinologist, Auckland District Health Board and **Professor Ian Reid**, Auckland Medical School, University of Auckland, and Consultant Endocrinologist, Auckland District Health Board for expert guidance in developing this article.

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