



Vitamin D deficiency in adults

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Summary

Vitamin D deficiency is a common condition that affects a significant number of Australians. Vitamin D is important in the maintenance of bone health, and deficiency leads to osteomalacia and contributes to fragility fractures. Deficiency has also been implicated in a wide variety of extra-skeletal conditions. Vitamin D can be easily assessed in patients by measuring serum 25-hydroxyvitamin D. Replacement of vitamin D needs to be tailored for each patient and depends on the severity of the deficiency. Toxicity is unlikely with vitamin D when it is administered as cholecalciferol as it has a wide safety window. The adequacy of replacement should be monitored and in cases of persistently low concentrations, malabsorptive conditions (especially coeliac disease) should be excluded.

Key words: calcitriol, cholecalciferol, ergocalciferol.

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Introduction

Australia is well known for its abundance of sunshine. Hence, it is perhaps surprising that vitamin D deficiency is a common condition affecting a large proportion of Australians. A recognised consequence of low vitamin D is osteomalacia in adults.¹ It also contributes to osteoporosis, that is fragility fractures, in part through increased risk of falls.² Vitamin D deficiency has also been implicated in other conditions including cardiovascular disease, increased cancer risk and mortality, falls, sarcopenia, diabetes, multiple sclerosis, osteoarthritis, epilepsy and cognitive dysfunction.

Metabolism and function of vitamin D

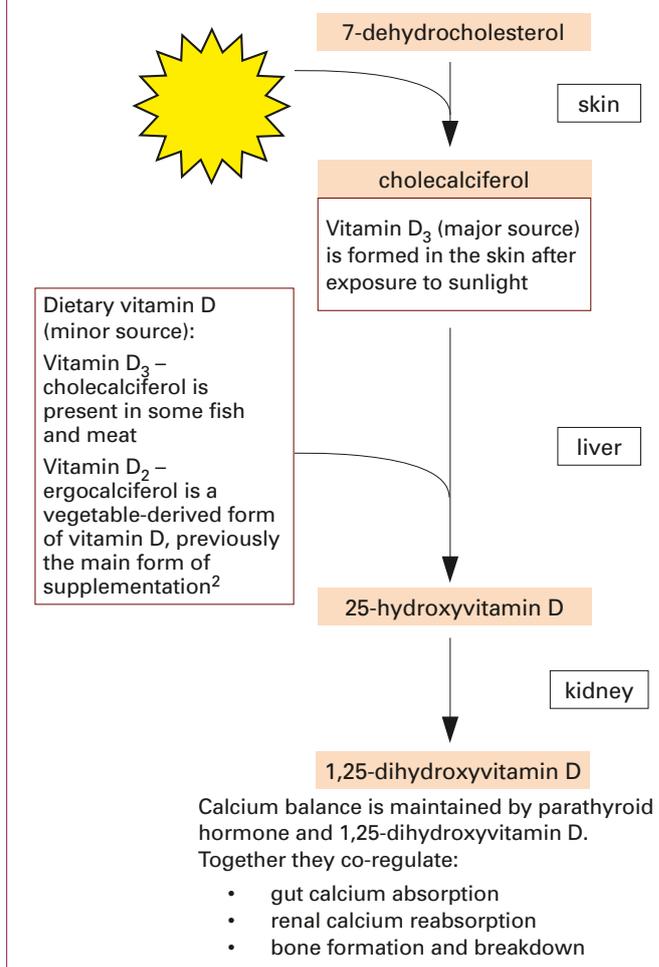
The two main forms are vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol) (see Fig. 1). These are transported to the liver and metabolised to 25-hydroxyvitamin D₃ and

25-hydroxyvitamin D₂ which are the major circulating forms of vitamin D and are measured in most assays. A second hydroxylation takes place in the kidney to form 1,25-dihydroxyvitamin D₃, also known as calcitriol, and 1,25-dihydroxyvitamin D₂. These are the activated forms of vitamin D and have three main functions:

- enhancing absorption of calcium and phosphate from the small intestine
- inhibiting parathyroid hormone synthesis and secretion
- mineralising the bone matrix.³

Fig. 1

Vitamin D metabolism



Impaired renal function results in reduced production of 1,25-dihydroxyvitamin D, whereas hepatic function, even if it is severely impaired, does not seem to have a major effect on vitamin D metabolism.

Sources of vitamin D

The main source of vitamin D comes from exposure of the skin to sunlight. Hence there is considerable seasonal variation with concentrations higher at the end of summer compared to other seasons. Vitamin D₃ is found in fatty fish such as herring, salmon and mackerel. Other sources include eggs, meat and fortified foods such as margarine (Fig 1). For most Australians, adequate vitamin D is unlikely to be achieved through dietary sources alone without fortification.⁴

Controversies regarding sun exposure

Guidelines on sun exposure must be tempered by the high prevalence of skin cancers in this country. Much controversy has surrounded the topic of how much sunshine is enough and how much is too much. It is a subject where there has often been a lack of consensus among medical specialists themselves and this problem is further compounded in transferring this message to the public.⁵

Recommending sun exposure

Recommended exposure of 5–15 minutes of sunlight 4–6 times a week outside the hours of 10 am–2 pm seems prudent (Table 1).¹ Certainly, avoidance of the most dangerous ultraviolet exposure in the middle of the day is appropriate, especially in summer, with responsible use of ultraviolet blocking agents. Guidelines on exposure to sunshine need to be tailored to the individual – one size does **not** fit all. Many factors need to be considered including geographical location such as latitude, season, time of day, skin colour, age and particularly clothing.

Dermatologists have expressed concern about relaxation of sun protection messages, which have played a large role in the media campaigns to reduce the incidence of skin cancers. Important caveats include some knowledge by the public of the ultraviolet index* – concentrations above 3 require sun protection. People who are at the highest risk of skin cancers, such as those who are immunosuppressed, should take even more stringent precautions in the sun.⁵ On the other hand, people with darker skin can require 3–4 times more sun to achieve the same vitamin D synthesis.³

* The ultraviolet index is an open-ended linear scale which rates the danger of solar ultraviolet radiation intensity on a daily basis. Each point on the scale is equivalent to 25 milliWatts/m² of ultraviolet radiation. A rating of 0–2 is low, 3–5 is medium, 6–7 is high, 8–10 is very high and 11+ is extreme.

Table 1

Recommendations of sun exposure for adequate vitamin D synthesis on exposed arms and legs (outside the hours of 10 am–2 pm) †

Region	Duration (minutes)	
	Summer	Winter
Cairns	6–7	9–12
Townsville	5–7	9–13
Brisbane	6–7	15–19
Sydney	6–8	26–28
Melbourne	6–8	32–52
Adelaide	5–7	25–38
Perth	5–6	20–28
Hobart	7–9	40–47

† Adapted from reference 3

Causes of vitamin D deficiency³

Reduced synthesis of cholecalciferol in the skin

Reduced sun exposure can result from ageing, veiling, illness or immobility (staying indoors). As people age, their ability to synthesise cholecalciferol from sun exposure decreases. Also, people with dark skin synthesise less cholecalciferol from sun exposure than do people with light skin.

Disorders of malabsorption

Small bowel disorders – especially coeliac disease and inflammatory bowel disease, infiltrative disorders (for example lymphoma, granuloma) and small bowel resection – can cause malabsorption of vitamin D. Other conditions such as pancreatic disorders (chronic pancreatitis, cystic fibrosis) or biliary obstruction (primary biliary cirrhosis) can have the same effect.

Enhanced degradation of 25-hydroxyvitamin D

Drugs such as rifampicin and anticonvulsants enhance the degradation of vitamin D which may contribute to or exacerbate vitamin D deficiency.

Groups at highest risk of vitamin D deficiency^{6,7}

Older people in residential care or those who are hospitalised, particularly people with hip fractures, are at risk of vitamin D deficiency, as are people living in institutional facilities. This is partly explained by age-related thinning of the skin and partly due to reduced sunlight exposure. Other at-risk groups include dark-skinned women (especially if veiled), ethnic minorities (Asian, Middle-Eastern origin) and refugees. Patients with malabsorptive syndromes or who are obese also are at increased risk of vitamin D deficiency. Hyperparathyroidism increases the metabolism of vitamin D and thus decreases its

half-life. Supplementary requirements are therefore greater in patients with hyperparathyroidism.

Diagnosing vitamin D deficiency

Vitamin D deficiency is usually asymptomatic, but signs and symptoms can include muscle aches and particularly weakness (proximal limb girdle). It is often seen in older people with osteoporosis. While there is debate about the benefit of vitamin D supplementation in preventing osteoporotic fractures, there is evidence that it may reduce falls risk.² Also, virtually all of the currently approved osteoporosis treatments have been evaluated in the presence of adequate vitamin D concentrations so these should be achieved as part of the approach to osteoporosis treatment.

Vitamin D deficiency can be detected using the 25-hydroxyvitamin D radioimmunoassay. While there is debate as to ideal concentrations, the following could be used to guide a clinical approach:

- vitamin D sufficiency > 75 nmol/L
- sub-optimal levels 50–75 nmol/L
- vitamin D insufficiency 25–50 nmol/L
- vitamin D deficiency 15–25 nmol/L
- severe vitamin D deficiency < 15 nmol/L.

This assay should also be used to monitor therapy. Virtually all commercial assays now measure 25-hydroxyvitamin D₂ as well as 25-hydroxyvitamin D₃. Parathyroid hormone and ionised calcium should be measured as an adjunct to 25-hydroxyvitamin D. Parathyroid hormone is usually elevated in the context of vitamin D deficiency. The aim of treatment is to normalise 25-hydroxyvitamin D, parathyroid hormone and calcium.

Vitamin D supplementation

The lower the 25-hydroxyvitamin D serum concentration, the more aggressive replacement therapy regimen is required to achieve acceptable concentrations rapidly. The greatest benefits are seen in high-risk individuals with decreased bone mineral density. In a meta-analysis of randomised controlled trials, vitamin D and calcium reduce the risk of falls and hip and other non-vertebral fractures in older people.⁸ However, the target range of 25-hydroxyvitamin D is still debated with values anywhere between 50 and 110 nmol/L being advocated. In patients treated with bisphosphonates, adequate calcium and vitamin D are required for efficacy of treatment. Many supplements only have 400 IU of vitamin D, but there is evidence that at least 800 IU is required for adequate benefit.

Benefits of vitamin D supplementation have also been reported in other conditions including diabetes and the metabolic syndrome,⁹ neoplasia^{10,11} and cognitive

dysfunction.¹² Although most of these studies are preliminary, they indicate potential benefits that may be of great significance in the future.

Daily requirements

Daily requirements for vitamin D are around 800–1000 IU, but larger doses are needed for patients who are already deficient. For moderate deficiency, that is 15–25 nmol/L, oral supplementation with 3000–5000 IU daily for 6–12 weeks can be used to replete stores followed by a maintenance dose of 1000–2000 IU per day. Vitamin D status should be assessed 3–4 months after commencing treatment as vitamin D is stored in fat and muscle and there is a lag time before normalisation of serum concentrations.³

For severe vitamin D deficiency, that is 25-hydroxyvitamin D less than 15 nmol/L, the intramuscular form of cholecalciferol 100 000 IU (megadose therapy) may be more suitable to replenish stores more quickly and effectively.³ This is especially pertinent for patients with malabsorption, acute medical illnesses and poor dietary compliance. Currently, such formulations are only available for specialists under a special access scheme.

Vitamin D in pregnancy

There is little consensus regarding the optimal dose of vitamin D required by pregnant women. The arbitrary addition of 400 IU vitamin D to most multivitamins sold for use during pregnancy is based on little evidence and is usually insufficient for most women who do not receive adequate sunshine or are dark-skinned or covered up. The pre-pregnancy 25-hydroxyvitamin D status is the best predictor of levels during pregnancy and hence the best gauge of requirements during pregnancy. Even supplements of 1000–1600 IU vitamin D have been found to be inadequate in many cases of deficiency. Supplementation with 2000–10 000 IU has usually resulted in acceptable concentrations without any adverse effects. Whether these observational studies can translate into widespread recommendations remains to be studied in large interventional studies.

The mother's vitamin D status is important because it will determine that of her infant – neonatal vitamin D concentrations correlate closely with those of the mother.¹³

Vitamin D supplements

Cholecalciferol (vitamin D₃) 1000 IU or 25 microgram is the supplement most commonly used and costs approximately 11–16 cents per capsule. It is not subsidised by the Pharmaceutical Benefits Scheme. Multivitamin supplements with 32–200 IU per tablet are not adequate to treat or prevent vitamin D deficiency.³

Calcitriol (1,25-dihydroxyvitamin D₃) is generally not suitable for treatment of vitamin D deficiency as it has a narrow therapeutic window resulting in an increased risk of hypercalcaemia or hypercalciuria. This is especially true in nursing home residents who often have quite severe vitamin D deficiency. Calcitriol has a role in the treatment of vitamin D deficiency in renal failure where there is inability to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Serum calcium concentrations and renal function must be monitored closely under these circumstances.

Adverse effects of treatment

Vitamin D toxicity can be caused by excess oral intake, but not by prolonged exposure to sunshine. No evidence of toxicity has been found in cholecalciferol doses up to 4000 IU daily. Even doses of 100 000 IU at more than three-monthly intervals have not been associated with toxicity. Vitamin D intoxication causes hypercalcaemia and can present with symptoms of anorexia, nausea, constipation and depression. Examination and investigations may demonstrate renal calculi, renal impairment and anaemia.

Conclusion

Vitamin D deficiency is common in Australia and contributes to significant morbidity. It is easily assessed by measuring serum 25-hydroxyvitamin D concentrations. Replacement needs to be tailored depending on the degree of insufficiency, and vitamin D concentrations should be monitored after 3–4 months. If vitamin D is low or proving difficult to replenish, ensure compliance and exclude malabsorption conditions such as coeliac disease.

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Professor Eisman has worked with Amgen, deCode, Eli Lilly, Merck Sharp and Dohme, Novartis, Sanofi-Aventis and Servier. He was Editor-in-Chief of the Journal of Bone and Mineral Research from 2003 to 2007, and is a chair or member of several committees for federal and state health departments, and the Royal Australian College of General Practitioners.

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Self-test questions

The following statements are either true or false (answers on page 131)

- Adequate vitamin D can be obtained from diet alone.
- Calcitriol should be used for vitamin D replacement in people with normal renal function.