Vitamin D
By Lynn Gould

Case study
Brian, a 58-year-old office worker, comes into the pharmacy asking for vitamin D tablets. He has fair skin and is grumbling that he doesn’t know why he needs them as, at his wife’s insistence, he takes a multivitamin already. When questioned he cannot remember why the doctor wants him to take them but thinks it has something to do with the results of a blood test he had recently.

Learning objectives
After reading this article you should be able to:
• Discuss the metabolism and physiological functions of vitamin D.
• Identify people who may be at risk of vitamin D deficiency.
• Counsel on the potential consequences of vitamin D deficiency and the importance of maintaining adequate vitamin D status.
• Provide advice on the treatment and prevention of vitamin D deficiency.

Competency standards (2010) addressed:
6.1.1, 6.1.2, 6.1.3, 6.2.1, 6.2.2, 6.2.3, 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.2.1, 7.2.2

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Background
Because it is almost impossible to obtain sufficient vitamin D from the diet, the main source of vitamin D for most Australians is through exposure to sunlight. Many Australians do not receive adequate vitamin D from sunlight and there is evidence that about 30% of adults in Australia have at least mild vitamin D deficiency. Severe deficiency can lead to rickets in children and osteomalacia in adults. Vitamin D deficiency is also associated with osteoporosis, a decrease in muscular strength, and increased risk of falls. In addition, there is growing evidence that vitamin D deficiency may increase the risk of several other health problems, including cardiovascular disease, diabetes and certain cancers. Because the symptoms of vitamin D deficiency are largely non-specific, it often goes unrecognised and untreated.

The name vitamin D is used to describe several closely related fat-soluble sterols (sterols are steroids containing a hydroxyl group at position 3 and a branched aliphatic side chain at position 17) including:
• Colecalciferol (cholecalciferol)
• Ergocalciferol
• Alfacalcidol (1-hydroxycolecalciferol)
• Calcifediol (25-hydroxycolecalciferol; 25(OH)D)
• Calcitriol (1,25-dihydroxycolecalciferol; 1,25(OH)2D)
• Dihydrotachysterol.

Sources
Humans acquire their vitamin D in two main forms:
• Vitamin D3 (colecalciferol) which is synthesised from 7-dehydrocholesterol in the skin on exposure of skin to the ultraviolet-B (UVB) spectrum in sunlight, and is also found in a narrow range of foods such as fatty fish (e.g. herring, mackerel, sardines, tuna, salmon), egg yolks and some dairy products.
• Vitamin D2 (ergocalciferol) which occurs in fungi (e.g. mushrooms) and plant foods.
Approximately 90% of our vitamin D is obtained through cutaneous synthesis, although this varies in response to several factors including:28

- The amount of UVB (e.g. latitude, season, time of day, cloud cover).
- The area of skin exposed.
- Duration of exposure.
- Age.
- Skin colour.

Metabolism

Vitamin D$_2$ and D$_3$ are prohormones. Both dietary and cutaneously synthesised forms are stored in, and then released from, fat cells when required. They are hydroxylated in the liver to 25(OH)D, the major form of vitamin D circulating in the blood (and the form measured to assess vitamin D status). Most of the 25(OH)D in the blood is bound to vitamin D binding protein. When active vitamin D is needed, unbound 25(OH)D undergoes further hydroxylation to 1,25(OH)$_2$D (calcitriol), the fully bioactive form of vitamin D. Until recently it was believed that this second hydroxylation occurred only in the kidneys. Although the kidneys are still recognised as the key site of 1,25(OH)$_2$D production, research has now shown that hydroxylating enzymes (e.g. 1-alpha hydroxylase) are also found in many other body tissues, including macrophages, the colon, prostate, breast, and within the skin itself. The conversion of 25(OH)D to calcitriol is regulated by serum levels of calcitriol, parathyroid hormone, calcium and phosphate.11–16

Calcitriol is transported in the blood mostly bound to albumin and vitamin D binding protein. A small fraction of the calcitriol circulates in its ‘free’ form to bind to specific vitamin D receptors which have been found in many locations in the body. The binding of calcitriol to its receptors results in a wide range of biological responses, including regulation of the synthesis of some proteins through activation and deactivation of genes.11–16

Functions

The major known functions of vitamin D are to maintain calcium homeostasis and facilitate bone formation and mineralisation.12 There is increasing evidence that vitamin D performs many other functions, including modulation of neuromuscular and immune function. It has direct effects on muscle strength, modulated by vitamin D receptors in skeletal muscles. Calcitriol has been shown to have immunomodulatory activity on monocytes and activated T and B lymphocytes and is thought to protect against infections, particularly tuberculosis. Epidemiological studies have also found evidence of a possible role for vitamin D in reducing the risk of other respiratory infections (including influenza), schizophrenia, seasonal affective disorder, preeclampsia in pregnancy, osteoarthritis and autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis, psoriasis).13–16,21–23

Vitamin D may also have a protective effect against several types of cancer. Many genes responsible for the regulation of cell proliferation, differentiation, apoptosis and angiogenesis are modulated in part by vitamin D.21 It is conjectured that, if cells becomes malignant, calcitriol can prevent angiogenesis and induce apoptosis, reducing the probability that the malignant cells will survive.14 Several studies have demonstrated that adequate levels of 25(OH)D can decrease the risk of and improve survival rates for cancers of the breast, colon, rectum, ovary, prostate, stomach, bladder, oesophagus, kidney, lung, pancreas and uterus, as well as non-Hodgkin lymphoma and multiple myeloma.4,24 However, a recent epidemiological study found a significant increase in the risk of pancreatic cancer with higher vitamin D status, demonstrating the need for further investigation into the association between vitamin D and cancer.13,25

There is epidemiological evidence that vitamin D may also protect against cardiovascular disease, hypertension and stroke. Calcitriol appears to inhibit vascular calcification and proliferation of vascular smooth muscle; control volume homeostasis and blood pressure via regulation of the renin-angiotensin-aldosterone system; and exert anti-inflammatory effects.27 Observational studies indicate that vitamin D may also play a role in endocrine function, stimulating pancreatic insulin production and...
Vitamin D deficiency

Causes

Causes of vitamin D deficiency include:11,12

- Inadequate intake or synthesis:
  - Inadequate sunlight exposure.
  - Reduced synthesis from a given UVB exposure (e.g. the elderly).
  - Inadequate consumption of foods containing vitamin D.
- Reduced absorption:
  - Small bowel disorders, e.g. coeliac disease; sprue; inflammatory bowel disorders; diarrhoeal disorders (lymphoma, granuloma, amyloid).
  - Pancreatic insufficiency, e.g. chronic pancreatitis, cystic fibrosis.
  - Biliary obstruction, e.g. primary biliary cholangitis, external biliary drainage.
- Abnormal metabolism (defects in the production of 25(OH)D or 1,25(OH)2D):
  - Chronic hepatic disorders, e.g. hepatitis, cirrhosis.
- Resistance to effects of vitamin D:
  - Type II hereditary vitamin D-dependent rickets due to mutations in the 1,25(OH)2D receptor. In this disorder, 1,25(OH)2D is abundant but ineffective because the receptor is not functional.

Risk factors

People at risk of vitamin D deficiency include:1,3,7,14

- Older people, especially those who are institutionalised or housebound.
- Dark-skinned people (particularly if veiled).
- Breast-fed infants of women with vitamin D deficiency.
- Pregnant women (particularly if dark skinned or veiled).
- Rapidly-growing adolescents and young children (especially in winter).

Table 1. Stages of vitamin D deficiency11

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum 25(OH)D (nmol/L)</th>
<th>Serum PTH (% increase)</th>
<th>Bone turnover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>25–50</td>
<td>15</td>
<td>High–normal</td>
</tr>
<tr>
<td>Moderate</td>
<td>12.5–25</td>
<td>15–30</td>
<td>High</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;12.5</td>
<td>&gt;30</td>
<td>Osteomalacia</td>
</tr>
</tbody>
</table>

Some medicines can cause or exacerbate vitamin D deficiency. These include:21,38,39

- Corticosteroids – reduce calcium absorption and impair production of biologically-active vitamin D.
- CYP450 inducers (e.g. carbamazepine, isoniazid, phenobarbitone, phenytoin, primidone, rifampin) – induce hepatic conversion of vitamin D to inactive metabolites and reduce circulating levels of active vitamin D.
- Orlistat and cholestyramine – reduce absorption of vitamin D (and other fat-soluble vitamins).

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics and calcium, and plasma calcium concentrations should be monitored.36

High doses of vitamin D should be given with caution to patients taking digoxin, because hypercalcaemia (which may result from excess vitamin D use) may precipitate abnormal heart rhythms.39

As well, recent studies have:

- Suggested a possible beneficial role of vitamin D in cognitive function. Vitamin D receptors are present in areas of the brain involved in complex planning, processing, and forming new memories. Neuroprotective functions of vitamin D are thought to include antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms. There is evidence that vitamin D has a beneficial role in the developing brain as well as in adult brain function.28
- Found that, in people with asthma, reduced vitamin D levels were associated with impaired lung function, increased airway hyperresponsiveness and reduced response to corticosteroids.29
- Found that vitamin D has a protective effect against Crohn’s disease.30

Vitamin D and medicines

Some medicines can cause or exacerbate vitamin D deficiency. These include:11,13,26,27

- People who are obese (vitamin D is fat soluble and is stored in adipose tissue; low serum 25(OH)D levels in obese people are believed to be due to vitamin D sequestration by adipocytes35).
- People taking drugs which can cause vitamin D deficiency.
- Rapidly-growing adolescents and young children (especially in winter).
- People with intestinal, renal or hepatic disease.

Symptoms

Signs and symptoms of vitamin D deficiency include:3,12,15

- Bone discomfort or pain (often throbbing) in the lower back, pelvis and legs.
- Muscle aches.
- Muscle weakness.
- Symmetrical lower back pain in women.
- Increase in body sway and falls.

Assessment

Serum 25(OH)D is used to assess vitamin D status, as it is produced from both dietary and cutaneous sources of the vitamin. The optimal serum 25(OH)D level for adults is >50 nmol/L (preferably about 75 nmol/L). Some researchers recommend levels of 75–100 nmol/L, especially for the elderly. Although an optimal paediatric level has not yet been specified, infants, neonates and young children with a 25(OH)D level <27.5 nmol/L are considered to be vitamin D deficient.1,33

Vitamin D deficiency in adults is classified according to the following serum 25(OH)D levels:1,2,32

- Mild: 25–50 nmol/L.
- Moderate: 12.5–25 nmol/L.
- Severe: <12.5 nmol/L.

Other biochemical markers which may aid in assessment of vitamin D status include elevated serum levels of alkaline phosphatase and parathyroid
Continuing Professional Development

Recommended intake of vitamin D

Recommendations for Adequate Intake (AI) are provided when a Recommended Dietary Intake (RDI) cannot be determined. AI is defined as ‘the average daily nutrient intake level based on observed or experimentally-determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate’.

Current AI recommendations for vitamin D are:

- 5 mcg (200 IU)/day for children and adults up to 50 years of age
- 10 mcg (400 IU)/day for adults 51 to 70 years of age
- 15 mcg (600 IU)/day for adults ≥71 years of age

However, many experts now agree that, in the absence of adequate sun exposure, 800–1,000 IU vitamin D per day is needed for children and adults of all ages.

Vitamin D deficiency in infants and children results in inadequate mineralisation of skeletal growth plates, which causes growth retardation and rickets. Symptoms of rickets include distortion of bones (notably bowing of the legs), limb pain and fractures.

Vitamin D deficiency in adults can precipitate or exacerbate osteomalacia and/or osteoporosis. Osteomalacia is caused by inadequate mineralisation of bone matrix, while osteoporosis develops due to a loss of density of previously constructed bone. Osteomalacia may be asymptomatic in the early stages, but may present radiologically as osteopenia (a condition of subnormally mineralised bone). As it progresses, symptoms may include dull, aching bone pain in the lower spine, pelvis and legs, fractures, muscle aches and muscle weakness. Patients with these symptoms may be misdiagnosed with fibromyalgia, degenerative joint disease, arthritis, or chronic fatigue syndrome. Osteoporosis leads to increased bone fragility and an increased risk of fracture.

Vitamin D deficiency is an independent predictor of falls in the elderly. It has also been reported to result in impaired immune function, including reduced capacity to respond to agents that cause tuberculosis.

Vitamin D deficiency may also increase the risk of developing:

- Cancer
- Diabetes
- Multiple sclerosis
- Hypertension
- Rheumatoid arthritis
- Schizophrenia
- Depression
- Preeclampsia in pregnancy.

Treatment

Treatment is recommended for anyone with 25(OH)D levels <50 nmol/L. Colecalciferol is preferred for treating vitamin D deficiency, as it is more potent than ergocalciferol, has a longer half-life and is more effective at raising and maintaining serum 25(OH)D levels. In addition, ergocalciferol is only available in Australia as an ingredient in OTC vitamin and mineral preparations. The quantity of ergocalciferol in these preparations (32–200 IU per tablet) is insufficient to treat vitamin D deficiency. Single-ingredient vitamin D products available in Australia contain 25 mcg (1,000 IU) colecalciferol (e.g. Blackmores Vitamin D3, Ostelin Vitamin D3, Ostevit-D). Halibut or cod liver oil capsules contain 400 IU colecalciferol, but they also contain vitamin A (4,000 IU), which may be detrimental (excessive vitamin A intake has been associated with increased fracture risk and fetal abnormalities). Because a patient’s response to ergocalciferol or colecalciferol depends largely on the ability of the kidneys to hydroxylate them to physiologically active calcitriol, their efficacy may be markedly reduced in patients with severe renal impairment.

Calcitriol is not recommended for treating patients with simple vitamin D deficiency, as it has a narrow therapeutic index and may cause significant hypercalcaemia. However, patients with severe renal impairment or rare causes of rickets or osteomalacia (e.g. X-linked hypophosphataemic rickets, vitamin D dependent rickets, tumour-induced osteomalacia, renal osteodystrophy) may require calcitriol and should be managed in specialised centres.

Prevention

Sunlight exposure

It is important to strike a balance between having sufficient sun exposure to maintain adequate vitamin D synthesis while minimising the risk of skin cancer. Although SPF 15 sunscreen has been reported to reduce vitamin D synthesis by up to 99%, an Australian study showed that normal SPF usage over summer
did not significantly affect 25(OH)D levels. Short exposure to sunlight is more efficient at producing vitamin D₃ as prolonged exposure results in the degradation of vitamin D₃ and its precursors to relatively inert products. Therefore, excessive exposure to sunlight cannot cause vitamin D toxicity.⁴,⁷,¹¹

It is almost impossible to specify the exact amount of sunlight exposure a person would need to obtain adequate vitamin D. Variable factors include season, latitude, time of day, age and skin colour. A person with very dark skin requires around six times more exposure to produce as much vitamin D₃ as someone with fair skin. Conversely, because of the different body proportions of children and the reduced capacity to synthesise vitamin D with ageing, children are likely to require less sun exposure than adults to produce an equivalent amount of vitamin D₃. Estimates from the USA suggest that, to get sufficient vitamin D from sunlight alone, infants need to be exposed for two hours a week if only the face is exposed, or need to be exposed for two hours a day if the whole body is exposed. Therefore, excessive exposure to sunlight cannot cause vitamin D toxicity.⁴,⁷,¹¹

Table 2. Recommended sunlight exposure to 15% of the body (face, hands, arms) for fair-skinned adults to produce vitamin D levels equivalent to current Australian recommended intakes, if exposure occurs three to four times a week (these exposures will give one-third MEDa).⁷,³⁷

<table>
<thead>
<tr>
<th>Region</th>
<th>October to March</th>
<th>April to September</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 12:00</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern (Townsville, Cairns)</td>
<td>2–5 minb</td>
<td>3–10 min³</td>
</tr>
<tr>
<td>Central (Brisbane, Perth)</td>
<td>2–6 minb</td>
<td>4–17 min³</td>
</tr>
<tr>
<td>Southern (Adelaide, Sydney, Melborne, Hobart)</td>
<td>2–10 minb</td>
<td>5–34 min³</td>
</tr>
<tr>
<td><strong>At 10:00 and 15:00</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern (Townsville, Cairns)</td>
<td>≤10 min³</td>
<td>≤16 min³</td>
</tr>
<tr>
<td>Central (Brisbane and Perth)</td>
<td>Around 10 minc</td>
<td>14–44 min³; Brisbaneb</td>
</tr>
<tr>
<td>Southern (Adelaide, Sydney, Melborne, Hobart)</td>
<td>≤15 minb</td>
<td>21 min to ≥1 hourb</td>
</tr>
</tbody>
</table>

- a. A minimal erythemal dose (MED) is the time taken in minutes for UV radiation to cause a slight erythema of the skin but not sunburn. Exposing the whole body to 1 MED produces serum vitamin D concentrations equivalent to an oral dose of 10,000–20,000 IU. Exposing 15% of the body to 1 MED would be equivalent to an oral dose of 1,500–3,750 IU.
- b. Extreme care: sun protection highly recommended; erythema can occur soon after the maximum exposure time is exceeded.
- c. Care: sun protection recommended if exposure is likely to exceed the maximum recommended time.
- d. Hobart exposure times will be higher (see Ref. 37 for further details).

For housebound or bedridden elderly people, who are at increased risk of vitamin D deficiency, it is safer to expose a greater body surface area to sunlight than to increase the exposure time. ‘Sunning’ elderly people behind closed windows does not significantly increase vitamin D synthesis as glass is an effective UVB filter. Vitamin D supplementation may be preferable to increased sun exposure for the elderly, to reduce the risk of skin cancer.²⁷

See Table 2 for estimates of recommended sunlight exposure in various areas of Australia.

Diet
It is almost impossible to obtain enough vitamin D from dietary sources, especially for older people, whose vitamin D requirements are two to three times those of younger people. Only a few foods contain significant amounts of vitamin D. The richest sources are fatty fish (e.g. sardines, salmon, herring, mackerel). Wild fish contain significantly greater quantities of vitamin D than farmed fish. Other important sources are red meat, liver, milk, eggs, mushrooms and fortified foods such as margarine. In Australia it is estimated that margarine provides up to 48% of the total dietary vitamin D intake in adults, followed by canned fish (16%), and eggs (10%). However, the average intakes are low – only 2.6 mcg (104 IU)/day for men and 2.0 mcg (80 IU)/day for women.²⁷

Supplementation
**Children** – Children who are dark-skinned, veiled, receive inadequate sunlight exposure, or who have an underlying medical condition predisposing to vitamin D deficiency should receive a daily supplement containing 400 IU vitamin D. Siblings of a child diagnosed with vitamin D deficiency should be screened.³²

**Adults** – Routine vitamin D supplementation is not recommended for most adults. Those at risk of deficiency (e.g. dark skinned, veiled, limited sun exposure, elderly) may require supplements to maintain adequate vitamin D levels. A daily supplement containing at least 400 IU vitamin D should be recommended for at-risk adults. Elderly people should take 800–1,000 IU vitamin D per day to reduce fracture risk and risk of falls. Intermittent (three-monthly) high doses of vitamin D might help to overcome the problem of poor long term compliance with supplements. However, high-dose vitamin D formulations are currently not registered in Australia and are generally only available for research purposes.¹¹,³¹,³³

Contraindications to vitamin D supplementation include hypercalcaemia, Williams syndrome (causes infantile hypercalcaemia) and metastatic bone disease. Certain medical conditions can increase the risk of hypercalcaemia in response to vitamin D, including primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma. People with these conditions should consult their doctor before taking supplements containing vitamin D.³,⁵,³⁸,⁴⁰

Case study
You explain to Brian that his recent blood test most likely indicated that he has a vitamin D deficiency. You point out that a vitamin D deficiency can increase the risk of developing a number of diseases. While taking multivitamin is generally a good thing it won’t provide Brian with the level of vitamin D necessary to address his deficiency. You recommend that Brian should take 75–125 mcg (3,000–5,000 IU) of colecalciferol daily for 6–12 weeks, then 25 mcg (1,000 IU) daily as maintenance therapy, as prescribed by his doctor.
Questions

1. The biologically active form of vitamin D is:
   a) alfalcacidol.
   b) colecalciferol.
   c) calcitriol.
   d) calcifediol.

2. What would be the vitamin D status of an adult with a serum 25(OH)D level of 35 nmol/L?
   a) Normal.
   b) Mild deficiency.
   c) Moderate deficiency.
   d) Severe deficiency.

3. Which one of the following biochemical markers is likely to be raised in vitamin D deficiency?
   a) Parathyroid hormone.
   b) Calcium
   c) Phosphate.
   d) 1,25(OH)2D.

4. Which of the following strategies would be most appropriate to prevent vitamin D deficiency in an elderly person in a residential care facility?

   a) Encourage them to eat fatty fish and eggs.
   b) Give them colecalciferol supplements.
   c) Encourage them to spend more time sitting at a sunny window.
   d) A score of 4 out of 5 attracts 1 CPD credit.

The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.