

Vitamin D — function and uses

Vitamin D has a number of essential functions in the body as well as several established clinical uses. In this article, Pamela Mason discusses the vitamin's metabolism and interactions and looks at growing evidence of its involvement in other conditions

Vitamin D was first identified in the early 1900s, when it was realised that cod liver oil contained a substance that could cure rickets. Strictly, it is incorrect to describe this substance as a vitamin because it can be synthesised in the skin; a dietary source only becomes essential when exposure to sunlight is inadequate. Moreover, vitamin D is converted to an active metabolite which acts like a steroid hormone, binding to receptors in a range of body tissues.

Its principle function is to maintain the plasma concentrations of calcium by actions in the intestine (to increase calcium absorption) the kidney (to reduce excretion of calcium) and the bone (to mobilise calcium, but later to replace bone loss).

Vitamin D has a number of other functions, including modulation of insulin secretion and the immune system. Vitamin D receptors have been found in more than 30 different tissues and the number of genes known to be regulated by calcitriol (see Panel, p228) is growing, giving credence to the idea that vitamin D has functions beyond that of calcium regulation.

Vitamin D has several well-established clinical uses, including the treatment of deficiency states resulting from primary deficiency or deficiency secondary to malabsorption. In combination with calcium it has established benefits in the treatment of hypoparathyroidism. In combination with phosphorus, it results in improved calcium and phosphorus balance in patients with hypophosphataemia. Both liver disease and end-stage renal disease result in compromised hydroxylation of vitamin D to produce its active metabolite. Supplementation of vitamin D in renal disease, therefore, requires active forms or analogues of vitamin D.

Vitamin D is found naturally only in foods of animal origin, especially oily fish and fish liver oil, and in smaller amounts in egg yolk, dairy fat, liver and other offal. Some other foods are fortified with added vitamin D. In the UK, these include breakfast cereals, margarine, soya milk and other processed milks and infant foods.

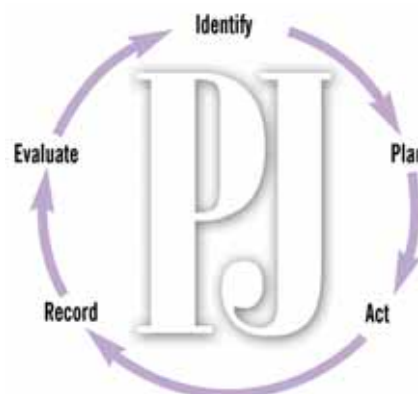
Human requirements

In the UK, there is no Reference Nutrient Intake (RNI) for vitamin D for most adults and school-aged children. This is because of an assumption that these groups of people normally manufacture enough of the vitamin in their skin during the summer to last the whole year. RNIs are therefore given only for babies and young children, for people over the age of 65 years and for pregnant and breastfeeding women. These vary between 7 and 10µg daily; the typical average UK di-



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Fish and fish oils are a good natural source of vitamin D



Identify knowledge gaps

1. List three foods in which vitamin D is found naturally.
2. Which groups of people are particular at risk of vitamin D deficiency?
3. What are the signs and symptoms of vitamin D toxicity?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" and "health education and promotion" (see appendix 4 of "Plan and record").

etary intake is only 2–3µg daily. Anyone whose skin is not regularly exposed to summer sunlight is unlikely to obtain enough vitamin D to meet these RNIs. It is, therefore, likely that there is a widespread need for supplements or fortified foods.

Synthesis of vitamin D in the skin

The main source of vitamin D is skin synthesis. Vitamin D (as calciferol) can be produced in the skin by conversion of the steroid, 7-dehydrocholesterol. The amount of vitamin D produced in the skin depends on length of exposure to sunlight, cloud cover, area of skin exposed, pollution, use of sunscreens and wavelength of UV light. In the UK, it is only in summer that there is adequate UV radiation of the appropriate wavelength (290–315nm) for vitamin D synthesis. Exposure of face, lower arms and hands to sunlight for 10–15 minutes each day in the summer is thought to be equivalent to 5µg (200units) of vitamin D throughout the year. Dark skins, however, require 10–50 times more exposure than pale skins to achieve the same degree of vitamin D synthesis; older people may have approximately half the capacity for synthesis of younger people.

Pamela Mason, PhD, MRPharmS, is a pharmaceutical writer with a special interest in nutrition

There is growing debate about the amount of sunlight exposure required to ensure adequate vitamin D synthesis. Exposing the skin to strong sunlight for longer than 30 minutes does not lead to increased vitamin D production but does increase the risk of skin cancer. Current guidelines to take precautions when exposing the skin to sunlight should continue to be followed.

Metabolism

Vitamin D is absorbed in lipid micelles and incorporated into chylomicrons. Some dietary fat is therefore needed to absorb dietary vitamin D. To become physiologically active, vitamin D must undergo two hydroxylation reactions.

Colecalciferol is hydroxylated in the liver to form 25-hydroxyvitamin D — 25-(OH)D — which is released into the circulation. The second stage of vitamin D metabolism occurs in the kidney where 25-(OH)D undergoes either 1-hydroxylation to yield 1,25-dihydroxyvitamin D (calcitriol) or 24-hydroxylation to yield 24,25-dihydroxyvitamin D. Renal synthesis of calcitriol is homeostatically controlled by parathyroid hormone (PTH). Synthesis of PTH is regulated by serum concentrations of calcium and phosphate.

Ergocalciferol from fortified foods and supplements undergoes similar hydroxylations to yield ercalcitriol. However, oral colecalciferol intake results in a 70 per cent higher plasma 25-(OH)D concentration compared with the same amount of ergocalciferol.

Deficiency

Vitamin D deficiency develops when there is inadequate exposure to sunlight, a lack of vitamin D in the diet, poor absorption from the gastrointestinal tract or inability of the liver and kidney to convert vitamin D to its active form.

Deficiency leads to hypocalcaemia, hypophosphataemia, poor mineralisation or demineralisation of the bone, bone pain, fracture and muscle weakness. In adults, the classic deficiency disease is osteomalacia; in children, in whom there may be growth retardation and skeletal deformity especially of the long bones, this disease is known as rickets. Rickets was thought to be a disease of the past, but has recently re-emerged in the UK, usually in areas of urban deprivation.

Groups of people are at risk of vitamin D deficiency and who may require supplementation are described in the Panel on p229.

Vitamin D toxicity

Vitamin D is potentially but rarely toxic. The most serious effect is hypercalcaemia, which can lead to contraction of blood vessels (and hence dangerously high blood pressure) and calcification of the soft tissues (including the kidney, heart, lungs and blood vessel walls). Associated signs and symptoms include arrhythmia, gastrointestinal distress (nausea, vomiting and constipation) and nephrotoxicity manifesting as polyuria, polydypsia and nocturia.

Vitamin D substances

There is a range of vitamin D compounds:

- **Ergocalciferol** (calciferol, vitamin D₂) is the main synthetic vitamin D compound which is added to supplements and fortified foods. It is formed when the fungal steroid, ergosterol, is irradiated with ultraviolet light.
- **Colecalciferol** (cholecalciferol, vitamin D₃) is the form found in animal products and fish oils. It is the naturally occurring form of vitamin D and is produced in the skin.
- **Alfacalcidol** (1 α -hydroxycholecalciferol) is used for vitamin D therapy by mouth or intravenous injection for people with severe renal impairment. It is a hydroxylated derivative of vitamin D₃.
- **Calcitriol** (1,25-dihydroxycholecalciferol) is also used for vitamin D therapy by mouth or intravenous injection for people with severe renal impairment. It is a hydroxylated derivative of vitamin D₃.
- **Dihydrotachysterol** is used mainly for hypocalcaemic tetany, due to hypoparathyroidism. It is a synthetic analogue of vitamin D.
- **Paricalcitol** is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. It is a synthetic vitamin D analogue.

Other new synthetic vitamin D analogues include doxercalciferol, falecalcitriol and maxacalcitol. These analogues are not currently used in the UK.

International units or micrograms? It should be noted that 1 IU of vitamin D is equivalent to 0.025 μ g of colecalciferol (ie, 1 μ g of colecalciferol is equivalent to 40 IU of vitamin D).

Some infants are sensitive to intakes of vitamin D as low as 50 μ g a day. The toxic threshold for adults is not known, but patients suffering from vitamin D intoxication who have been investigated were taking more than 250 μ g daily. However, a Food Standards Agency report mentions one study which suggested that some cases of hypercalcaemia occurred in elderly people given doses of 50 μ g daily. This report suggested that long-term intakes of up to 25 μ g daily should be safe for the general population, but doses exceeding this might need to be given under medical supervision.¹

Interactions

A number of interactions are possible with vitamin D. Barbiturates and other anticonvulsants induce cytochrome P450, resulting in increased catabolism of 25-(OH)D and hence drug-induced osteomalacia. Isoniazid inhibits the hydroxylation of vitamin D in the liver and again prolonged administration can lead to the development of osteomalacia. Preliminary evidence suggests that vitamin D is effective in the treatment of drug-induced osteomalacia and that ergocalciferol may be the most effective form in the restoration of bone in patients on anticonvulsant treatment.²

Drugs such as colestyramine, colestipol, orlistat and liquid paraffin may compromise the absorption of vitamins D and other fat-soluble vitamins. If a supplement is given, doses of the drug and the vitamin should be separated by at least two hours.

In high doses, corticosteroids directly inhibit the vitamin D-mediated uptake of calcium in the gastrointestinal tract and may deplete levels of active vitamin D. Vitamin D may indirectly antagonise the effects of calcium-channel blockers by increasing the absorption of calcium. A patient whose atrial fibrillation had been successfully treated with verapamil began taking calcium and high dose vitamin D, but the atrial fibrillation reappeared, requiring management with intravenous verapamil.³

Current issues and controversies

There is growing evidence that vitamin D insufficiency is involved in the development of a number of other conditions, including osteoporosis, poor muscle function, cancer, cardiovascular disease, diabetes mellitus, multiple sclerosis, rheumatoid arthritis and other autoimmune conditions.

Osteoporosis Optimum calcium and vitamin D status throughout life is important for bone health but, until recent years, only calcium has attracted significant attention for influencing the risk of osteoporosis. In some, but not all studies, high or supplemented dietary intake of calcium is associated with lowered risk of hip and appendicular fractures, but vitamin D is also important. People with osteoporosis and history of fracture show a high prevalence of vitamin D insufficiency. At latitudes between 35 and 60 de-



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Rickets was thought to have been a disease of the past but has recently re-emerged in the UK

grees, hip fracture incidence is greater in the winter months. This may be associated with seasonal variation in vitamin D and PTH levels. A single injection of vitamin D given at the onset of winter will prevent the seasonal increase in PTH concentrations.

Trials investigating the influence of vitamin D supplementation on fracture incidence have shown mixed results, probably due to differences in study populations, their risk of vitamin D deficiency and risk of fracture and doses of vitamin D. However, a recent meta-analysis of four randomised controlled trials (RCTs) each of which used a dose of 20µg vitamin D (800IU) daily found that this dose prevents approximately 30 per cent of hip or non-vertebral fractures compared with placebo in adults over the age of 65 years and concluded that lower intakes are not effective.⁴ Another recent meta-analysis, which included five RCTs for hip fracture and seven for non-vertebral fracture risk, concluded that oral vitamin D supplementation between 700 and 800IU daily appears to reduce the risk of hip and any non-vertebral fractures in ambulatory or institutionalised elderly persons but that an oral vitamin D dose of 400IU/day is not effective.⁵ Indeed, a trial published after this meta-analysis found that a calcium dose of 1,000mg daily with vitamin D 400 IU did not significantly reduce hip fracture.⁶ However, a trial in a primary care setting involving 3,314 women aged over 70 years with one or more risk factors for hip fracture found that calcium 1,000mg daily and vitamin D 800IU did not reduce the risk of clinical fractures overall.⁷

Whether vitamin D or vitamin D analogues have a different effect on fracture incidence is unclear. A meta-analysis found that the vitamin D analogues, alfacalcidol and cal-

People who may require vitamin D supplementation

The following groups are at risk of deficiency and may require vitamin D supplementation:

- **Infants who are exclusively breastfed** In infants, vitamin D requirements cannot be met by breast milk alone, particularly after the age of six months and if there is poor exposure to sunlight. The Department of Health recommends a paediatric supplement containing vitamins A, C and D from the age of six months to five years, unless a good diet can be assured.
- **Older people** As people age, the skin cannot synthesise vitamin D as efficiently and the kidneys may be less able to convert vitamin D to its active form. Concentrations of plasma 25-(OH)D below 25nmol/L, which is low enough to cause osteomalacia to develop, have been demonstrated in older people in the UK during the winter months. In the US, it has been estimated that as much as 30–40 per cent of older adults with hip fracture have inadequate vitamin D status. There is particular concern about vitamin D status in the institutionalised elderly, but all older adults may benefit from supplementation.
- **People with dark skin** The high melanin content in dark skin appears to reduce the skin's ability to produce vitamin D. Individuals in the UK who have dark skins, who get low sun exposure and who do not get enough vitamin D from the diet may benefit from a supplement.
- **People with fat malabsorption** Absorption of vitamin D requires some fat so people with fat malabsorption (eg, pancreatic enzyme deficiency, Crohn's disease, cystic fibrosis, coeliac disease, short bowel) may require vitamin D supplements.
- **People who are obese** Obesity is often associated with vitamin D deficiency. This occurs because vitamin D — whether dietary or from sunlight — is efficiently deposited in the large body fat stores and is not bioavailable.

citriol, were better than plain vitamin D in preventing spinal fractures.⁸ A Cochrane review found no evidence for this and also concluded that vitamin D alone had no significant effect on hip fracture, vertebral fracture or any new fracture, while vitamin D given with calcium was associated with fewer hip and other non-vertebral fractures.⁹ The anti-fracture effect of vitamin D and calcium is likely to be due to their effect on bone mineral density, although again the results of RCTs are inconsistent.

Vitamin D may also improve neuromuscular co-ordination, preserve muscle function and, as a consequence, decrease the risk of falling and falls-related fractures. A meta-analysis of five RCTs involving 1,237 participants found that vitamin D reduced the risk of falls among both ambulatory and institutionalised older people by 20 per cent.¹⁰ A trial published more recently found that supplementation with both colecalciferol (700IU daily) and calcium (500mg daily) over a three-year period reduced the risk of falling in ambulatory older women by 46 per cent and in less active women by 65 per cent, but supplements had no effect in men.¹¹

Cancer Evidence from epidemiological studies suggests that enhanced exposure to sunlight is associated with reduced death rates from certain common cancers, including cancer of the colon, breast, prostate and ovary.^{12,13} Prospective studies show relative risks for colon cancer of 0.33 to 0.74 with higher vita-

min D intake or concentrations of 25-(OH)D above 65nmol/L. Supplemental vitamin D and calcium has been associated with reduced recurrence of colorectal adenomas, although the association was weak.¹⁴ However, an RCT involving 36,282 postmenopausal women found that daily supplementation for seven years with calcium 1,000mg daily and vitamin D 400IU daily had no effect on the incidence of colorectal cancer.¹⁵ Prostate cancer risk has been found to be higher in men with low serum 25-(OH)D concentrations, but this protective role seems to be strongest in younger men in whom serum androgen levels are higher.¹⁶ A recent prospective study in men found an inverse association between low vitamin D levels and risk of total cancer and mortality, particularly for cancers of the digestive system.¹⁷

Cardiovascular disease and diabetes

Epidemiological studies have demonstrated a weak inverse relationship between serum 25-(OH)D levels and blood pressure while some clinical trials have shown that administration of vitamin D, or 1- α vitamin D, or exposure to UVB radiation can reduce blood pressure in people with hypertension. There is also evidence that poor vitamin D status is associated with high concentrations of various inflammatory markers (eg, tumour necrosis factor and interleukin-6) which contribute to the development of atherosclerosis, and that vitamin D supplementation can improve the profile of these markers.¹⁸ Reduced vitamin D status is also associated with a higher incidence of both type 1 and type 2 diabetes mellitus, insulin resistance, low insulin concentrations and, in some studies, high blood glucose levels.

Miscellaneous Vitamin D has an important role in the immune system. There is growing evidence for an involvement of vitamin D in infections, particularly in tuberculosis, and also in various autoimmune and inflammatory conditions, such as rheumatoid arthritis, multiple sclerosis and inflammatory bowel diseases, including ulcerative colitis and Crohn's disease. Vitamin D supplementation has been shown to improve symptoms of rheumatoid arthritis and multiple sclerosis.

Vitamin D has an important role in the immune system

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Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

- Discuss this article with another pharmacist.
- Make your staff aware of the products in your pharmacy that contain vitamin D.
- Make a list of people whom you think might benefit from vitamin D supplementation.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?