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Vitamin D

A review

Background
Vitamin D status affects musculoskeletal health. More recently, the nonmusculoskeletal actions of vitamin D have become increasingly documented including endocrine effect on kidneys and intestine, local autocrine effects on cell differentiation, proliferation and immune modulation, and cell membrane effects including promotion of the intestinal absorption of calcium and the secretion of insulin.

Objective
This article discusses the actions, sources and measurement of vitamin D, and the treatment of established deficiency. It explores what is known about vitamin D, what remains to be discovered, and how clinicians should manage their patients in the interim.

Discussion
Vitamin D is produced by the same solar radiation that causes skin cancer and aging. Levels in breast milk are low in vitamin depleted breastfeeding women. Despite these realities, there is an opportunity to use existing public health messages to treat the widespread deficiency of vitamin D.

Historically, vitamin D denoted a constituent of cod liver oil, which cured rickets.[1] It also prevented rickets in children and osteomalacia in adults. More recently, other actions of vitamin D have been discovered in addition to its crucial role in calcium homeostasis.

Most body tissues have receptors for $1,25[OH]_2$ vitamin D (calcitriol, $1,25[OH]_2D$). Vitamin D is produced in the skin or ingested. After hepatic hydroxylation, 25[OH] vitamin D (calcidiol, 25[OH]D) is further hydroxylated in the kidneys to $1,25[OH]_2D$ to exert its endocrine effect on bone, kidneys and intestine.

This activated form acts at the cell nucleus (gene upregulation) and cell membrane (rapid response) in over 30 tissues and organs,[2] targeting over 200 genes.[3] Examples of gene upregulation include the above endocrine actions and additional paracrine actions when tissues, under cytokine control, locally hydroxylate 25[OH]D to $1,25[OH]_2D$ to modulate immune function, cell proliferation and cell differentiation.[4,5]

Rapid response actions of vitamin D include promoting the intestinal absorption of calcium, the secretion of insulin, the rapid migration of endothelial cells and some osteoblast cell functions.[2]

The importance of vitamin D

Vitamin D is important for muscle and bone health. A prospective population based study in the Netherlands showed increased loss of muscle strength and mass with aging in those with low vitamin D levels.[6] Vitamin D deficiency is associated with cortical bone loss,[1] increased bone turnover,[7] and increased parathyroid hormone levels,[5] predisposing to osteoporosis.[8] Vitamin D supplementation increases bone density in established deficiency.[9] A study in the United Kingdom found vitamin D reduced the risk of fracture in a prospective, randomised, double blinded community based trial.[10] An interventional study in Saudi Arabia found a 95% improvement in symptoms related to idiopathic low back pain following treatment with vitamin D.[11]

Vitamin D deficiency has associations with:

- cardiovascular disease[12]
- insulin resistance and β-cell dysfunction[13,14]

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Table 1. Adequate daily dietary intake of vitamin D by age

Age	Adequate dietary intake[20]	Supplementation recommended?[20]	Regular sunlight sufficient?#
0–12 months	200 IU		Yes
1–18 years	400 IU		Yes
19–50 years	200 IU		Possibly
51–70 years	400 IU		Possibly not
>70 years	600 IU		Probably not
Institutionalised or housebound elderly		Yes, 400–1000 IU	No, consider screening
Pregnant women	200 IU		Consider screening
Pregnant women, limited sunlight	400 IU		Consider screening
Lactating women	200 IU	Consider supplementation*	Yes, but consider screening*
Breastfed child	200 IU		Yes
Breastfed child at risk (mother dark skinned and/or veiled)		Yes, 400 IU for first 12 months	Possibly not

* Further supplementation may be considered to increase vitamin D content in milk[33]
# Indicates whether regular sufficient sun exposure is likely to be adequate to maintain vitamin D levels

- the development of autoimmune disease (including type 1 diabetes, rheumatoid arthritis and multiple sclerosis), and
- colon, breast and prostate cancers.[4,15]

There is experimental evidence in animals that fetal deprivation produced (permanent) neurodevelopmental change[16] and in vitro evidence that certain human antimicrobial responses are vitamin D dependent.[17] Additionally, a prospective interventional study noted increased mood with vitamin D supplementation,[18] and a prospective randomised trial noted a reduced nonskin cancer risk with vitamin D supplementation.[19] These associations and results merit further research.

Sources of vitamin D

Vitamin D is found in two forms: vitamin D_3 – c(h)olecalciferol, occurring in humans and animals; and vitamin D_2 – ergocalciferol, occurring in plants. Both forms have been commercially synthesised.

Dietary sources

Food sources include:

- fatty fish (eg. herring, mackerel, sardines, tuna, salmon)
- eggs, and
- fortified foods.

Mandatory fortification of margarine and edible oil spreads occurs in Australia. Voluntary fortification of other foods also occurs, however, overall, dietary intake of vitamin D is low. Adequate intake of vitamin D is unlikely to be achieved purely through dietary means, particularly in those at high risk.

Table 1 summarises the recommended daily intake of vitamin D. Upper levels of dietary intake are currently 1000 IU/day for infants (0–12 months) and 3200 IU/day for all other ages and for pregnant or lactating women.[20]

Sunlight exposure

The main source of vitamin D is exposure to sunlight. Approximately 90% of vitamin D is obtained this way and most Australians receive their vitamin D requirements from the sun. At comparible latitudes, higher UV levels have been found in the southern hemisphere.[20] In many people, adequate sunlight exposure will maintain adequate 25(OH)D serum levels. The skin uses ultraviolet B (UVB) light (280–315 nm wavelength) to form previtamin D_3 from 7-dehydrocholesterol (the immediate precursor of cholesterol). Previtamin D_3 changes in the skin to vitamin D_3, which has a serum half life of 2–3 weeks. Vitamin D_3 production in the skin is limited to 10 000–20 000 IU/day.[3] Serum levels of 25[OH]D plateau at about 150 nmol/L as UVB inactivates the excess cutaneous previtamin and vitamin.[21] Vitamin D binding protein transports vitamin D, the active hormone and its metabolites in the circulation.

Skin production of vitamin D depends on:

- the amount of UVB energy (eg. latitude, season, time of day, cloud cover)
- amount of skin exposed
- duration of exposure, and
- skin type.

Certain medications can increase or decrease 25[OH]D metabolism.[22,23]

Ultraviolet light also produces skin erythema, sunburn (increasing melanoma risk), and cumulatively, skin aging and increased nonmelanoma skin cancer risk. It is therefore important to give nonconflicting public health messages as we promote healthy behaviours (eg. skin protection, regular physical activity, breastfeeding) and targets (eg. adequate vitamin D levels). For incidental sun exposure (less than half the time required to produce minimal skin erythema) it may be reasonable to omit sunscreen.[9] Sunscreen sun protection factor 15 (adequately applied) reduces previtamin D synthesis by >99%.[4] Guidelines for adequate sun exposure in Australia are summarised in *Table 2*.

Serum 25[OH]D levels show seasonal fluctuation, with peaks and troughs at the end of summer and winter respectively. At latitudes greater than 35 degrees, UVB energy is insufficient to produce vitamin D during the winter months,[4] producing a 'vitamin D winter' of variable duration, centered on the winter solstice.[3] During these times of no cutaneous vitamin D production, dietary intake of vitamin D and previous vitamin stores become important.

Vitamin D deficiency

Low 25(OH)D levels are termed 'hypovitaminosis D'.[1] When combined with pathological abnormalities which are corrected by physiological doses of vitamin D, the term 'vitamin D deficiency' is used. Significantly low 25(OH)D levels can be termed 'deficiency' because of the known abnormal metabolic effects of low vitamin D levels. Rarer conditions exist which require pharmacological doses of vitamin D to overcome either reduced renal 1α-hydroxylase activity or vitamin D receptor resistance. Vitamin D deficiency can be classified as:

- mild (25–50 nmol/L)
- moderate (12.5–25.0 nmol/L), and
- severe (<12.5 nmol/L)

with levels of 50–100 nmol/L thought of as being vitamin D insufficient.

Screening

People at risk of significant deficiency include:

- the institutionalised or housebound[9]
- those with sun avoidant behaviour
- refugees[24]
- those with coeliac disease[25] (or other malabsorbtive conditions)
- those from areas of high vitamin D deficiency prevalence
- those in whom osteoporosis therapy is considered
- those with chronic idiopathic musculoskeletal pain, and
- pregnant women (particularly if dark skinned or veiled).[26]

The type of assay is important with different methods giving differing results, particularly at higher serum levels. Liquid chromatography is the criterion standard.[15]

Treatment

The current recommended daily intake of vitamin D is adequate for bone health. Our total requirement for vitamin D (sun exposure and dietary intake) is about 4000 IU/day to keep 25(OH)D levels above 100 nmol/L.[27]

The tolerable upper limit of ingested vitamin D for adults will depend on sun exposure and is currently being debated.[28–30] The tolerable upper limit might be as high as 10 000 IU/day, however current recommendations are significantly lower (*Table 1*). The level of 25[OH]D causing toxicity in healthy adults is also debated but probably occurs at levels >500 nmol/L.[28,30] Hypercalciuria occurs before hypercalcemia.[1]

In Australia, megadose administrations of vitamin D_3 have been described,[8] including 100 000 IU orally every 4 months[10] and 600 000 IU intramuscularly once per year.[31] Serum 25[OH]D levels for vitamin D associated with health benefit are listed in *Table 3*.

Treating deficiency involves correcting the vitamin D deficit and ensuring continuing maintenance of vitamin D status. To normalise stores:

- adults require 3000–5000 IU/per day for 6–12 weeks[9]
- children aged <1 month require 1000 IU/day

Table 2. Sun exposure guidelines

Region	October to March		April to September	
	At 12:00	At 10:00 or 15:00	At 12:00	At 10:00 or 15:00
North (Townsville and Cairns)	2–5 minutes with extreme care	10 minutes with care	3–10 minutes with care	16 minutes with care
Central (Brisbane and Perth)	2–6 minutes with extreme care	~10 minutes with care	4–17 minutes with care	14–44 minutes with care or extreme care in Brisbane
South (Adelaide, Sydney, Melbourne, Hobart*)	2–10 minutes with extreme care	15 minutes with extreme care	5–34 minutes with care	21–60 minutes with care

Recommended solar radiation exposure to 15% of the body (face, hands, arms) at various times of the day and in various regions of Australia for fair skinned people to produce vitamin D levels equivalent to current recommended daily intakes, assuming exposure occurs 3–4 times per week. Such exposures will give one-third minimal erythema dose, and assumes average solar radiation intensity

Fair skinned = Fitzpatrick type II skin; care = sun protection is recommended if exposure is likely to exceed maximum recommended time; extreme care = sun protection is highly recommended, as erythema can occur soon after maximum exposure time is exceeded

* Exposure times will be higher in Hobart (see citation for further details)

Adapted from: Samanek AJ, Croager EJ, Gies P, et al. Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres. Med J Aust 2006;184:338–41

Table 3. Levels of 25(OH)D producing health benefit

Beneficial effects of vitamin D	Minimum serum 25(OH)D required
Prevent rickets/osteomalacia[3]	37.5 nmol/L
Dramatically suppress parathyroid hormone levels[3]	50–75 nmol/L
Optimise intestinal calcium absorption[3]	87 nmol/L
Optimise neuromuscular function[3,5]	60–87 nmol/L
Produce sufficient breast milk concentrations for infant health[33]	110 nmol/L (in one study)
Treatment of chronic musculoskeletal pain[11]	Treat identified deficiency
Suggested general target[15]	>100 nmol/L year round

- children aged 1–12 months require 3000 IU/day, and
- children aged >12 months require 5000 IU/day.[26]

Treatment is for 3 months, with adequate daily calcium.

An alternative of 1000 IU, three capsules/tablets three times per day for 1 week then one capsule/tablet per day thereafter, with check of serum 25[OH]D in 5 weeks and attention to adequate calcium intake has been suggested.[32]

In practice, given the multiple interacting factors, it is appropriate to treat vitamin D deficiency in adults with 2–3 months of supplementation, checking the 25[OH] level and if satisfactory, rechecking the level at the end of winter to ensure the trough is >100 nmol/L.[3] The optimal interval between retesting has not been established.

Future research

The extent to which initial interventional studies, epidemiological associations and experimental studies are replicated will affect future recommended vitamin D intake levels. The use of vitamin D as therapy in infection, cancer and cell regulation is being increasingly explored. The effect of vitamin D on mood and neurodevelopment and in primary cancer prevention is also being studied.

Conflict of interest: none declared.

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