Vitamin D Expert Review Cancer Research UK

Introduction

Vitamin D is an essential nutrient that maintains the body's levels of calcium within a normal range, working together with parathyroid hormone and calcitonin. It regulates the efficiency of calcium absorption in the small intestine, promotes the mobilisation of calcium from the skeleton and increases its reabsorption in the kidneys. Low levels of 25(OH)D are clearly associated with secondary hyperparathyroidism and low bone mineral density and, thus, a higher risk of fractures. Prolonged deficiency leads to rickets in infants and children and osteomalacia in adults. It is also associated with osteoporosis and hip fractures.

Vitamin D is produced naturally when our skin is exposed to ultraviolet B (UVB) radiation from the sun. UVB converts 7-dehydrocholesterol precursors into previtamin D_3, which spontaneously changes to vitamin D_3. Vitamin D_3 is converted via two hydroxylation reactions into 25-hydroxyvitamin D_3 (25(OH)D) and its final active form, 1,25-dihydroxyvitamin D_3 (1,25(OH)D).[1] The level of 25(OH)D in the blood is the most reliable indicator of vitamin D status.

Vitamin D requirements

There is consensus that levels below 25nmol/L (10ng/ml) qualify as 'deficient',[2, 3] but beyond this there is currently no standard definition of 'optimal' 25(OH)D levels.[4] Some sources suggest that levels above 50nmol/L (30ng/ml) are 'sufficient', while 70–80nmol/L (28-32ng/ml) is 'optimal'.[2, 5, 6]

However, raising the definition of "deficiency" or "sufficiency" is currently inappropriate since no results from randomised trials suggest that maintaining such levels of 25(OH)D prevents chronic diseases. It is also unclear whether these levels are practical for all individuals. The production of previtamin D_3 to vitamin D_3 in the skin is tightly regulated, and both compounds can be converted into inert products so that prolonged exposure to UV does not lead to excess amounts. Various studies have found that 25(OH)D levels plateau at around 70-80 nmol/L after UV exposure, with wide variation across individuals.[7, 8] For example, a Hawaiian study found that half of healthy, young surfers had levels below 75nmol/L despite extensive unprotected outdoor exposure and tanned complexions.[8]

For the general population, the Department of Health has set dietary recommendations for people under the age of 4, those over the age of 64, and pregnant or lactating women. It also recommends that people at risk of low sun exposure should get 10 µg of vitamin D a day, mostly through supplements.[3] The National Institute for Health and Clinical Excellence (NICE) also emphasises the importance of maintaining adequate vitamin D during pregnancy and breastfeeding, and suggests that women may choose to take up to 10 µg of vitamin D a day during these periods.[9]

Factors affecting vitamin D levels and groups at high risk of vitamin D deficiency

The amount of UVB in sunlight changes substantially with season, latitude and time of day.[10] These factors greatly affect vitamin D production, which is greatest around two hours either side of solar noon, and during summer months. According to one study, during the summer and autumn, 3%, 15% and 61% of British adults have 25(OH)D levels under 25, 40 and 75 nmol/L respectively.[11] During the winter and spring, those proportions rise to 16%, 47% and 87% respectively.

Physical characteristics also affect vitamin D production, with darker skin requiring longer UV exposures to produce the same amount of vitamin D.[12, 13] Elderly people have a reduced ability to make vitamin D through their skin, due to falling levels of the 7-dehydroxycholesterol precursors.[14] Obese people have lower 25(OH)D levels, which may be due to less sun exposure or greater storage of vitamin D by fat tissue.[15]

Certain groups of people have a higher risk of vitamin D deficiency including those with darker skin,[12, 13] those who wear whole-body coverings,[16, 17] elderly people,[14] pregnant women,[18] infants born to vitamin D-deficient mothers, obese people,[15] skin cancer patients, and those who avoid the sun.[19]

Some studies have found that sunscreen use reduces vitamin D production.[20] However, sunscreens do not provide complete protection against UVB and there is great variation in the way people use these products. Based on studies and trials that reflect actual sun exposure habits, it is unlikely that these products contribute significantly to vitamin D deficiency.[21, 22]

Sun exposure

Exposure to UVB radiation in sunlight is the most efficient way to boost vitamin D supply but it is still unclear how much sunlight is required to produce a given level of 25(OH)D. Environmental and personal factors greatly affect vitamin D production in the skin (see above), making it impossible to recommend a one-size-fits-all level of exposure for the general population.

However, the best estimates suggest that for most people, everyday casual exposure to sunlight is enough to produce vitamin D in the summer months, provided optimal environmental conditions, such as lack of cloud cover.[23, 24] The area of skin exposed will also influence the amount of vitamin D made after sun exposure.[25] In a recent study, white British people were given a simulated dose of a summer exposure to sunlight, while dressed in casual summer clothes that revealed a third of their skin. Under these controlled conditions, the equivalent of 13 minutes of midday exposure to the summer sun, three times a week for six weeks during winter, raised 25(OH)D levels to greater than 50 nmol/L in 90% of people but to greater than 70 nmol/L in only 26% of people.[26] The true amount of time may be greater and will vary depending on other factors including skin type, posture, time of day, outdoor activities, atmospheric conditions, and the presence of shading structures.

It has been consistently shown that vitamin D can be efficiently and sufficiently produced at doses of UV below those which cause reddening of the skin or sunburn.[20, 24, 26-31] After prolonged UV exposure, vitamin D is converted into inert substances in the skin.[10, 32] Thus, additional UV exposure provides no additional vitamin D but linearly increases levels of DNA damage and risk of skin cancer. Some short, unprotected exposure in the hours close to solar noon may be necessary,[33] but the specific recommendations about time are impractical due to the many confounding factors. As an example, Holick calculated that suberythemal (before the point of sunburn) doses of sunlight to the hands, arms, and face between the hours of 10am and 3pm for approximately 5-15 minutes two to three times per week can satisfy the vitamin D requirements of a Caucasian person with skin type II living at approximately 42N in June on a clear day.[23] However, long exposures increase the risk of sunburn and skin cancer, without concomitantly providing extra benefits through vitamin D. When it comes to sun exposure, little and often is best.[26, 33]

During winter months in the UK, there is not enough UVB for vitamin D synthesis and people rely on tissues stores, supplements and dietary sources.[10] If people achieve sufficient circulating levels of vitamin D in the summer, supplementation, and possibly dietary sources, can maintain these levels in the winter. [34-36]

Dietary sources

Vitamin D is found in only a few foods, with fatty fish and fish oils, liver, meat and eggs being the main natural sources. In the UK, processed and some powdered milks, margarine, and breakfast cereals are often fortified with vitamin D.

The potential contribution of diet to vitamin D supply is a topic of debate. Widely quoted estimates suggest that more than 90% of vitamin D requirements come from exposure to sunlight.[37] The International Agency for Research into Cancer (IARC) concluded that results do not support this,

noting that many studies have found that use of vitamin D supplements and oily fish consumption correlate as well with vitamin D levels as well as outdoor activities, holidays in sunny areas and sunbed use.[38] Even people with genetic disorders that necessitate sun avoidance can maintain sufficient vitamin D levels through diet alone, without supplementation.[39]

However, the D-FINES study (currently unpublished) concluded that dietary vitamin D intake currently makes little contribution to the 25(OH)D status of British Caucasians and Asians, and that too few foods provide a valuable source**.** Dietary sources can certainly contribute to vitamin D status, but on their own, they are unlikely to sufficiently raise levels of 25(OH)D in people who experience deficiency.

Supplements

Vitamin D is present in a range of dietary supplements (including fish oil products) and licensed medicines, which typically come in doses of 5 or 10µg.[34] A study commissioned by the FSA concluded that it takes 9 micrograms/day of supplements for the vast majority of the population to achieve 25(OH)D levels greater than 25 nmol/L in the winter. To achieve levels greater than 50 nmol/L and 80 nmol/L, it takes 28µg/day (1100 IU) and 41 µg/day (1600 IU) of supplements respectively.[40] This supports earlier work that suggested 55 µg/day were necessary to increase 25(OH)D levels from 20-40 nmol/L to 80 nmol/L.[34]

Supplements may be warranted for groups with high-risk of vitamin D deficiency and the Department of Health already recommends that people at risk of low sunlight exposure should take 10 micrograms of vitamin D supplements per day. Supplements that contain only vitamin D are preferable over multivitamins, since other trials have shown that most vitamin supplements are ineffective for cancer prevention, and some can increase the risk of cancer.[41] Supplements that contain vitamin A, including cod liver oil, are unsuitable for older people or pregnant women.

Our bodies avoid building up toxic levels of vitamin D, leading to hypercalcaemia, by limiting the amount that is produced in the skin in response to UV light.[42] Vitamin D taken through supplements is not subject to the same controls that regulate vitamin D production in response to UV light. As such, it is premature to recommend vitamin D supplements for the general population. In Europe and the USA, safe upper limits are set at 25 µg/day (1,000 IU) for children and 50 µg/day (2,000 IU) for adults, although these levels are controversial, given that some studies have only documented vitamin D toxicity and hypercalcaemia at far higher doses of greater than 1,000 µg/day.

There is little evidence that long-term supplementation between 10-25 µg per day would be harmful and, indeed, a meta-analysis of randomised trials in elderly people with low vitamin D status found that daily supplementation of 10-20 µg (400-800 IU) led to a 7% lower risk of all-cause mortality.[43] However, there is a lack of evidence about the possible risks of chronically raising levels of vitamin D in healthy people through supplementation.[38] Studies like NHANES III suggest that high levels of vitamin D beyond the threshold of 75nmol/L could be associated with adverse effects, including increased all-cause mortality and incidence of cardiovascular diseases.[44] Past experience has also shown that high-dose supplements of other micronutrients have led to increased risk of cancer, despite promising early studies.

Vitamin D and the risk of diseases

It is clear that vitamin D is essential for bone health and prevention of diseases such as rickets, osteomalacia and osteoporosis. However, some studies have suggested that low vitamin D levels are associated with a variety of other chronic diseases, including several cancers, multiple sclerosis, heart disease and diabetes, as well as overall all-cause mortality.[44] These links are still inconclusive and causal relationships cannot be drawn from existing evidence.

Levels of 25(OH)D in the blood are the only reliable indicators of vitamin D status,[45] and common proxies such as latitude and average solar irradiance are comparatively poor markers.[46] IARC recently concluded that low vitamin D levels are linked to a higher risk of bowel cancer, but the evidence is limited for breast cancer, non-existent for prostate cancer and too sparse for all other cancer types to draw firm conclusions.[38] These results are consistent with other meta-analyses and systematic reviews.[47-51] Even where bowel cancer is concerned, it is unclear if a lack of vitamin D causes an increased risk of cancer, or is simply a consequence of poor health or bowel malfunction. Two clinical trials have assessed the effects of vitamin D supplementation on cancer risk. Both showed that such supplements are ineffective at reducing the risk of cancer (over and above calcium supplementation),[52, 53] but both have been criticised for methodological weaknesses.[38] Further trials are needed.

Much of the support for a protective role of vitamin D against cancer comes from laboratory, animal and ecological studies.[54] Ecological studies report that several cancers are more common at higher latitude, which is taken as a proxy for lower UV exposure and lower vitamin D levels.[55, 56] However, this approach is prone to confounding by other factors such as socioeconomic status and skin type and it does not account for variations in individual behaviour, which are stronger predictors of UV exposure than latitude.[57-59] In Europe, vitamin D levels actually tend to be higher as latitude increases.[38]

Sunbeds

Sunbeds do not grant protection against vitamin D deficiency.[38] Sunbed use is accompanied by a high frequency of sunburns, which are linked to a higher risk of melanoma.[60] While sunbed exposures can increase vitamin D levels, these benefits plateau rapidly and are outweighed by the risks. Sunbeds also emit high levels of UVA, which can cause melanoma but do not contribute to vitamin D production.[61]

Conclusion

Everyone needs vitamin D, which is essential for good bone health. The consensus is that levels of 25(OH)D below 25nmol/L qualify as 'deficient' and there is currently no standard definition of an 'optimal' level of vitamin D. Low levels are clearly linked to bone conditions such as rickets and osteoporosis although evidence of a causal link to cancer, heart disease, diabetes, multiple sclerosis and other chronic diseases is still inconclusive.

Sun exposure is the most important source of vitamin D. The many factors that affect vitamin D production make it impractical to offer a one-size-fits-all sun exposure recommendation, but the time required to make sufficient amounts is typically short and suberythemal. Regularly going outside for a matter of minutes around the middle of the day without sunscreen, while taking care to avoid sunburn, should be enough to provide the benefits of vitamin D without unduly raising the risk of skin cancer.

It is premature to recommend widespread vitamin D supplementation or food fortification for the general population, given the lack of evidence around possible risks of raising levels of vitamin D in healthy people for a long time. However, people at risk of vitamin D deficiency and low sun exposure are advised to maintain sufficient levels by taking 10 µg of supplements a day, or by eating dietary sources such as oily fish.

Further research

There are many questions around vitamin D that still need to be answered.

- What is the optimal level of 25(OH)D for various health outcomes?

- Can higher levels of 25(OH)D directly reduce the risk of cancer or other chronic diseases, and can supplementation achieve the same effects?
- How much sun exposure is needed to ensure optimal levels of vitamin D in people of different skin types and under different environmental conditions?
- What roles do dietary sources and supplements have in achieving optimal vitamin D levels, particularly in the winter?
- Are there any adverse consequences of chronically high levels of 25(OH)D, raised through supplementation or food fortification?
- Does body fat act as a sink or source of vitamin D in winter?

Declaration of Interests.

The primary author (Ed Yong) is an employee at Cancer Research UK and contribute to the SunSmart campaign. The organisation has a direct interest in the matter of vitamin D and has expressed public statements on this topic on our website.

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