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REVIEW

Vitamin D – The Vitamin Hormone

GL Muntingh

Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria.
Corresponding author, email george.muntingh@up.ac.za

Abstract

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. For most people sunlight is the most important source of vitamin D. The time required to make sufficient vitamin D varies according to a number of environmental, physical and personal factors, but is typically short and less than the amount of time needed to damage the skin e.g. reddening and burns. Enjoying the sun safely, while taking care not to burn, can help to provide the benefits of vitamin D without unduly raising the risk of skin cancer. Vitamin D supplements and specific foods can aid in maintaining sufficient levels of vitamin D, particularly in people at risk of deficiency. However, there is still a lot of uncertainty around what are "optimal" or "sufficient" levels, how much sunlight different people need to achieve a given level of vitamin D, and whether vitamin D protects against chronic diseases such as cancer, heart disease and diabetes, and the benefits and risks of widespread supplementation

Keywords: vitamin D, deficiency, chronic diseases

Introduction

> *"Whoever wishes to investigate medicine properly should proceed thus: in the first place to consider the seasons of the year.* ~ Hippocrates, the father of medicine (circa 400 B.C.)"[1]

The "sunshine" vitamin is a hot topic. It's shocking for most people when they have never had a problem before and believe nothing has changed to make it a problem now. The truth is that a lot has changed, and vitamin D deficiency and insufficiency is now a global public-health problem affecting an estimated 1 billion people worldwide.

The most well-known consequences of not having enough vitamin D are rickets in children and osteomalacia in adults. These are far from the only problems associated with a vitamin D deficiency. The consequences are numerous and include skeletal diseases, metabolic disorders, cancer, cardiovascular disease, autoimmune diseases, infections, cognitive disorders, and/or mortality. The majority of our knowledge about vitamin D has been gained over the past 15 years, and with the growing issue of deficiencies, more health connections with vitamin D levels are being made.[2]

Biological fate of Vitamin D

Vitamin D, although commonly known as a vitamin, is actually a hormone precursor that is present in 2 forms. Cholecalciferol, or vitamin D3, is synthesized in the skin by exposure to sunlight. Ergocalciferol, or vitamin D2, is present in plants, some fish and fortified foods. Humans can fulfil their vitamin D requirements by either ingesting vitamin D or being exposed to the sun for sifficient time to produce adequate amounts. In addition, recent epidemiologic studies have observed relationships between low vitamin D levels and multiple disease states, probably related to its anti-inflammatory and immune-modulating properties and possible effects on cytokine levels.[3]

Following its synthesis, vitamin D binds to vitamin D binding protein (VDBP) and finds its way into the circulation. Dietary and endogenous vitamin D appear to act similarly with half-lives between 12 and 24 h, depending on how quickly the liver converts vitamin D to 25-hydroxy-vitamin D (also known as calcidiol). Vitamin D is measured in international units (IU) or micrograms with a known conversion of 40 IU equal to 1 microgram.

While there appears to be a differential conversion rate of the two forms of vitamin D to 25(OH)D,[4] the conversion of either form is dependent on a functional liver and the activity of 25-hydroxylase. Thus, those with impaired liver function will have diminished conversion of vitamin D to 25(OH)D. Following its synthesis, 25(OH) then enters the circulation where it is tightly bound to Vitamin D Binding Protein (VDBP). Only a small amount of 25(OH)D is unbound or "free". The half-life of 25(OH)D is 2-3 weeks, making it a much better indicator of the body's vitamin D status than vitamin D.

Once 25(OH)D is formed in the liver, it enters the circulation. Best known is the processing of 25(OH)D by the kidney where

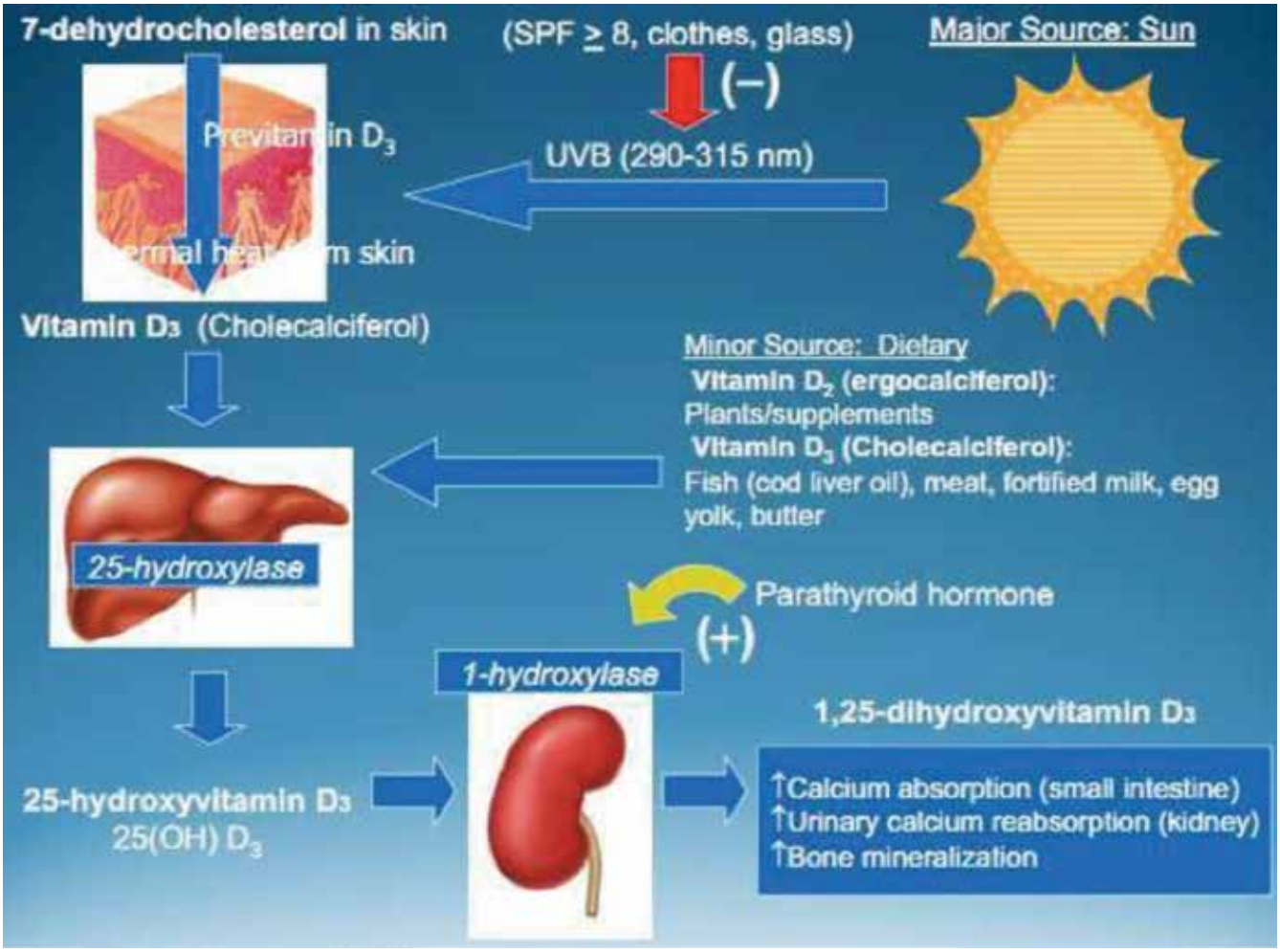

Figure 1: Biological fate of vitamin D

25(OH)D complexed with VDBP and megalin is taken up by the epithelial cells of the proximal tubules and converted to the active hormonal form of vitamin D, di-hydroxy-vitamin D (1,25(OH)2D or calcitriol)- by the action of the mitochondrial enzyme 1-a-hydroxylase (Fig 1).[5]

1,25(OH)2D's endocrine effects include the following classic triad of action: (1) increase intestinal calcium (as Ca2+ ions) absorption through the actions of calbindin; (2) increase urinary calcium reabsorption; and (3) regulation of parathyroid hormone in a negative feedback loop that allows calcium to be absorbed from the gastrointestinal tract, reabsorbed from urine, and metabolized from bone in order to maintain calcium homeostasis within the body. Because calcium is essential to all tissues and organs, particularly the heart, skeletal muscle and brain, the body will claim calcium if necessary from the skeleton. Adequate vitamin D must be on hand to provide enough substrate to form 25(OH)D, which in turn, is converted to 1,25(OH)2D, whose half-life is about 15 hours.

Common causes of vitamin D deficiency

Most people should be able to get all the vitamin D they need from sunlight, especially summer sun, and a healthy balanced diet. However, more and more of the population are exhibiting low levels of vitamin D.

Not getting enough sunlight is one reason some people suffer from vitamin D deficiency, putting them at risk of bone problems, including rickets in children and osteomalacia in adults.[6]

Vitamin D deficiency at-risk groups:

- Pregnant and breastfeeding women, especially teenagers and young women.
- Infants and children under 5 years of age.
- 65 year olds and over.
- People who have little or no exposure to the sun. This includes covering-up for cultural reasons; people who are housebound or who stay indoors for long periods of time.
- People with darker skin, such as African, African-Caribbean and South Asian origin. These groups are not able to make as much vitamin D as those with paler skin. Other causes are mentioned in Table 1.[7]

Vitamin D Receptor (VDR)

VDR is a member of the nuclear receptor superfamily, and it regulates numerous genes whose promoters contain vitamin D response elements. These genes are involved in regulatory processes of potential relevance to cardiovascular disease (CVD), including cell proliferation and differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, tissue mineralization, and cell adhesion.[8] VDRs have been found

Table 1. Other Causes of Vitamin D Deficiency

Causes	Example
Reduced skin synthesis	Sunscreen, skin pigment, season/latitude/ time of day, aging, skin grafts
Decreased absorption	Cystic fibrosis, celiac disease, Whipple disease, Crohn's disease, gastric bypass, medications that reduce cholesterol absorption
Increased sequestration	Obesity
Increased catabolism	Anticonvulsant, Decreased synthesis of 25-glucocorticoid, highly active antiretroviral treatment, and some immunosuppressants
Breastfeeding	
Decreased synthesis of 25-hydroxyvitamin D	Hepatic Failure
Increased urinary loss of 25-hydroxyvitamin D	Nephrotic proteinuria
Decreased synthesis of 1,25dihydroxyvitaminD	Chronic renal failure
Heritable disorders	Genetic mutations causing rickets, or vitamin D resistance
Acquired disorders	Tumour-induced osteomalacia, primary hyperparathyroidism, hyperthyroidism, granulomatous disorders such as sarcoidosis, tuberculosis, and some lymphomas
Insufficient diet e.g., vegetarian	Decreased intake of natural sources: animal-based, including fish and fish oils, egg yolks, cheese, fortified milk, and beef liver

in all the major cardiovascular cell types, including VSMC, EC, cardiomyocytes, most immune cells, and platelets.[9-13]

Vitamin D and osteoporosis

Osteoporosis is the most common metabolic bone disease in the world. A low vitamin D level is an established risk factor for osteoporosis. Inadequate serum vitamin D levels decrease the active trans-cellular absorption of calcium.

Although combination calcium and vitamin D supplementation is associated with higher bone mineral density and decreased incidence of hip fractures, the evidence for vitamin D supplementation alone is less clear. A recent evidence summary found that vitamin D supplementation at doses of more than 700 IU daily (plus calcium) prevented bone loss compared with placebo. However, vitamin D supplementation (300 to 400 IU daily) without calcium did not affect fractures.[14] A 2014 Cochrane review found unclear evidence that vitamin D alone affected hip, vertebral, or other fracture rates but supported the use of vitamin D with calcium in frail, elderly nursing home residents:[15]

- Vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people. Supplements of vitamin D and calcium may prevent hip or any type of fracture. There was a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium. This review found that there was no increased risk of death from taking calcium and vitamin D.

The Cochrane analysis looked at the role of vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. In the results, the authors note:

- There is high quality evidence that vitamin D alone, in the formats and doses tested, is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; risk ratio (RR) 1.12, 95% confidence intervals (CI) 0.98 to 1.29) or any new fracture (15 trials, 28,271 participants; RR 1.03, 95% CI 0.96 to 1.11).

- There is high quality evidence that vitamin D plus calcium results in a small reduction in hip fracture risk (nine trials, 49,853 participants; RR 0.84, 95% confidence interval (CI) 0.74 to 0.96; P value 0.01). In low-risk populations (residents in the community: with an estimated eight hip fractures per 1000 per year), this equates to one fewer hip fracture per 1000 older adults per year (95% CI 0 to 2). In high risk populations (residents in institutions: with an estimated 54 hip fractures per 1000 per year), this equates to nine fewer hip fractures per 1000 older adults per year (95% CI 2 to 14).

- There is high quality evidence that vitamin D plus calcium is associated with a statistically significant reduction in incidence of new non-vertebral fractures. However, there is only moderate quality evidence of an absence of a statistically significant preventive effect on clinical vertebral fractures. There is high quality evidence that vitamin D plus calcium reduces the risk of any type of fracture (10 trials, 49,976 participants; RR 0.95, 95% CI 0.90 to 0.99).

A subsequent meta-analysis of trials looking at vitamin D and fracture rates concurred that calcium was also necessary to effect a significant difference.[16]

The optimal intake of calcium and vitamin D is uncertain. Based on the meta-analyses discussed below, 1200 mg of calcium (total of diet and supplement) and 800 international units of vitamin D daily for most postmenopausal women with osteoporosis is suggested. Although the optimal intake (diet plus supplement) has not been clearly established in premenopausal women or in men with osteoporosis, 1000 mg of calcium (total of diet and supplement) and 600 IU of vitamin D daily are generally suggested.[17]

Vitamin D and falls among the elderly

Vitamin D status is increasingly recognized as an important factor in fall status among elderly patients. Several trials have demonstrated that vitamin D supplementation decreases the risk of falling. One proposed mechanism is that higher vitamin D levels are associated with improved muscle function.

A randomized, controlled trial from Australia evaluated women with at least one fall in the preceding 12 months and with a plasma 25-hyroxyvitamin D level < 24.0 ng/mL.[18] All women were given calcium 1000 mg per day and were randomized to receive either ergocalciferol 1000 IU per day or placebo. Women in the study group as a whole had fewer falls after 12 months, but this was not a significant difference (53% versus 62.9%; odds ratio,

0.66; 95% CI, 0.41–1.06). After correction for height difference in the 2 groups, the ergocalciferol group had a significantly lower risk of falling (odds ratio, 0.61; 95% CI, 0.37– 0.99).

A dose of 800 IU daily significantly reduced the risk of falling compared with a placebo in a dose- stratified analysis of the effect of 5 months of vitamin D supplementation on fall risk (72% lower incidence rate ratio; rate ratio, 0.28; 95% CI, 0.10 –0.75). Lower doses of vitamin D, however, did not significantly change the rate of fall incidence compared with placebo.[19]

A review of 12 randomized, controlled trials studying the effect of vitamin D supplementation on fall risk among both nursing home residents and community dwellers found a small benefit of supplementation on fall risk (odds ratio, 0.89; 95% CI, 0.80 – 0.99), an effect that was also shown in a review of randomized, controlled trials with strict inclusion criteria, which included 1237 men and women with a mean age of 70 years and supplementation for 2 months to 3 years. The pooled results showed a significant 22% decrease in fall risk among those treated with vitamin D versus placebo or calcium only. The number needed to treat from the pooled results was 15 to prevent 1 person from falling.[20] Assessing vitamin D levels in a population at high risk for falling and supplementing with 800 to 1000 IU daily of vitamin D should be a part of any fall prevention program.

The extreme dosing of vitamin D in this population should also be cautioned. In a study by Bischoff-Ferrari *et al.* it was found that although higher monthly doses of vitamin D were effective in reaching a threshold of at least 30 ng/mL of 25-hydroxyvitamin D, they had no benefit on lower extremity function and were associated with increased risk of falls compared with 24 000 IU.[21]

Vitamin D and cardiovascular involvement

Cardiovascular vitamin D receptors have been shown to be present in vascular smooth muscle, endothelium, and cardiomyocytes and may have an impact on cardiovascular disease. Observational studies have shown a relationship between low vitamin D levels and blood pressure, coronary artery calcification, and existing cardiovascular disease. A large cohort study that included more than 1700 participants from the Framingham offspring study looked at vitamin D levels and incident cardiovascular events.[8] During a period of 5 years, participants who had low 25(OH) D levels were more likely to experience cardiovascular events. The relationship remained significant among people with hypertension but not among those without hypertension.[22]

Some clinical studies have shown that high levels of 25(OH)D are associated with favourable lipid profiles.[23,24] However, these observations are subject to confounding, and a recent meta-analysis of 12 clinical trials (1346 participants) of the influence of vitamin D supplementation on lipid profiles showed little evidence of a beneficial effect. In a large population-based study (n=107811) using serial laboratory results, Ponda *et al* have also cast doubt on the impact of vitamin D on lipid levels. In a subgroup of 6260 subjects with vitamin D deficiency at baseline, and biochemical evidence of improved vitamin D status 4 to 26 weeks later (resulting from vitamin D2 supplementation), there was no improvement in lipid profile.[24]

Vitamin D and diabetes

Several cross-sectional studies have demonstrated a consistent relationship between vitamin D deficiency and diabetes mellitus. Recent studies in animal models and humans have suggested that vitamin D may also play a role in the homeostasis of glucose metabolism and the development of type 1 and type 2 diabetes mellitus (DM).

Several physiologic mechanisms have been proposed, including the effect of vitamin D on insulin secretion, the direct effect of calcium and vitamin D on insulin action, and the role of this hormone in cytokine regulation.[25,26,27]

In NHANES III, a 25(OH)D level in the first versus fourth quartile was associated with diabetes mellitus with an odds ratio of 1.73 (95% CI, 1.38–2.16). There is a negative correlation between insulin resistance and β cell function in individuals at risk of type 2 diabetes mellitus.[28] Longitudinal studies have also shown that higher baseline vitamin D status reduces the risk of incident diabetes mellitus.[29] Despite the experimental and human observational evidence implicating vitamin D in diabetes mellitus, interventional studies have been inconsistent or inconclusive.[30,31]

Vitamin D and its role in many other conditions have also been investigated for possible supplementary benefits and these include:

Depression

A Norwegian trial of overweight subjects showed that those receiving a high dose of vitamin D (20,000 or 40,000 IU weekly) had a significant improvement in depressive symptom scale scores after 1 year versus those receiving placebo. The result determines a correlation between vitamin D and the risk of depression.[32]

Cognitive impairment

In the Invecchiare in Chianti (InCHIANTI) Italian population-based study, low levels of vitamin D were associated with substantial cognitive decline in the elderly population studied during a 6-year period. Low levels of 25(OH)D may be especially harmful to executive functions, whereas memory and other cognitive domains may be relatively preserved.[33]

Parkinson's disease

Parkinson's disease is a major cause of disability in the elderly population. Unfortunately, risk factors for this disease are relatively unknown. Recently, it has been suggested that chronic inadequate vitamin D intake may play a significant role in the pathogenesis of Parkinson's disease. A cohort study based on the Mini-Finland Health Survey demonstrated that low vitamin D levels may predict the development of Parkinson's disease.[34]

Autoimmune diseases

Vitamin D deficiency can contribute to autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis, and autoimmune thyroid disease.[35]

A prospective study of Caucasian subjects found that those with the highest vitamin D concentrations had a 62% lower risk of developing MS versus those with the lowest concentrations.[36]

Influenza

Some evidence is now emerging that indicates that a vitamin D deficiency in the winter months may be the seasonal stimulus that triggers influenza outbreaks. In a Japanese randomized, controlled trial, children given a daily vitamin D supplement of 1200 IU had a 40% lower rate of influenza type A compared with those given placebo; there was no significant difference in rates of influenza type B.[37]

Age-related macular regeneration (AMD)

High vitamin D blood levels appear to be associated with a decreased risk for the development of early age-related macular degeneration (AMD) among women younger than 75 years. Among women younger than 75 years, there is a lower risk for early AMD with higher vitamin D levels, with a threshold effect at 15.22 ng/L serum 25 (OH)D.[38]

Testing for vitamin D deficiency

There are many causes of vitamin D deficiency, as listed in Table 1, and despite growing attention to this deficiency, there are no established guidelines to help clinicians decide which patients warrant screening laboratory testing. One approach is to consider serum testing in patients at high risk for vitamin D deficiency but treating without testing those at lower risk.

If electing to test vitamin D status, serum 25-hydroxyvitamin D is the accepted biomarker.[38] Al though 1,25-OH(D) is the active circulating form of vitamin D, measuring this level is not helpful because it is quickly and tightly regulated by the kidney. True deficiency would be evident only by measuring 25-OH(D). Of note, questions have been raised regarding the need for standardization of assays.[39] A large laboratory (Quest Diagnostics) recently reported the possibility of thousands of incorrect vitamin D level results.[40] Sunlight exposure questionnaires are imprecise and are not currently recommended.[41]

Controversy exists regarding the optimum level of serum 25-hydroxyvitamin D in a healthy population. Most experts agree that serum vitamin D levels <20 ng/mL represent deficiency. However, some experts recommend aiming for a higher minimum target level of 30 ng/mL of 25-hydroxyvitamin D in a healthy population. Vitamin D intoxication can occur when serum levels are greater than 150 ng/mL and the risk is relatively high because vitamin D is a fat-soluble vitamin and also because 25-(OH)D has a particularly long half-life ≈ 15 days. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness probably caused by the resultant hypercalcaemia. Of note, sun exposure alone cannot lead to vitamin D intoxication as excess vitamin D3 is destroyed by sunlight.

Conclusion

It appears that the number of people with vitamin D deficiency is on the increase; the importance of this hormone vitamin in health overall and in the prevention of disease is receiving increased research attention. Vitamin D deficiency can occur in any age group with certain groups at increased risk of deficiency. Very few foods contain vitamin D, therefore guidelines recommend supplementation of this vitamin at tolerable UL levels. It is suggested that serum 25-(OH)D level is measured as the initial diagnostic test in patients at risk for deficiency. In these patients, treatment with either vitamin D2 or vitamin D3 is recommended. More research on the non-calcaemic benefits of vitamin D is required before prescribing in other therapeutic areas.

References available on request.