An interesting D-lemma: what is all the excitement about vitamin D?

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Abstract

There has been a dramatic interest in the importance of vitamin D, "the sunshine vitamin", in the past few years with regard to its impact on various aspects of health and disease. Research into well-known skeletal effects, as well as extra-skeletal effects, has been overwhelming. At times it has been difficult to make informed clinical decisions regarding replacement, if needed at all. This article aims to provide the family practitioner with a summary of the most important clinical effects of vitamin D, as well as give guidelines on testing for possible deficiency and consideration of replacement thereof.

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Introduction

Extensive research over the past decade has led to major advances in our understanding of the importance of vitamin D in health and disease. A PubMed search, using the term "vitamin D", limited to English articles that have been published in the past five years, revealed over 10 000 results. This renewed interest may be attributed to large studies that confirm the high level of nutritional vitamin D deficiency worldwide, to observational studies and meta-analyses that show a strong association between vitamin D deficiency and various chronic diseases, as well as to new insights that have emerged regarding the autocrine, paracrine and nonhormonal functions of activated vitamin D in humans.[1] The above information explosion poses a challenge for clinicians. This article aims to provide a brief review of the issues that relate to vitamin D deficiency in the South African context.

Overview of vitamin D metabolism

Vitamin D exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). There are also numerous circulating metabolites in humans. Vitamin D3 is produced in the skin under the influence of ultraviolet light (80%), or can be obtained from the diet (fatty fish and egg yolks). Vitamin D2 is found in some plant sources and manufactured commercially by the irradiation of ergosterol produced by yeast.[2] Supplementation can either be with vitamin D2 or D3. Both forms can be stored in adipose tissue or can undergo hydroxylation in the liver, whereby 25-hydroxyvitamin D 25 (OH) vitamin D (calcidiol) [25(OH)D] is produced. This form is converted in the kidney (via 1α hydroxylase) to 1,25(OH)2 vitamin D (calcitriol), the biologically active form of vitamin D.

The vitamin D receptor is a nuclear receptor of the thyroid hormone receptor superfamily. All tissues in the body express the vitamin D receptor and can respond to circulating calcitriol.[3] Furthermore, it has been shown that many tissues, including the colon, pancreas, breast, prostate, immune system, macrophages, vascular endothelium, epidermis and placenta, possess the enzymes to produce 1,25(OH)2 vitamin D locally. This may explain why vitamin D appears to play an essential role in overall health.[3,4]

Measurement of vitamin D status

The 25(OH)D level best reflects the body's overall vitamin D status, as it is more stable than 1,25(OH)2 vitamin D, with a much longer half-life.[5] The level reflects both dietary intake and sunlight exposure, as well as converted vitamin D, previously stored in fat. However, 25(OH)D assays are not standardised at the present time. It is essential for the clinician to use method-specific reference ranges and carry out patient follow-up at the same laboratory.

Vitamin D deficiency

Currently, normal vitamin D status is defined as a 25(OH)D serum level of > 30 ng/ml (> 75 nmol/l). The World Health Organization previously defined (true) deficiency as levels below 10 ng/ml (< 25 nmol/l).[5] However, the lower limit of normal still remains a topic of much debate. More recently, the term "vitamin D insufficiency" has been introduced to describe suboptimal levels (typically between 10 and 30 ng/ml (25-75 nmol/l) of 25(OH)D associated with adverse outcomes[2,5] (Table I).

Various reviews have described functional measures that are used to evaluate the adequacy of vitamin D levels.[1,2]

Table I: Interpretation of 25-hydroxyvitamin D 25 (OH) vitamin D level

Normal status	> 30 ng/ml (75 nmol/l)
Vitamin D insufficiency	10-30 ng/ml 25-75 nmol/l
Vitamin D deficiency	< 10 ng/ml < 25 nmol/l

These include the 25(OH)D level at which there is maximal intestinal calcium reabsorption and no further increase in 1,25(OH)2 vitamin D levels with replacement and the level which maximally suppresses parathyroid hormone (PTH) secretion. The measurement of 25(OH)D is the most suitable indicator of vitamin D status.[2] In a South African study, it was found that PTH levels rose significantly once the 25(OH)D level dropped below 10 mg/ml (25 nmol/l), but that more than half these patients still had calcium levels in the normal range.[6]

There has been a substantial increase in the prevalence of vitamin D deficiency in the past few years, as demonstrated by population-based studies like the National Health and Nutrition Examination Survey (NHANES) in the USA, where 25-30% of the population had frank vitamin D deficiency.[1] This was noted across all age groups. Males and females were equally affected and non-Caucasoid populations were at the highest risk. Associated factors with this decline in vitamin D levels include a decrease in the intake of milk products, more liberal sunscreen use and sun avoidance, race, season, as well as the global increase in the prevalence of obesity.[1]

Diseases and outcomes associated with vitamin D deficiency

The classic outcomes of vitamin D deficiency are nutritional rickets (affecting growing bone) and osteomalacia (in adults). However, recently, it has become apparent that there are numerous other skeletal, as well as interesting nonskeletal benefits in having adequate vitamin D levels.[2]

These will be discussed here.

Skeletal health

Vitamin D is critical for bone health. Vitamin D levels are often lower in those who fracture. However, trials that assess the effectiveness of supplementation mostly include the addition of calcium as well. A Cochrane meta-analysis found no significant effect of vitamin D supplementation alone on the risk of fractures, but supplementation with both calcium and Vitamin D had a positive effect on the reduction of hip fractures in frail and institutionalised people.[7]

Observational studies indicate that there is an increased risk of falls in institutionalised persons that is associated with low vitamin D levels.[8] This risk is also associated with poorer physical performance in community-dwelling older individuals and is a predictor of adverse events.[9] Vitamin D supplementation reduces the risk of falls in older adults through effects on muscle and the nervous system (both central and peripheral), whereby it improves gait and balance.[8,10]

Vitamin D supplementation of > 800 IU per day, aiming to achieve 25(OH)D levels of at least 30 ng/ml, was somewhat favourable in preventing hip fractures and nonvertebral fractures in persons who were 65 years and older.[11]

Cardiovascular health

Observational data have linked vitamin D deficiency with a range of cardiovascular diseases, which include strokes, myocardial infarction and hypertension.[12-14] Recently, a large study found reduced cardiovascular survival in vitamin D-deficient patients. Supplementing these patients was significantly associated with better survival.[15] Interventional studies like these are encouraging, but many questions remain regarding dosing and optimal levels, as well as the issue of concomitant calcium supplementation (which is somewhat contentious at present).[15]

Diabetes mellitus

Low vitamin D is a risk factor for the development of type 1 diabetes mellitus, based on animal and human observational studies. Increased vitamin D intake is a possible preventative strategy for the disease.[16] This may relate to the immunomodulatory actions of vitamin D, which influences lymphocytes and interleukins.[17]

Observational data suggest that altered vitamin D and calcium metabolism may also play a role in the development of type 2 diabetes mellitus.[18,19] Our understanding of the exact mechanisms for this association remains incomplete and is an area of active research. Vitamin D receptors and binding proteins are present in pancreatic islet tissue. The role of vitamin D in the pathogenesis of diabetes seems relate to its role in the regulation of plasma calcium, which in turn regulates insulin secretion. In addition, it also has a direct effect on pancreatic B cells, as well as effects on inflammatory mediators.[17,20] It has been demonstrated that obesity (a known risk factor for type 2 diabetes mellitus) is associated with low vitamin D levels. However, interventional studies showing benefit are still lacking at this stage.[21]

Skin diseases

In a country renowned for its sunshine, the beneficial as well as harmful effects of ultraviolet (UV) radiation are apparent. Protection against UV radiation is advocated in order to reduce the risk of cancer, although this can lead to a marked reduction in vitamin D levels.[22] Further work is necessary to define the adequate amount of sun exposure to obtain optimal vitamin D levels, especially in the South African climate. However, it is imperative that a balanced view is maintained of the positive (vitamin D) and negative (skin cancer risk) effects of UV radiation. Monitoring and supplementation with vitamin D is essential in patients at risk of developing vitamin D deficiency (the elderly and

people who cover up for religious reasons).[23] Interestingly, topical vitamin D derivatives are also used in the treatment of psoriasis.[24]

Infectious diseases and immunity

The relationship between vitamin D and the immune system was recognised a number of years ago with the demonstration of increased circulating levels of 1,25(OH)2D and hypercalcuria and hypercalcaemia in sarcoidosis. This is because of the increased local activity of 1-α-hydroxylase which is found in activated macrophages.[25] It is now clear that dysregulation of vitamin D homeostasis is not only present in sarcoidosis, but also in other forms of granulomatous disease and cancer.

Today, it is recognised that vitamin D plays a more active role in the immune system.[26] It is involved in the differentiation of monocytes to mature phagocytic macrophages, and more recently, has been demonstrated to affect the phagocytic process by stimulating the expression of the antibacterial protein, cathelicidin.[27] Regulation of this protein has also been described in other cell types, notably keratinocytes, lung epithelial cells, myeloid cells and placental trophoblasts.[26]

Low-serum vitamin D levels are associated with a higher risk of active tuberculosis.[28] Considerable work has been carried out into the role of vitamin D supplementation in the management of tuberculosis, but to date the results have been conflicting. It has not been demonstrated to have a convincing effect on sputum conversion or mortality.[29,30]

Vitamin D deficiency is also very prevalent in human immunodeficiency virus (HIV)-infected individuals.[31] It has been shown that there is inadequate 1-α-hydroxylation and decreased levels of 1,25(OH)2, possibly because of increased levels of TNF-α. This may contribute to the impaired immune response and the pathogenesis of HIV-related immunodeficiency.[32] Moreover, non-nucleoside reverse transcriptase inhibitors, notably efavirenz, have been implicated in lowering vitamin D levels.[33]

Observational epidemiological studies have shown an increased risk of other viral infections (influenza and respiratory tract infections) associated with vitamin D deficiency.[34]

Cancer risk

The active form of vitamin D, calcitriol, has been shown to slow tumour growth in animal models.[35] Various mechanisms are postulated, including inhibition of cell proliferation and enhanced apoptosis, inhibiting angiogenesis and suppressing inflammation and metastases. Observational studies also show vitamin D deficiency to be associated with an increased risk of developing cancer, notably breast, colon and prostate cancer.[36] As a result of encouraging preclinical data, vitamin D has been studied extensively as an anti-cancer drug, but the results have been disappointing to date.[37]

Rheumatologic diseases

Vitamin D is thought to protect against rheumatic diseases [rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)] through its effects on immune tolerance.[27] A lower vitamin D level is associated with more severe and active disease in RA.[38] The seasonal variation in vitamin D levels (lower in winter and higher in summer) negatively correlates with disease activity both in RA and SLE.[22,24,39]

Other diseases

Vitamin D deficiency has also been associated with various other diseases, including multiple sclerosis,[40] asthma,[41] schizophrenia,[42] gastrointestinal and liver disease[43] and dementia.[44]

So how much is enough?

There is little consensus in the literature regarding the exact dosing, as well as optimal route of administration that is most beneficial. It is recommended that vitamin D supplementation should not be offered routinely, but that individuals at risk of deficiency (Table II) should be screened. In cases of severe deficiency, large doses (e.g. a once-weekly dose of 50 000 IU of D2 or D3 for six weeks, followed by a maintenance dose of 400-1000 IU per day) may be required, and this may even increase in obese patients, patients with malabsorption syndromes and patients on medication that affects vitamin D metabolism.[45]

Table II: Individuals at risk of vitamin D deficiency[45]

Rickets, osteomalacia
Osteoporosis
Chronic kidney disease
Liver disease
Malabsorption syndromes Cystic fibrosis Inflammatory bowel disease Baratric surgery Radiation enteritis Coeliac disease Chronic pancreatitis
Hyperparathyroidism
Medications Anti-seizure Glucocorticoids Acquired immune deficiency syndrome Antifungals, e.g. ketoconazole Cholestyramine
Pregnant and lactating women
Older adults with a history of falls and nontraumatic fracture
Obese adults and children (body mass index > 30 kg/m^2)

Conclusion

Vitamin D deficiency has been linked to a number of diseases. However, until now, interventional studies have been fairly disappointing, other than proving that vitamin D

is beneficial in skeletal disease. There is still some debate regarding the recommended daily allowance and the required optimal dose for standard supplementation, but meeting daily requirements in adults of 800-1000 IU should be adequate in most people who are at risk of vitamin D deficiency.

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