

Review

Vitamin D: Panacea unexplored?

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Introduction

The traditional role of vitamin D has been in the regulation of bone metabolism and calcium-phosphorus homeostasis. During the last two decades, numerous *in vitro* and *in vivo* studies have reported several “non-calcaemic” effects of vitamin D metabolites. Heterogeneous tissue such as skeletal muscle, cardiac muscle, pancreatic beta cells, vascular endothelial cells, neurons and immune cells express vitamin D receptors (VDR)¹ suggesting multiple biological pathways that influence health and disease.

Vitamin D deficiency, is linked with the onset and progression of diseases such as autoimmune diseases, respiratory infections, diabetes mellitus, cardiovascular disease, neuromuscular disorders, and cancer.

Prevalence of vitamin D deficiency is approximately 30-50% in developed countries,² caused mainly by inadequate sunlight exposure. Pigmentation reduces the cutaneous vitamin D production³ and although the prevalence of vitamin D deficiency is not known in Sri Lanka, hypovitaminosis D is most likely to be compounded by dietary inadequacies. Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks.⁴ Low income, high cost of food and vegetarianism are potential reasons that may lead to inadequate dietary intake of vitamin D in Sri Lanka. Low vitamin D status in old age is a concern because of the growing elderly population in this country.

The aim of this review is to study the non-traditional roles of vitamin D; i.e, the evidence for its association with diseases, its postulated protective mechanisms and the role of vitamin D supplementation in diseases.

Cardiovascular disease (CVD)

Vitamin D deficiency has emerged as a potential, novel CVD risk factor. A number of experimental

studies have established a role for vitamin D metabolites in pathways that are integral to cardiovascular function and disease.

In a cross-sectional study involving 15,088 subjects from the NHANES III national cohort registry, 25(OH)D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia and obesity.⁵ In a prospective study among the 1,739 Framingham Offspring Study participants who were free of CVD at baseline, the rate of composite cardiovascular end points (fatal or nonfatal MI, ischemia, stroke, or heart failure) was 53% to 80% higher in people with low vitamin D levels.⁶ In the Health Professionals Follow-up Study (n=18, 225) in men aged 40-75 years who were free of CVD at baseline, there was a graded independent relationship between low levels of 25(OH)D and risk of myocardial infarction⁷. The association between vitamin D deficiency and elevated blood pressure perhaps provides the most convincing evidence for the association of vitamin D metabolism in the pathogenesis of CVD.⁸ Low 25(OH)D status is associated with an increased risk of symptomatic ischemic stroke.⁹ In one large study of 10,170 participants and a meta-analysis of 10 studies with 58,384 participants, a stepwise increase in the risk of symptomatic ischemic stroke was found with decreasing plasma 25(OH)D concentrations.⁹ Sun et al (2012) in a prospective study and meta-analysis of women found that low vitamin D levels have a modest association with risk of stroke.¹⁰

Vitamin D confers potential benefits to cardiovascular health via its actions on cardiac myocytes, vascular endothelial function and renin-angiotensin-aldosterone system (RAAS). Thus, low 25(OH)D levels may adversely affect cardiovascular health via multiple pathways: eg. ventricular dilatation and defective electromechanical coupling due to direct effects on cardiomyocytes,¹¹ endothelial dysfunction that includes increased expression of adhesion molecules¹² and activation of the RAAS predisposing to hypertension and left ventricular hypertrophy.¹³ Vitamin D deficiency also increases parathyroid hormone levels, which leads to insulin resistance which is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk.¹⁴

Despite experimental and epidemiological evidence linking low 1,25(OH)₂D to many aspects of

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cardiovascular health, a meta-analysis of 51 trials of vitamin D supplementation in the prevention of various cardiovascular outcomes has not shown an overall benefit.¹⁵

Diabetes mellitus

Vitamin D deficiency has long been suspected to be a risk factor for glucose intolerance. Even though the relationship between type 1 diabetes and vitamin D deficiency has been extensively reported, the relationship with type 2 diabetes has been less clear. Several observational longitudinal studies in heterogeneous populations have shown an inverse association between the vitamin D status and the development of type 2 diabetes.¹⁶

The expression of the VDR in many cell types and organs, and the local production of $1,25(\text{OH})_2\text{D}$ in several extra-renal organs, including pancreatic beta cells, support the potential effects of vitamin D on glucose metabolism. Both direct (by activation of the VDR) and indirect (by regulation of calcium homeostasis) actions of vitamin D are possibly related to the pathophysiology of type 2 diabetes.¹⁷ Vitamin D deficiency is associated with disorders of insulin synthesis, secretion and sensitivity. The postulated mechanisms by which vitamin D may influence glycaemic control include, modulation of pancreatic Renin-Angiotensin System activity, regulation of calcium ion transfer across beta cells that directly affect insulin synthesis and secretion and abnormal immune responses that lead to an inflammatory milieu and subsequent insulin resistance¹⁸.

Obesity is associated with type 2 diabetes and vitamin D deficiency, and the poor bioavailability of vitamin D in fat stores probably explains why a significant proportion of obese persons are vitamin D deficient¹⁹.

Studies have shown that the prolonged treatment of osteomalacia with vitamin D increases insulin secretion and improves glucose tolerance¹⁹. In randomized-controlled trials (RCTs), vitamin D supplementation did not show any beneficial effects on glycemic measures among persons with normal glucose tolerance but there were beneficial effects among patients with glucose intolerance or insulin resistance at baseline.¹⁶ However, in their meta-analysis in 2014, Seida et al failed to show beneficial effects of vitamin D₃ supplementation on glucose homeostasis or diabetes prevention.²⁰

Metabolic syndrome

Metabolic syndrome is a constellation of metabolic derangements comprising central obesity, insulin resistance, hypertension and dyslipidaemia. Elevated

inflammatory markers are also a feature of metabolic syndrome. With its effects on insulin resistance and hypertension as described above, it is no surprise that vitamin D deficiency is linked to metabolic syndrome. Studies have revealed that vitamin D deficiency is associated with obesity, diabetes, inflammation, and hypertension. A study among 8,421 participants revealed that the mean vitamin D concentrations in plasma were significantly lower in participants with metabolic syndrome compared to others.²¹ In a study of 3262 middle aged Chinese men and women, low plasma vitamin D significantly increased the risk of metabolic syndrome and insulin resistance.²² In a dose-response meta-analysis it was found that vitamin D levels were associated with a risk of metabolic syndrome in cross-sectional studies but not in longitudinal studies.²³ The fact that insulin resistance is a major underlying mechanism for the metabolic syndrome could explain the pathophysiology of why metabolic syndrome is associated with vitamin D deficiency. Furthermore as Vitamin D is sequestered in body fat, obesity is associated with decreased bioavailability of vitamin D,¹⁹ and central obesity is a key feature of metabolic syndrome. High serum vitamin D levels are associated with a favorable lipid profile²⁴ and low serum vitamin D levels have been associated with dyslipidemia including elevated LDL cholesterol and low HDL-C levels in Indian participants.²⁵ The postulated mechanisms include vitamin D-mediated calcium absorption reducing hepatic triglyceride formation and secretion, regulation of VLDL cholesterol receptor expression, increased peripheral removal of triglycerides and reduction of VLDL cholesterol and triglycerides secondary to reducing insulin resistance.²⁵

Cancer

Many studies have confirmed an association between low serum levels of vitamin D and incidence and mortality of several types of cancers such as melanoma, breast, prostate, colorectal, ovarian, kidney, esophagus, stomach and non-Hodgkin's lymphoma.²⁶⁻²⁹

A number of *in vitro* studies have demonstrated that exposure of tumor cells to high concentrations of vitamin D compounds inhibit their proliferation and induce differentiation. Numerous epidemiologic studies have shown the association between factors that reduce vitamin D levels (e.g., geography and latitude, history of sun exposure, lifestyle) and increased rates of cancer, drawing attention to the potential protective effects of vitamin D on various types of tumors.²⁶⁻³⁰ Significantly high expression of VDR in the immune cells such as monocytes, macrophages, antigen-presenting cells and CD4 cells has raised the possibility that vitamin D and its analogs may exert an immunomodulatory activity.³¹

Giovannucci et al. who developed and validated an estimate of serum 25(OH)D level, reported that among over 40,000 individuals, an increase in 25(OH)D level to 62.5 ng/ml was associated with a reduction in the risk of head and neck, esophagus and pancreas cancers, and acute leukemia by >50%.³²

Falls

Vitamin D prevents falls probably via improving muscle function.³³ A meta-analysis of 10 double-blind RCTs of older individuals revealed, that 700-1000 IU a day of supplemental vitamin D reduced the risk of falling by 19%.³³ It was postulated that binding of vitamin D to muscle VDR may lead to muscle protein synthesis, leading to muscle strengthening and reduction in falls in older patients.³³ In one double-blind, RCT of 302 ambulant women of 70 to 90 years with vitamin D insufficiency, adding ergocalciferol 1000 IU/day to calcium, resulted in a 19% reduction in the relative risk of falling.³⁴ However, Bolland et al, 2014 report contrasting findings in a meta-analysis of 20 RCTs (n=29, 535), where vitamin D supplementation, with or without calcium, does not reduce the risk of falls by 15% or more.³⁵

Central nervous system (CNS)

The role of vitamin D in the functioning of the brain emerged over 2 decades ago with the finding of vitamin D in cerebrospinal fluid and the presence of VDR in many areas of the brain.³⁶ Vitamin D deficiency is now linked to many adverse brain outcomes, including cognitive impairment, schizophrenia, stroke, Parkinson disease, Alzheimer disease, multiple sclerosis and depression.³⁷ A meta-analysis of 7 studies including 7,688 participants showed that low vitamin D levels significantly increased the risk of cognitive impairment.³⁸

Vitamin D is a neuroactive steroid that acts on brain development, and vitamin D deficiency has shown to lead to alterations in brain neurochemistry and function.³⁷ Vitamin D acts on VDR and triggers many neuronal protective actions including anti-inflammatory, antioxidant and anti-atrophic effects, and regulates calcium homeostasis³⁹ and the genetic expression of numerous neurotransmitters; eg. acetylcholine, dopamine, serotonin, and g-amino butyric acid.⁴⁰ Vitamin D₃ has been shown to clear amyloid plaques, which could explain why low vitamin D levels are associated with Alzheimer disease and dementia.⁴¹

The immunomodulatory role of vitamin D in the CNS, through a T-helper cell mediated response, is a potential mechanism for the association of vitamin D deficiency with multiple sclerosis (MS)⁴². A recent study in patients with MS mainly treated with interferon beta-1b, low 25(OH)D levels early in the disease was a

strong risk factor for long-term disease activity and progression.⁴³ In a retrospective cohort analysis of 181 patients with relapsing-remitting MS, vitamin D deficiency was associated with a higher risk of disability, with levels correlating with the degree of disability.⁴⁴

Depression

Vitamin D may play a role in psychiatric illness such as depression since it is involved in many brain processes including neuroimmunomodulation and neuroplasticity. The observational studies to date provide evidence for a relationship between vitamin D deficiency and depression, but RCTs are needed to determine whether vitamin D can be used to prevent and treat depression.⁴⁵

Chronic pain

Vitamin D could alleviate chronic pain by the suppression of inflammatory cytokines.^{1,46} One study found a high prevalence of vitamin D deficiency in patients with non-specific musculoskeletal pain, headache and fatigue.⁴⁶ However, a Cochrane review by Straube et al (2010) reviewing four studies, with a total of 294 participants, found no convincing evidence that treatment with vitamin D is beneficial in improving chronic pain in adults.⁴⁷

Mortality

With the numerous benefits of vitamin D surfacing, it is of no surprise that evidence is accumulating to support the role of vitamin D in reducing mortality. A recent Cochrane review of 56 RCT with 95,286 participants found that Vitamin D₃, but not vitamin D₂, alfalcidol or calcitriol, appeared to reduce mortality in elderly people living independently or in institutional care.⁴⁸ A recent meta-analysis of 8 prospective cohort studies including 26,018 men and women aged 50-79 years found that the lowest quintile of serum 25(OH)D levels were associated with increased all-cause and cardiovascular mortality.⁴⁹ Vitamin D deficiency was linked to cancer mortality only in subjects with a history of cancer.⁴⁹ Other meta-analyses and studies have found similar results with regard to all-cause⁵⁰ and cardiovascular mortality.⁵¹

Pregnancy

Vitamin D is linked to several fetal and maternal outcomes in pregnancy. Vitamin D deficiency is common during pregnancy especially in South Asian women.⁵² Vitamin D deficiency in pregnancy has been shown to be associated with maternal complications like hypertension, pre-eclampsia and gestational diabetes^{53,54} and fetal complications such as small for gestational age, neonatal hypocalcaemic seizures,

impaired growth and bone development and childhood asthma.^{54,55} Hypocalcemia is likely to contribute to seizures and impaired fetal growth. Vitamin D may cause preeclampsia by gene regulation and expression affecting early placental development and gestational diabetes due to its effect on causing insulin resistance.⁵⁴ The pathways linking bio-molecular mechanisms and many fetal and maternal outcomes are however not firmly defined. However conflicting evidence for the above is present and there are no randomised trials proving that vitamin D supplementation reduces these complications. Further studies and more conclusive evidence should be available before recommending routine screening for vitamin D deficiency in pregnancy.

Immunity

Possible pathways whereby vitamin D deficiency can impair immune function, resulting in over activity and increased risk of autoimmune disease and immune suppression with poor resistance to infection have been described in the recent years.⁵⁶ Several studies have reported associations between low vitamin D levels and increased rate of infections, including upper respiratory tract infections,⁵⁷ influenza,⁵⁸ and HIV.⁵⁹ Results of studies that have looked at potential benefits of administering vitamin D to reduce infections are largely inconclusive mainly because of methodological inconsistencies, but at least one well-designed clinical trial has reported reduced influenza rates with vitamin D⁶⁰.

Vitamin D deficiency has been linked to development and progression of autoimmune diseases. It has been reported that low serum vitamin D predicts development of autoimmune diabetes mellitus and rheumatoid arthritis.^{18,61} Vitamin D deficiency is shown to be a common association in patients with SLE and the disease activity and severity correlates inversely with vitamin D.⁶²

Evaluating vitamin D status

Measuring the serum level of 25(OH)D is the best way to assess vitamin D status.^{1,40,47,63} As only a fraction of 25(OH)D is converted to its active metabolite 1, 25(OH)2D, measurement of total 25(OH)D levels in the serum is the best measure of diagnosis and the management of vitamin D deficiency.⁶³ Quantification of 25(OH)D2 and 25(OH)D3 fractions may be useful in monitoring treatment.⁶³ Classically Vitamin D deficiency has been defined as 25(OH)D level <50 nmol/L (<20 ng/mL) generating a secondary hyperparathyroidism response¹. However, recent guidelines differ on cutoffs for vitamin D deficiency, eg. 25(OH)D cutoffs for Vitamin D deficiency and insufficiency being considered as <20 ng/ml (50 nmol/liter) and <21-29 ng/ml (52.5-72.5 nmol/liter) by the US Endocrine Society,⁶⁴ <20 ng/mL (<50

nmol/L), 20-30 ng/mL (50-75 nmol/L) by Central European Guidelines⁶⁵ and <30 nmol/L (12 ng/dL) and 30-50 nmol/ (12-20 ng/dL) by National Osteoporosis Society Guidelines.⁶⁵ There are no clear cut guidelines established for South Asians. Different studies thus have used varying threshold. Further-more, vitamin D thresholds established may not be the optimum for other disorders linked to vitamin D; eg. 25(OH)D level <10 ng/mL is associated with a higher risk of cognitive decline.³³

Management

The desirable vitamin D level is in the range of 75-125 nmol/L.^{4,65} Noon-time sun exposure for 12 minutes is estimated to generate vitamin D equivalent to an oral dose of 3000 IU (75 micrograms)³ in Caucasians, but South Asians being dark skinned are thought to form less vitamin D despite abundant sun exposure. Vitamin D supplementation is relatively inexpensive, and the risk of toxicity is minimal at supplementation levels of up to 2,000 IU per day.^{4,64} However, there are no standards established as to when and how much vitamin D is necessary as supplements for the non-traditional disorders linked to vitamin D deficiency.

Vitamin D Toxicity

Vitamin D toxicity is a rare event, mostly reported in children and adolescents. Increased use of vitamin D supplementation, lack of consensus on optimal level of vitamin D and use of higher doses at times due to misunderstanding physicians' instructions, have led to the possibility of increased incidence of toxicity.⁶⁶ Vitamin D toxicity clinically manifests as features of hypercalcemia and hypercalciuria. The diagnosis of vitamin D intoxication is based on elevated serum 25OHD concentrations, which are associated with hypercalcemia or hypercalciuria, while serum 1,25(OH)2D levels are normal and PTH is suppressed. Serum concentrations exceeding 150 ng/mL (375 nmol/L) have been proposed to define intoxication. Vitamin D levels up to 100 ng/mL (250 nmol/L) are cited as safe for both children and adults.⁶⁴ The same principles for treatment of hypercalcemia and hypercalciuria are used in the treatment of symptomatic vitamin D toxicity and include hydration, loop diuretics, corticosteroids, calcitonin and bisphosphonates.⁶⁶ The source of vitamin D is removed, and the levels are allowed to decrease with time, which takes several weeks.⁶⁶ Since vitamin D has a long half-life, serum 25OHD concentrations may occasionally continue to rise after discontinuation of vitamin D administration. Therefore, in asymptomatic patients with excessively high 25OHD levels, it is advisable to observe for symptoms of toxicity. Haemodialysis lowers serum calcium rapidly and is used in life-threatening cases. Current recommendations regarding vitamin D toxicity and treatment includes awareness of healthcare

providers regarding various vitamin D preparations and proper counsel of patients, avoidance of empirical therapy with high doses of vitamin D, monitoring of serum vitamin D levels in infants and children receiving treatment doses in the upper ranges, inclusion of vitamin D toxicity in the differential of hypercalcaemia and hypercalciuria and monitoring of clinical symptoms and serum 25OHD and calcium levels.

Conclusions

Multiple functions of vitamin D are now identified, including the regulation of anti-inflammatory, immunomodulatory, antioxidant and anti-atrophic activities, calcium metabolism and gene expression. Apart from its effects on bone metabolism, studies have shown the association of vitamin D deficiency with diverse disorders such as cancer, CVD, cognitive dysfunction, chronic pain, MS and schizophrenia, with plausible mechanisms to link their pathophysiology to vitamin D deficiency. These observations have raised exciting possibilities of the use of vitamin D in prevention and treatment of such disorders. Although low vitamin D levels are linked to many non-traditional disorders, it is still not fully established if the correction of vitamin D deficiency is actually beneficial. Large, well designed RCTs are required to evaluate the actual causal effect of low vitamin D in the above disorders, and to examine if supplemental vitamin D is beneficial in their treatment and prevention.

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