Review Article

Vitamin D and Cardiovascular Health

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The emergence of vitamin D deficiency as a global epidemic coupled with its nonskeletal effects has recently garnered lot of interest in the medical fraternity. This "sun vitamin" deficiency is related to the limited cutaneous synthesis due to inadequate sun exposure, pigmented skin and inadequate dietary intake. The crucial role of the vitamin D in calcium metabolism physiology and its association with increased risk of CVD, autoimmune diseases, cancers, type 2 diabetes mellitus (T2DM) and infectious diseases has gained attention. In this article we will focus on the relationship between vitamin D statuses on the cardiovascular system.

Physiology of Vitamin D

Vitamin D is a pro-hormone, produced either in the skin via the effects of ultraviolet light or ingested with food and/or supplements. This absorbed/produced vitamin D enters circulation and undergoes hydroxylation in liver to produce 25(OH) vitamin D; it is then converted to the biologically active form of vitamin D, the hormone 1, $25(OH)_2$ vitamin D by the renal enzyme 25(OH)vitamin D-1-hydroxylase. 25(OH) Vitamin D-1-hydroxylase enzyme is a cytochrome 450–like mixed function oxidase in proximal convoluted tubule. The biological functions of 1, $25(OH)_2$ vitamin D are meditated by its binding to a nuclear receptor. The major steps involved in the control of gene transcription by the vitamin D receptor (VDR) include ligand binding, heterodimerization with retinoid X receptor, binding of the heterodimer to vitamin D response elements and recruitment of other nuclear proteins into the transcriptional preinitiation complex. $1,25(OH)_2$ vitamin D also has some biological rapid effects through nongenomic VDR-mediated pathways (1).

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The effect of vitamin D is mediated by $1,25(OH)_2$ vitamin D and tightly regulated by the parathyroid hormone, calcium and fibroblast growth factor-23. Vitamin D activation was first thought to be limited to the kidney but it is now evident that it also takes place locally in vitamin D target tissues which include pancreatic islets, gut, arterial walls, myocardium, skin and placenta. These tissues are able to activate vitamin D locally and also respond to it (2,3). This "local" tissue $1,25(OH)_2$ vitamin D production has both autocrine and paracrine effects (2). *In vitro* studies indicate that the paracrine process may be involved in a wide range of physiological functions, including regulation of cytokines, inflammatory and/or fibrotic pathways, the renin–angiotensin system, vascular and cardiac cell function, immune-response modulation, cell growth and differentiation and others (2). Several of the biological pathways through which the effects of $1,25(OH)_2$vitamin D are mediated remain poorly understood but may account for its role in cardiovascular health.

Defining Vitamin D Status

Circulating level of 25 (OH) vitamin D is considered the best indicator of the vitamin D status. It has been difficult to define exact cut off values for vitamin D deficiency as the methodology for 25(OH) vitamin D estimation varies. According to the latest Endocrine Society Guidelines, serum levels of 25(OH) vitamin D between 20 and 30 ng/mL indicate vitamin D insufficiency and levels less than 20 ng/mL indicate vitamin D deficiency (4). Severe deficiency is defined as a 25(OH)vitamin D level less than 10 ng/mL. However, vitamin D intoxication does not occur until 25(OH) vitamin D concentrations is 150 ng/mL.

An Internal Osteoporosis Foundation review by one of the authors on the global status of vitamin D deficiency has pointed out that levels below 30 ng/mL are common worldwide. High prevalence of severe vitamin D deficiency among all age groups in South Asia and Middle East countries was underscored in this study (5). Various studies have demonstrated widespread severe vitamin D deficiency in urban Indians (6–8).

Potential Mechanisms

Several mechanisms have been postulated to explain the link between vitamin D deficiency and cardiovascular disease (CVD). Proposed mechanisms for the cardioprotective role includes the effects on the renin–angiotensin aldosterone system, glycemic control, inflammatory cytokines, direct effects on the vasculature and regulation of PTH levels, and calcium deposition in vascular smooth muscle.

Effect of vitamin D on renin–angiotensin aldosterone axis

Various studies indicate the role of 1,25-$(OH)_2$vitamin D in the regulation of renin-angiotensin aldosterone axis (RAAS) by directly suppressing renin gene expression (9–12). VDR knockout mice have elevated blood pressure, cardiac hypertrophy, and activation of the renin-angiotensin-aldosterone system, which can be reversed with an angiotensin-converting enzyme inhibitor. 1,25 $(OH)_2$vitaminD inhibits renin gene expression by sequestering cyclic adenosine monophosphate response element binding, which is necessary for the transcription of rennin (12).

Effect of vitamin D on glycemic control

There is ample evidence suggesting the role of vitamin D in insulin secretion. VDR is present in β-cells and the vitamin D–dependent calcium-binding proteins (DBPs) are present in pancreatic tissue (13). Vitamin D mediates β-cell insulin secretion through a rise in intracellular calcium concentration via nonselective voltage-dependent calcium channels that facilitate the conversion of proinsulin to insulin. Calcium is not only necessary for insulin exocytosis but also for β-cell glycolysis. Vitamin D effect on insulin secretion is also mediated by activation of protein biosynthesis in pancreatic islets (14).

Effect of vitamin D on cardiac tissues and the vasculature

Mechanisms have been proposed to explain the role of vitamin D in blood pressure regulation and the pathophysiology of arterial hypertension. Firstly, studies have shown that vitamin D deficiency predisposes to upregulation of the RAAS and hypertrophy of both smooth muscle cells and the left ventricle (12). Secondly, vascular smooth muscle cells and endothelial cells express receptors for vitamin D that have the ability to convert circulating 25-OH D to 1,25-$(OH)_2$ vitamin D (15). Thirdly, vitamin D deficiency triggers secondary hyperparathyroidism that promotes myocyte hypertrophy and vascular remodeling (16,17).

Directly or indirectly, 1,25-dihydroxyvitamin D regulates the expression of a number of proteins relevant to the arterial wall, such as vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, elastin and type I collagen. Matrix metalloproteinase, proteins that contribute to aberrant cardiomyocyte remodeling in response to injury and atherosclerosis, are upregulated in VDR knockout mice (18).

Cardiovascular Risk Factors Associated with Vitamin D Deficiency

A wide range of diseases has been associated with vitamin D deficiency.

Vitamin D deficiency and hypertensive vascular disease

Various studies have implicated the association of vitamin D as an antihypertensive agent. Krause *et al*. studied the effect of UVA and UVB on blood pressure. They studied 18 subjects with stage I hypertension exposed to UVA and UVB (which stimulate vitamin D formation with skin) for 6 weeks and demonstrated a significant fall in systolic and diastolic blood pressure in subjects receiving UVB therapy (19). Similar results were demonstrated in a tanning study, exposure to UVB radiation three times a week for 3 months led to a nearly 200% increase in 25(OH)D levels and a 6 mm Hg decrease in blood pressure (19). According to the NHANES III study, subjects with the highest quartile of 25(OH) vitamin D had 3 mm Hg lower systolic blood pressure compared to subjects in the lowest quartile (20). A study of patients with T2DM and low baseline 25(OH) vitamin D levels demonstrated that on supplementation by a single dose of 100,000 IU vitamin D2 results in reduction of systolic blood pressure by 14 mm Hg and improvement of endothelial function (21).

In contrast, several smaller studies in Denmark, Taiwan and UK among elderly subjects have demonstrated no effect of vitamin D supplementation on blood pressure (22–24). The Women's Health Initiative Study (WHI) conducted 7 years followup study in US and demonstrated no significant difference in systolic or diastolic blood pressure in women randomized to calcium and vitamin D (400 IU) (25). Therefore, studies on vitamin D supplementation have not consistently

demonstrated a positive effect on regulating blood pressure.

Vitamin D deficiency and diabetes mellitus

T2DM is characterized by insulin resistance and altered insulin secretion. It has been suggested that vitamin D deficiency may play role in both these processes.

A large study of over 15,000 adults showed lower level of 25(OH) vitamin D among diabetics, women, elderly, racial minorities and groups having chronic kidney disease (24,26). Low 25(OH) vitamin D levels were associated with the presence of DM or glucose intolerance in another study (27). A large 30-year followup study of >10,000 Finnish children who during the first year of life received 2,000 IU vitamin D_3 per day demonstrated a 78% reduced risk of T1DM (28). This finding was subsequently confirmed by a meta-analysis of five observational studies in England (29).

Similarly 6 months followup study on 81 South Asian women with insulin resistance treated with 1,000 IU vitamin D daily showed reduced insulin resistance, improved insulin sensitivity and reducing fasting insulin levels without changing the insulin secretion (30). Data from the Third National Health and Nutrition Examination Survey also showed an inverse association between vitamin D status and diabetes in non-Hispanic white and Mexican American people (27).

However the controversies still persist. A recent major review by Pittas *et al*. of 13 observational studies (14 cohorts) and 18 trials reported a lower incidence of T2DM in the highest versus the lowest vitamin D status group. Eight trials found no effect of vitamin D supplementation on glycemia or incidence of T2DM (31). Thus the controversy of beneficial role of vitamin D in diabetes remains unanswered.

Vitamin D deficiency and peripheral vascular disease (PVD)

Various studies have suggested that hypovitaminosis D is associated with obesity, diabetes and hypertension, all of which increase the risk of PVD. One study showed a positive association between 25-(OH) vitamin D levels and prevalence of PVD. For each 10 ng/mL decrease in 25-(OH) vitamin D, the prevalence ratio of PVD was 1.35 (95% CI 1.15–1.59) after multivariable adjustment (32). Similar association was evident in another study, where a significantly higher amputation rate was observed in subjects with vitamin D deficiency (<20 ng/mL) compared with those who were not vitamin D deficient (6.7% and 4.2%, $P = 0.029$) (33). Thus these studies showed positive association of hypovitaminosis D with risk of PVD.

Vitamin D deficiency and lipid metabolism

Theories favor that obesity is associated with decreased sunlight exposure, from less outdoor activity or clothing habits that restrict cutaneous vitamin D synthesis. Also vitamin D is fat-soluble; therefore the sequestration of vitamin D metabolites in fat compartments decreases their bioavailability in obese compared with nonobese people. Evidence also suggests that 1,25-hydroxyvitamin D modulates adipogenesis through VDR-dependent inhibition of critical molecular components of adipogenesis such as peroxisome proliferator–activated receptor γ and C/EBPα (34). In the Framingham study on 3,890 nondiabetic individuals, the prevalence of vitamin D deficiency (25[OH]D <20 ng/mL) was threefold higher in those with higher level of subcutaneous adipose tissue and visceral adipose tissue than in those with lower level (35). Similarly, a cross-sectional study on 8,018 nonsmoking subjects showed significant positive associations between serum 25(OH) vitamin D and serum total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and significant negative associations between serum 25(OH) vitamin D and both LDL-C/HDL-C ratio and TG (36).

Vitamin D deficiency and coronary artery disease

The Framingham Offspring Study showed a hazard ratio of 1.80 (95% CI, 1.05–3.08) for developing a first cardiovascular event after 5 years of followup in subjects with no previous history of CVD and severe vitamin D deficiency (25(OH) vitaminD <10 ng/mL) compared to subjects with higher levels of 25(OH) vitamin D (>15 ng/mL) (37).The Health Professionals Follow-up Study (HPFS) showed a twofold increased rate of myocardial infarction in subjects without previous CVD and vitamin D deficiency (25(OH) vitamin D <15 ng/mL). Kendrick *et al*. in NHANES 1988–1994 showed that individuals with vitamin D deficiency (25(OH) vitamin D <20 ng/mL) had higher prevalence of angina, myocardial infarction, heart failure, hypertension, diabetes, elevated body mass index (>30), elevated triglyceride level and microalbuminuria compared to those with higher levels of vitamin D (38). The NHANES 2000–2004 showed similar association of vitamin D deficiency (25(OH) D <20 ng/mL) with increased prevalence of coronary

heart disease, heart failure and PVD (39). Shanker *et al*. also found that low vitamin D levels were associated with increased risk for CAD (40).

Accumulating evidence has stipulated a strong correlation between vitamin D deficiency and CVD including higher risk of myocardial infarction, CV death and overall mortality. However the severity of CAD could not be related with deficiency.

Vitamin D deficiency and heart failure

Studies suggest that vitamin D deficiency in heart failure is not a negligible laboratory finding. It was hypothesized that in patients with heart failure, vitamin D supplementation may reduce disease progression and symptom severity through suppression of the renin–angiotensin–aldosterone system and parathyroid hormone, downregulation of inflammatory mediators, suppression of cardiac remodeling, promotion of cell growth and differentiation, reduction of blood pressure and improvement in muscle strength (41,42). Ameri and colleagues showed that patients having serum 25 (OH) vitamin D level <25 nmol/L had significantly higher left ventricular dimensions and volumes, as compared to patients with a 25 (OH) vitamin D level >25 ng/mL (43). A double-blind randomized trial was conducted by Schleithoff and colleagues among 123 heart failure patients with NYHA class >II. They randomly assigned younger patients with heart failure to receive either a combination of vitamin D_3 (cholecalciferol) at a dose of 2,000 IU daily and calcium (500 mg daily) or calcium and placebo. The 9 months followup showed that patients replenished with vitamin D had higher levels of anti-inflammatory cytokine interleukin 10 without change in proinflammatory cytokine tumor necrosis factor alpha level (TNF-α). In the patients treated with calcium alone, a significant (12% from baseline value) increase was seen in the concentration of TNF-α (44). The results of this study shed light on the possible role of vitamin D supplementation in the reduction of the inflammatory state in patients with heart failure.

Vitamin D deficiency and arrhythmia

Intracellular calcium modulates the activity of sodium channels which transmit these action potentials throughout the myocardial tissue to keep the heart rate under control; disruption in calcium homeostasis leads to arrhythmia. It has been postulated that the ability of vitamin D to promote calcium homeostasis may enable it to prevent arrhythmias (45). A study on 34,580 veterans in the southeastern US showed that 34.8% (12,030) patients having arrhythmias were vitamin D deficient (25(OH) vitamin D <20 ng/mL) (46).

Vitamin D deficiency and mortality

The NHANES III study in 13,331 adults followed up for a median of 8.7 years showed inverse association of mortality with vitamin D levels having a 26% increased mortality in the lowest quartile (47). The study also suggested a U-shaped relationship for 25(OH) vitamin D, with a slight increased mortality noted at high level (>50 ng/mL). A prospective cohort study by Dobnig *et al*. of 3,258 showed similar results among patients posted for coronary angiography followed for median 7.7 years. Study showed higher all-cause mortality and cardiovascular mortality in lowest quartile compared with patients in the highest 25-(OH) vitamin D quartile (48). Thus, the epidemiological findings seem to suggest that poor vitamin D status is associated with poor cardiovascular outcomes.

Conclusion

Vitamin D deficiency is widespread globally. Several epidemiological studies have demonstrated a beneficial association between vitamin D and cardiovascular health. However a solid evidence to support the role of vitamin D in risk and outcome of CVD still remains elusive.

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