Chapter

Vitamin D and Cardiovascular Disease: The Final Chapter?

Jeremy I. Purow and Seth I. Sokol

Abstract

Vitamin D deficiency is globally prevalent and has been associated with the pathogenesis and complications of cardiovascular disease (CVD) and its risk factors. Defining these relationships has been challenging, and the clinical applications of vitamin D screening and supplementation for CVD risk prevention and modification have only recently become clearer. Most of the available evidence includes large observational studies and smaller randomized trials that scarcely evaluate CV outcomes as primary endpoints. Additionally, these studies include methodological inconsistencies, making it difficult to ascertain the benefits of vitamin D supplementation. However, more recently, randomized trials have been conducted which utilize CVD outcomes as primary endpoints, while assessing the effects of high dose vitamin D supplementation on CV health. Despite observational evidence as well as a conventional consensus that vitamin D supplementation improves CV health, these studies suggest that vitamin D supplementation likely has no benefit in this regard, at least in the follow-up period and populations evaluated.

Keywords: vitamin D deficiency, cardiovascular disease, endothelial function, hypertension, heart failure, renal disease, prevention, vitamin D

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death in the developed world and is forecasted to be the leading cause of death and morbidity in developing countries by 2020 [1]. According to the American Heart Association, 9.0% (24.3 million in 2016) of adults (≥20 years of age) in the United States live with CVD (including coronary heart disease, heart failure, and stroke). This number increases to 48.0% when including hypertension [2]. CVD is a multifactorial disease that includes a complex interplay between genetics, environmental factors, and risk factors.

Despite effective measures for control and modification of traditional risk factors, a significant amount of risk remains. Therefore, the identification of easily modifiable novel risk factors has been heavily investigated over the past few decades.

In addition to the well-known relationship between vitamin D and bone health, there has been considerable interest of the possible linkage between vitamin D and CV health due to the expression of the vitamin D receptor (VDR) on cardiomyocytes and vascular cells [3, 4]. Vitamin D plays an extensive role in the regulation of numerous pathways implicated in CVD pathogenesis. Interestingly, various studies note that CVD events are higher in the winter months, a time when vitamin D

levels are known to be at their lowest due to lack of sunlight [5, 6]. A similar trend is noted in certain populations with poor cutaneous vitamin D production, such as African Americans, who are more prone to developing hypertension and CV disease [6]. Lastly, low vitamin D levels (<20 ng/mL) have been independently linked to increased morbidity and mortality [7, 8]. Although convincing, this evidence does not demonstrate causality, but supports a hypothesis for further study.

Prior to 2017, randomized controlled trials had mostly relied on surrogate or secondary endpoints for CV risk reduction. Study methodologies have been heterogeneous, and results have often been conflicting. In the absence of results from these trials, regular supplementation has not been recommended for CV risk modulation. Despite the lack of recommendations, use of vitamin D supplements for this purpose had risen dramatically.

However, more recent trials have been conducted that have assessed CV risk reduction as a primary endpoint. These trials have given researchers and clinicians a better understanding of the effects of vitamin D supplementation and whether it should be indicated to reduce the risk of developing CVD [9, 10].

The following chapter will discuss the prevalence of vitamin D deficiency, describe vitamin D synthesis and metabolism, and provide an overview on the biologic plausibility and current state of the evidence linking vitamin D to CV health and disease.

2. Vitamin D deficiency

Vitamin D deficiency is found in 30–50% of the general population, and prevalence estimates suggest that more than 1 billion people worldwide are vitamin D insufficient or deficient [4, 11].

Vitamin D deficiency is indicated by serum levels of 25(OH)D < 20 ng/mL [4]. Serum levels >30 ng/mL are likely optimal for bone health, but some studies have shown benefits with lesser values. Parathyroid hormone (PTH) suppression appears to plateau at levels between 30 and 40 ng/mL [12]. There has been no agreement on optimum 25(OH)D levels required for purported health benefits beyond skeletal health. One study suggested that 25(OH)D levels below 11–14 ng/mL signify increased CVD risk [13]. Levels in the range of 21–29 ng/mL are considered by some as insufficient, a definition that would label the majority of the U.S. population vitamin D insufficient [4].

The Endocrine Society does not recommend screening for vitamin D deficiency in individuals who are not at risk for it [12]. Many of the risk factors for vitamin D deficiency have been identified. Some of these include inadequate cutaneous synthesis stemming from insufficient sun exposure or dark skin pigmentation and inadequate dietary intake. Other noted risk factors include aging, obesity, renal disease, liver disease, disorders that affect fat absorption (e.g. celiac disease, inflammatory bowel diseases, types of bariatric surgery), increased catabolism due to medications (e.g. steroids, anticonvulsants etc.), and other hereditable (e.g. rickets) and acquired disorders (e.g. hyperthyroidism) [4].

3. Vitamin D metabolism

Vitamin D's active form, 1a,25-dihydroxyvitamin D (1,25[OH]2D3) plays a critical role in influencing a myriad of metabolic pathways [14].

Natural sunlight exposure contributes to more than 90% of vitamin D (D3-cholecalciferol) production in humans [15]. UV-B irradiation absorbed by skin

keratinocytes triggers photolysis of 7-dehydrocholesterol (pro-vitamin D3) in the plasma membrane, which is then swiftly modified into vitamin D3 by heat [4, 16].

Dietary supply of vitamin D (D2-ergocalciferol) contributes to the remainder of the total amount of vitamin D in the body. Foods containing vitamin D include oily fish (salmon, sardines, and mackerel), cod liver oil, egg yolk, mushrooms, and fortified milk, orange juice, cereals, and cheese [11, 12].

D3 and D2 from the skin and diet, respectively, each undergo two sequential hydroxylation's: 25-hydroxylation in the liver and then 1,25-dihydroxylation in the kidney. In order to assess vitamin D status from oral intake and endogenous production, the primary metabolite of vitamin D, 25(OH)D, should be measured [11, 15, 17]. The hydroxylation of 25(OH)D to its biologically active form, 1,25(OH)2D3, is controlled by PTH [11, 18].

Most of the known biological effects of 1,25(OH)2D3 are mediated through the vitamin D3 receptor (VDR), part of the superfamily of nuclear hormone receptors, which mediates transcriptional gene regulation [19].

Over 200 genes are regulated by 1,25(OH)2D3. These include genes directly or indirectly responsible for renin and insulin production, anti-inflammatory cytokine release, proinflammatory cytokine suppression, and regulation of vascular smooth muscle cell (VSMC) and cardiomyocyte proliferation [11, 20].

1,25(OH)2D3 is also involved in non-genomic mediated intracellular signaling, demonstrating immunomodulatory, antiproliferative, and pro-differentiative activities in experimental settings [19].

4. Biologic plausibility

Characterizing vitamin D deficiency as a primary risk factor for CVD is challenging due to the multitude of complex interacting pathways involving vitamin D. The vitamin D receptor is nearly ubiquitous in human cells including vascular smooth muscle cells (VSMC), endothelial cells, cardiac myocytes, juxtaglomerular, and most immune cells, all implicated in the pathogenesis and progression of CVD [11, 18].

Immune cells such as activated CD4+ and CD8+ T cells, B cells, neutrophils, macrophages, and dendritic cells are capable of converting 25OHD3 into 1,25OHD3, its active form. Moreover, 1,25 hydroxylase, the rate-limiting enzyme in this pathway, is present in activated macrophages [21–23]. Lastly, VSMC and endothelial cells also express 1,25 hydroxylase, suggesting that these cells have an autocrine mechanism allowing them to modulate the effects of vitamin D on the vasculature [24, 25].

Vitamin D has various direct and indirect effects on CV function. 1,25(OH)2D3 directly modulates VSMC and expression of vascular endothelial growth factor via the VDR and CYP27B1 expression in VSMC's and endothelial cells. 1,25(OH)2D3 has an inhibitory effect on hypertrophy and proliferation of VSMC in vitro and in cultured cardiac myocytes. It also plays an important role in inflammation and thrombosis [21, 24]. In a swine model of atherosclerosis, vitamin D deficiency accelerated plaque progression by enhancing inflammation in epicardial adipose tissue [26]. Inverse associations between vitamin D deficiency and thrombogenicity, vascular inflammation, and vascular calcification have been demonstrated [27–29].

Indirectly, the expression of renin in vivo is strongly regulated by vitamin D, and an inverse relationship between vitamin D levels and renin expression has been demonstrated experimentally [30–32]. 1,25(OH)2D3 binds to the renin promoter region and inhibits renin transcription [30]. VDR knockout mice were shown to have increased levels of renin and angiotensin II and, therefore, a higher prevalence

of hypertension [32]. Thus, vitamin D is implicated in blood pressure regulation and myocardial thickening.

Another indirect effect of vitamin D on CVD is the regulation of matrix metalloproteinase 2 and 9 production. Increased metalloproteinases have been associated with cardiac fibrosis, hypertrophy and heart failure in mice [33, 34].

Vitamin D deficiency may also indirectly harm the CV system by inducing hyperparathyroidism, which may act upon parathyroid hormone (PTH) receptors within the blood vessel wall and the myocardium [35]. Multiple studies have been able to demonstrate an association between elevated PTH levels and hypertension, cardiac dysfunction and vascular disease [35, 36].

Lastly, hyperlipidemia has also been associated with vitamin D deficiency. This is likely a result of decreased transcriptional activity of the VDR, leading to the increase of hepatic cholesterol production [37].

5. The clinical evidence

Vitamin D deficiency is prevalent in CVD patients [11]. Most studies showing an association between inadequate 25OHD3 and poor outcomes in CV health are observational, hindering the establishment of a causal relationship. Furthermore, significant differences across studies hamper the ability to make valid and consistent conclusions. These differences include varying definitions of vitamin D deficiency and lack of seasonal adjustment and properly defined CV outcomes. Further difficulties include the use of single baseline measurements of vitamin D (which may be an inaccurate assessment of overall vitamin D status), a poor understanding of the role of high PTH on CVD, and the use of other disease modulating drugs such as calcium and statins in active and placebo groups, which may affect study results.

However, newer studies implement clearly defined primary endpoints, differing frequencies of vitamin D supplementation, and a diverse cohort of participants. These studies allow for a clearer understanding of the effects of vitamin D supplementation on CVD health.

6. Observational data

Several large-scale observational studies have been completed over the past decades. The NHANES III national cohort registry found a significant inverse relationship between 25(OH)D levels and all-cause mortality, but a non-significant association between 25(OH)D levels and CVD mortality [8].

In the Intermountain Heart Collaborative Study Group, significantly higher rates of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease were found in those with serum 25(OH)D levels below 30 ng/mL. Additionally, low serum 25(OH)D levels were also linked to coronary artery disease, myocardial infarction (MI), heart failure, stroke and incident death [38].

In the Health Professionals Follow-up Study, men deficient in 25(OH)D (≤15 ng/mL) had a higher risk of MI than men with sufficient levels (≥30 ng/mL) [39].

In contrast, other prospective studies have had discordant results. In the MIDSPAN family study, with a median follow up of 14.4 years, plasma levels of 25OHD less than 15 ng/mL were associated with all-cause mortality, but not the risk of CV diseases [40].

Similiarly, in the MrOS Sleep Study, no relationship between circulating 25(OH)D levels and risk of CVD events was found [41].

Additionally, in a study involving 746 patients undergoing coronary angiography, no correlation was found between vitamin D levels (<20 ng/mL vs. >20 ng/mL) and the degree and severity of coronary artery disease [42].

7. Randomized controlled trials

Prior to 2017, most randomized interventional studies have assessed surrogate endpoints rather than hard CV outcomes. In the available studies, there has been considerable variation in defining baseline vitamin D status, assessing adequate vitamin D dosage, and ascertaining study outcomes.

In a double-blind, placebo controlled, randomized trial where elderly participants in the United Kingdom received vitamin D3 supplements of 100,000 IU every 4 months for 5 years, no benefits on CVD outcomes were shown [43].

Additionally, in a systematic review of 18 randomized trials studying the efficacy of supplementation with vitamin D (with or without calcium) on various cardiometabolic outcomes, only four reported on incident CVD. There were no significant reductions in CVD risk found in these trials [44].

Postmenopausal women in the Women's Health Initiative (WHI) receiving calcium carbonate (1000 mg/day) and vitamin D (400 IU/day) had no reduction in their risk of coronary events or stroke during the 7 year follow-up period. Treatment with calcium and vitamin D also had no effect on blood pressure reduction, hypertension development and coronary artery calcification. In the overall participant cohort, supplementation did not reduce the overall incidence of heart failure, yet some benefits were noted in participants considered to be at low risk for heart failure. Lastly, in a follow-up 4.9 years after the culmination of the study, no positive effects on CVD were found [45–49].

More recent studies on vitamin D supplementation have made use of well-defined CV outcomes as primary endpoints. In 2017, the results of the Vitamin D Assessment study (VIDA), a randomized, double blinded, placebo-controlled study on the effects of high-dose, monthly vitamin D supplementation in the general population aged 50–84, were published. 5,110 patients were randomized to receive either an initial oral vitamin D dose of 200,000 IU followed by 100,000 IU monthly or placebo. Primary outcomes included incident CVD and death. Secondary outcomes included MI, angina, heart failure, hypertension, arrhythmias, chronic ischemic heart disease, arteriosclerosis, stroke, and venous thrombosis. Additionally, pre-specified subgroup analysis for the primary endpoint was done for patients with vitamin D deficiency (<20 ng/mL) and established CVD. Results of the study showed that high doses of monthly vitamin D supplementation provided no benefit to CV health over placebo. However, the study is limited by a low event rate and decreased power, especially for subgroup analysis in those deficient at baseline. Supplementation was monthly, leaving the question of whether daily dosing may be better. Finally, the funding of the clinical trial only allowed for a median follow-up time of 3.3 years and, therefore, the long-term effects of high dose, monthly vitamin D supplementation remain in question [10].

Another recent placebo-controlled trial, known as the VITAL study, assessed the effects of more frequent vitamin D supplementation (2,000 IU of vitamin D and 1 g of omega-3 per day) on CVD and cancer. The primary endpoint in the CV arm was major CV events, which included MI, stroke, and cardiac related death. 25,871 subjects participated in the study and the median follow-up time was 5.3 years. The trial found that daily vitamin D supplementation had no benefit on CV health. The strengths of the study included daily vitamin D supplementation, longer follow-up times, and participant diversity [9].

A recent updated meta-analysis, including VITAL and VIDA, with a total of 83,291 patients, indicated that vitamin D supplementation had no benefit on CV health. Only 4 of the 21 trials used CVD as a primary endpoint. It has also been shown that vitamin D supplementation provided no benefit toward the secondary endpoints of MI, stroke, CVD mortality, and all-cause mortality [50]. This meta-analysis, though, lacks complete and specific patient level data and, therefore, subgroup analysis is difficult.

8. Hypertension

Low vitamin D status has been heavily linked to an increased prevalence of hypertension. A prospective examination of 1,211 non-hypertensive men, over a 15 year follow-up period, demonstrated an inverse association between vitamin D levels and hypertension development [51].

In addition to the demonstrated link between low vitamin D levels and hypertension development, the Framingham Offspring Study suggested that low vitamin D levels may also increase the risk associated with already existing hypertension, which may substantially augment the risk of future CV events [52].

Contrary to observational evidence, randomized controlled trials of vitamin D repletion have not shown significant changes in blood pressure in vitamin D deficient individuals with prehypertension or hypertension [53, 54].

In a randomized, double blind trial involving 283 black subjects given either placebo, 1,000, 2,000, or 4,000 IU/day of vitamin D for 3 months, significant modest reductions in systolic blood pressure were seen. Systolic blood pressure decreased by 0.2 mmHg for every 1 ng/mL increase in vitamin D, but no effect on diastolic pressure was demonstrated [55].

In VITdish, another small (N = 159) randomized, double-blind, placebo-controlled trial, there was no effect of vitamin D supplementation on blood pressure or other markers of vascular health in older adults with systolic hypertension [56].

A 6 month study of vitamin D3 supplementation including patients with resistant hypertension showed similar results. Effects on left ventricular hypertrophy were also negligible, although the short follow-up may have limited this assessment [57].

In the VIDA study, with monthly high dose vitamin D supplementation, there were no significant differences between the vitamin D and placebo groups regarding incident hypertension [10].

Lastly and likewise, in the VITAL study using high daily doses of vitamin D, hypertension incidence was not significantly different in the vitamin D and placebo groups [9].

9. Endothelial dysfunction

Vitamin D deficiency has been associated with endothelial dysfunction. A study involving 23 asymptomatic subjects demonstrated impaired brachial artery flow-mediated dilatation (FMD) in subjects with significant vitamin D deficiency. Improvement was seen with vitamin D repletion [58].

In contrast, there was no improvement in endothelial-dependent vasodilation with active treatment (ergocalciferol 50,000 IU/week) versus placebo in an 8 week trial in non-hypertensive, overweight, vitamin D deficient individuals [59].

Similarly, a prospective placebo-controlled pilot study evaluated the effects of vitamin D repletion on endothelial function and inflammation in subjects with both vitamin D deficiency and coronary artery disease. The study was conducted over a 12-week period in 90 subjects. No significant differences between the groups were found in reactive hyperemia index (using RH-PAT), blood pressure, and levels of hs-CRP, IL-6, IL-12, interferon gamma (INF-gamma), and CXCL-10 [60].

Additionally, in the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) (N = 852), vitamin D levels were positively related to endothelial-independent vasodilation in women only. There were no significant relationships between vitamin D levels and indices of endothelium-dependent vasodilatation in both men and women [61].

Lastly, a recent systematic review including 31 trials and individual-level meta-analysis (2,571 patients) assessed the relationship between vitamin D and various markers of vascular function. The analysis found that most vascular markers studied were not significantly effected by vitamin D supplementation [62].

10. Heart failure

The impact of vitamin D supplementation on patients with heart failure has not been the focus of large randomized trials.

The RECORD trial (Randomized Evaluation of Calcium Or vitamin D) was a trial designed for the secondary prevention of fractures in 5292 participants aged ≥70 years (conducted between 1999 and 2002). Subjects received oral vitamin D3 (800 IU/d) plus calcium (1,000 mg calcium carbonate/d), vitamin D3 alone, calcium alone, or a placebo. An analysis of unpublished data from the trial, suggested that vitamin D supplementation may decrease heart failure events in the elderly. The trial had pre-specified CV endpoints of time to first cardiac failure, time to first MI, time to first stroke, and time to first composite outcome of cardiac failure, MI, or stroke. The trial, though, was not designed as a CV outcomes trial, and outcomes were not subject to an adjudication committee nor verified against medical records. Furthermore, significance for heart failure event reduction was reached only when off-trial data were used [63].

Several small placebo-controlled studies have been conducted to analyze the effects of vitamin D supplementation on differing endpoints in patients with heart failure. Results have been conflicting.

In a small randomized, double-blind, placebo-controlled trial (N = 105) in older adults with vitamin D deficiency (25-vitamin D < 20 ng/mL) and systolic heart failure, subjects were given 100,000 IU of oral vitamin D2 or placebo at baseline and 10 weeks. Functional outcomes, quality of life and biomarkers (B-type natriuretic peptide (BNP) and tumor necrosis factor (TNF alpha)) were measured at baseline, 10 and 20 weeks. BNP was significantly reduced in the active treatment group versus placebo, but TNF alpha was not. Despite reduced BNP levels, physical function, as measured by the 6-minute walk test and the timed get up and go test, did not improve. There was also no change in the Functional Limitations Profile measure in the active versus placebo group. A small, but significant worsening in quality of life with active treatment was noted, despite a non-significant increase in activity level, suggesting a chance finding [64].

Schleithoff et al. examined cytokine profiles with vitamin D3 supplementation in younger patients with heart failure. A dose of 2,000 IU per day reduced the pro-inflammatory marker TNF-alpha levels and increased the anti-inflammatory cytokine interleukin-10 levels, but no significant effects on BNP levels were seen [20].

A recent randomized, controlled trial assessed the effects of 50,000 IU of weekly vitamin D or placebo for 6 months on various measures of physical performance (primary endpoint: peak VO2; secondary endpoints: 6-Minute Walk test, timed get up and go test, isokinetic muscle strength) in patients with heart failure. The study failed to demonstrate any benefits, despite considerable increases in serum 25(OH)D levels in the active treatment group [65].

In VINDICATE, a double-blind, randomized, placebo-controlled trial, subjects with systolic dysfunction (ejection fraction (EF) ≤ 45%) and vitamin D deficiency (<20 ng/mL) were randomized to 4,000 IU of vitamin D3 or placebo. At 12 months, there was no significant difference in 6-minute walking distance (primary endpoint), but there was significant improvement in left ventricular (LV) systolic function and a reduction in LV end diastolic and end systolic diameter with active supplementation [66].

In the EVITA trial, 400 patients with heart failure were randomized to receive 4,000 IU of vitamin D or placebo daily for 3 years. There was no benefit of supplementation on the primary endpoint of all-cause mortality. Additionally, secondary endpoint analysis suggested that vitamin D supplementation was associated with an increased frequency of implantation of mechanical circulatory support [67].

11. Renal disease

Observational studies show that there are potential benefits to vitamin D supplementation in patients with chronic kidney disease (CKD). In a meta-analysis of some of these studies, it was determined that receiving treatment with any vitamin D derivative reduces all-cause mortality as well as CV mortality [68]. In another, more recent, meta-analysis of observational studies, it has been shown that vitamin D treatment may pose benefits toward reducing all-cause mortality and CV related mortality [69].

To further assess some of the available randomized, clinical trials for renal patients, a meta-analysis was done to test the efficacy of vitamin D supplementation in these patients. The 13 trials used for the meta-analysis showed no significant benefits for serious adverse CV events, all-cause mortality, or CV related mortality in CKD patients who supplemented with vitamin D. Unfortunately, there is a lack of patient level data relating to patients with CKD, making it difficult to draw any conclusions regarding the effects of vitamin D supplementation on CV health in this population [70].

In many of the previous studies in patients with CKD, the dosage of vitamin D has been limited in order to protect patients from developing hypercalcemia. Additionally, a lack of standardization in vitamin D formulations has made it especially difficult to compare results in different trials. Larger randomized trials with well-defined primary outcomes need to be conducted in order to further define vitamin D's effect on CVD in renal patients. In 2025, the SIMPLIFIED trial is expected to conclude and expectantly give insight into the effects of vitamin D supplementation on hard endpoints of all-cause mortality and CV related mortality in CKD patients [71, 72].

12. Conclusions

Epidemiologic, observational and laboratory evidence have implicated vitamin D deficiency in the pathogenesis and complications of CVD. This lent extensive biologic plausibility to the theory that vitamin D levels would be an effective target

for CVD prevention. However, like many other trials of vitamin supplementation, large randomized placebo-controlled trial data from the general population have refuted this theory. Therefore, vitamin D supplementation for the purpose of CVD prevention is not recommended for the general public.

13. Future directions

Based on the findings in the most recent clinical trials, it appears that the last chapter may have been written regarding the role of vitamin D for CVD prevention in the general population. However, many questions still remain and will likely fuel ongoing investigation and debate. Was the follow-up in these recent trials long enough? Do large trials randomizing by baseline vitamin D status need to be conducted since the mean vitamin D levels in VITAL and VIDA were both above the deficient threshold of 20 ng/mL? [9, 10]. Are there benefits to vitamin D repletion for heart failure outcomes? What is the true benefit of vitamin D repletion on CVD outcomes in the chronic kidney disease and dialysis population? These questions and others regarding both CVD and other chronic disease states will likely keep the book open on vitamin D for the foreseeable future.

Author details

Jeremy I. Purow[1] and Seth I. Sokol[2,3]*

1 Yeshiva University, New York, New York, United States

2 Department of Medicine, Division of Cardiology, Jacobi Medical Center, Bronx, New York, United States

3 Albert Einstein College of Medicine, Bronx, New York, United States

*Address all correspondence to: seth.sokol@nychhc.org

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