Vitamin D Deficiency and Risk for Cardiovascular Disease

Suzanne Judd, MPH, PhD[2] and **Vin Tangpricha, MD, PhD**[1,3,4]

[1]Department of Biostatistics. University of Alabama at Birmingham

[2]Division of Endocrinology, Metabolism and Lipids. Department of Medicine. Emory University School of Medicine

[3]Center for Clinical and Molecular Nutrition, Department of Medicine. Emory University School of Medicine

[4]Staff Physician, Atlanta VA Medical Center, Decatur, Georgia

Abstract

Vitamin D is an important pro-hormone for optimal intestinal calcium absorption for mineralization of bone. Since the vitamin D receptor is present in multiple tissues, there has been interest in evaluating other potential functions of vitamin D, particularly in cardiovascular diseases. Cross-sectional studies have reported that vitamin D deficiency is associated with increased risk of cardiovascular disease, including hypertension, heart failure and ischemic heart disease. Initial prospective studies have also demonstrated that vitamin D deficiency increases the risk of developing incident hypertension or sudden cardiac death in individuals with pre-existing cardiovascular disease. Very few prospective clinical studies have been conducted to examine the effect of vitamin D supplementation on cardiovascular outcomes. The mechanism for how vitamin D may improve cardiovascular disease outcomes remains obscure; however, potential hypotheses include the down regulation of the renin-angiotensin-aldosterone system, direct effects on the heart and vasculature or improvement of glycemic control. This review will examine the epidemiologic and clinical evidence for vitamin D deficiency as a cardiovascular risk factor and to explore potential mechanisms for the cardio-protective effect of vitamin D.

Keywords

INTRODUCTION

The classic function of vitamin D is to increase the intestinal absorption of calcium for proper mineralization of bone[1]. The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$), acts as a steroid hormone by binding to the vitamin D receptor (VDR) which is present in many cells throughout the body including cardiomyocytes[2], vascular smooth muscle[3] and endothelium[4]. Recent evidence has demonstrated that individuals deficient in vitamin D are more likely to have cardiovascular disease or are at risk of developing incident cardiovascular disease. The mechanism for how vitamin D may protect individuals from cardiovascular disease has not been fully elucidated. Several mechanisms have been proposed including negatively regulating renin to lower blood pressure, improving vascular compliance,

Corresponding Author Vin Tangpricha M.D., Ph.D. Emory University Division of Endocrinology, Metabolism & Lipids 101 Woodruff Circle NE Woodruff Memorial Research Building, Room 1301 Atlanta GA 30322 Ph 404-727-7254 Fax 404-727-1300.

decreasing parathyroid hormone levels and improving glycemic control. The purpose of this review is to summarize the epidemiologic and early pre-clinical and clinical evidence for a protective role for vitamin D in the cardiovascular system.

PHYSIOLOGY OF VITAMIN D

Vitamin D can be produced in the skin as vitamin D_3 upon exposure to ultraviolet- B (UVB) from the sun or obtained from the diet as vitamin D_2 or vitamin D_3. After vitamin D enters the body, it circulates bound to vitamin D binding protein (DBP) and is rapidly converted to its major circulating form, 25-hydroxyvitamin D (25(OH)D) by the liver. Under the influence of parathyroid hormone (PTH), 25(OH)D is converted by the 1-alpha-hydroxylase (1α-OHase) in the kidney to form the hormonal form of vitamin D, 1,25-dihydroxyvitamin D (1,25 (OH)$_2$D). Other tissues in the body have the 1α-OHase and can convert 25(OH)D to 1,25 (OH)$_2$D[5]. However, only the renal 1α-OHase significantly contributes to circulating 1,25 (OH)$_2$D levels. It is speculated that the presence of the extra-renal 1α-OHases allow 25(OH) D to be converted to 1,25(OH)$_2$D to work as a paracrine or autocrine hormone

Circulating 1,25(OH)$_2$D enters the target cell, either in its free form or facilitated by megalin, and binds to the vitamin D receptor (VDR) in the cytoplasm which then translocates to the nucleus and heterodimerizes with the retinoic x receptor (RXR)[6]. The 1,25(OH)$_2$D-VDR-RXR complex then binds to vitamin D response elements (VDRE) on DNA to increase transcription of vitamin D regulated genes. Classic functions regulated by vitamin D include genes important for mineralization of bone and calcium transport in the intestine[7]. Non-classic or novel functions of vitamin D under investigation include genes important for innate immunity, cancer proliferation, muscle (both skeletal and smooth) function and endothelial cell proliferation[5].

Vitamin D status is best determined by a serum 25(OH)D as opposed to 1,25(OH)$_2$D, for several reasons including 1) its long circulating half life (~3 weeks versus ~8 hours), 2) the concentration of 25(OH)D is 1000x higher in circulation compared to 1,25(OH)$_2$D (ng/mL vs pg/mL) and 3) the production of 1,25(OH)$_2$D is mainly under the influence of PTH which tightly regulates calcium levels. Thus, 1,25(OH)$_2$D levels could be elevated in individuals with severe vitamin D deficiency in order to maintain normal serum calcium levels. As a mediator of cardiovascular disease, it is believed that 25(OH)D is the best biomarker to describe vitamin D status, although this has not been proven.

CROSS-SECTIONAL AND EPIDEMIOLOGIC EVIDENCE EVALUATING VITAMIN D STATUS AND CARDIOVASCULAR DISEASE RISK

Several observations in the early 1980s and 1990s suggested that an environmental factor such as vitamin D could explain differences in mortality from ischemic heart disease (IHD). Fleck recognized higher mortality rates with increased distance from the equator[8]. Grimes et al also recognized that mortality from IHD was inversely proportional to the amount of hours of sunlight in the United Kingdom [9]. He proposed vitamin D as a protective factor by regulating serum cholesterol levels or by inhibiting *Chlamydia pneumoniae*, once thought to be a cause of coronary heart disease. Douglas et al recognized that incidence and mortality rates from coronary heart disease demonstrated a strong seasonal pattern with higher rates in the winter, when vitamin D levels are lowest [10]. Rostand reported that blood pressure increased with increasing distance from the equator and suggested that cutaneously synthesized vitamin D could be playing a role in the regulation of blood pressure[11].

The National Health and Nutritional Examination Surveys (NHANES) (1988-1994, 2000-2004) conducted in the United States have provided a means to explore cross-sectional associations between vitamin D status and cardiovascular disease (CVD). Kendrick et al

reported that individuals surveyed in NHANES 1988-1994 with vitamin D deficiency (25(OH)D <20 ng/mL) had higher prevalence of self reported angina, myocardial infarction and heart failure compared to individuals with higher levels of vitamin D, (OR (95% CI) 1.20 (1.01, 1.36))[12]. In the most recent NHANES 2000-2004 survey, vitamin D deficiency (25(OH)D <20 ng/mL) was associated with increased prevalence of self reported coronary heart disease, heart failure and peripheral vascular disease[13]. Several cardiovascular risk factors have been associated with lower vitamin D status including hypertension, diabetes, elevated body mass index (>30), elevated triglyceride level and microalbuminuria in NHANES 1988-1994[14,15]. Prevalence of peripheral arterial disease is also increased comparing lowest quartile of 25(OH)D to highest quartile of 25(OH)D[16]. Judd et al determined in non-hypertensive individuals from NHANES 1988-1994, optimal vitamin D status (>32 ng/mL) provided a 20% reduction in the rate of blood pressure rise with age[17]. In contrast, smaller cross-sectional studies from Germany[18] and the Netherlands[19] have not been able to confirm an association between vitamin D status and blood pressure in older adults.

Melamed et al examined all cause mortality by quartile of 25(OH)D and found that the lowest quartile of 25(OH)D had significantly increased adjusted mortality rate ratios (MRR (95% CI) 1.28 (1.11-1.48) compared to individuals with the highest quartile of 25(OH)D[20]. There was a trend towards increased mortality rate in the lowest quartile of 25(OH)D due to cardiovascular mortality; however, this did not reach statistical significance (MRR (95% CI) 1.22 (0.90 - 1.65)). Thus, several epidemiologic findings seem to suggest that poor vitamin D status is associated with poor cardiovascular outcomes.

COHORT AND CASE-CONTROL STUDIES EVALUATING VITAMIN D STATUS AND CARDIOVASCULAR DISEASE RISK

Several studies have evaluated a baseline measurement of vitamin D status and prospectively evaluated long-term cardiovascular outcomes in subjects with no previous history of CVD. During a 10 year follow-up period, men in the Health Professionals Follow-up Study (HPFS) without previous CVD and vitamin D deficiency (25(OH)D < 15 ng/mL) exhibited a 2-fold increased rate of myocardial infarction.[21]. In the Framingham Offspring Study, subjects with no previous history of CVD and severe vitamin D deficiency (25(OH)D <10 ng/mL) experienced a hazard ratio of 1.80 (95% CI, 1.05 - 3.08) for developing a first cardiovascular event after 5 years of follow-up compared to subjects with higher levels of 25(OH)D (>15 ng/mL)[22].

Vitamin D status and risk of CVD has also been evaluated in subjects with established cardiovascular disease or end stage kidney disease (ESRD). In over 3000 subjects undergoing coronary angiography, severe vitamin D deficiency (25(OH)D <10 ng/mL) had 3 - 5 times risk of dying from sudden cardiac death or heart failure over a 7 year follow-up period compared to optimal levels of vitamin D (25(OH)D >30 ng/mL)[23]. Further, in these same subjects, vitamin D deficiency imparted a 50% increase in fatal stroke[24]. Subjects in the lowest quartile for 25(OH)D had increased hazard ratios for all cause and cardiovascular mortality compared to subjects in the highest quartile for 25(OH)D[25]. Similar findings have been reported in incident hemodialysis patients[26]. An earlier and smaller study from India did not establish any benefit from having optimal levels of 25(OH)D in subjects with established CVD[27]. In contrast, they reported that very high levels of 25(OH)D (>89 ng/mL) were associated increased risk of ischemic heart disease.

Several studies have examined the relationship between vitamin D status and incident hypertension. Men and Women participating in the HPFS and the Nurses' Health Study with vitamin D deficiency (< 15 ng/mL) had 3 - 6 fold increased risk of developing incident hypertension over a 4 year follow-up period compared to subjects with optimal vitamin D

status[28]. Similar protection with having optimal vitamin D status and the development of incident hypertension was seen in the Nurses Health Study II, a group of younger female subjects[29]. A large cohort study from the United Kingdom also reported that vitamin D status was inversely related to the development of components of the metabolic syndrome including hypertension[30].

RANDOMIZED CONTROLLED TRIALS OF VITAMIN D SUPPLMENTATION AND RISK OF CARDIOVASCULAR DISEASE

Given the early epidemiologic associations between vitamin D and hypertension, early studies of vitamin D supplementation have focused on vitamin D as a potential anti-hypertensive agent. A randomized controlled trial conducted in elderly German women demonstrated that modest amounts of vitamin D (400IU) plus calcium given over 8 week period significantly reduced systolic blood pressure by 9%[31]. Krause et al randomized 18 subjects with stage I hypertension to UVA exposure to skin (which does not produce vitamin D) and to UVB exposure to skin (which produces vitamin D_3) and demonstrated that systolic and diastolic blood pressure significantly decreased after 6 weeks of therapy in those subjects receiving UVB therapy, suggesting that cutaneously produced vitamin D resulted in lowered blood pressure[32]. In contrast, several smaller studies conducted primarily in elderly subjects have demonstrated no effect of vitamin D supplementation on blood pressure in Denmark[33], in Taiwan[34], and in the UK[35]. The Women's Health Initiative Study (WHI) conducted in the U.S. demonstrated no significant difference in systolic or diastolic blood pressure in women randomized to calcium and vitamin D (400 IU) at the end of 7 years of follow-up. Therefore, studies on vitamin D supplementation have not consistently demonstrated a positive effect on regulating blood pressure. However, several caveats should be noted including relatively low doses of vitamin D used as the intervention (typically ~400 IU), most studies did not demonstrate adequate improvement of 25(OH)D to optimal levels (>30 ng/mL), and adherence was low particular in the WHI study.

Very few studies have been conducted to evaluate vitamin D supplementation on risk of cardiovascular mortality. Two studies prospectively examined vitamin D supplementation on cardiovascular mortality. In the WHI, women randomized to vitamin D 400 IU daily and 1000 mg of calcium had no difference in all cause or cardiovascular mortality[36]. In a European study by Trivedi et al, elderly individuals receiving a daily equivalent dose of 800 IU of vitamin D did not have improved cardiovascular survival compared to controls[37]. A recent meta-analysis examined 9 randomized controlled trials and found a 8% reduction in all cause mortality with supplementation of very modest amounts of vitamin D (~500 IU). In this meta-analysis, cardiovascular mortality was reported only by two studies as discussed above[36,37]. The Institutes of Medicine currently recommend a daily intake of 400 - 600 IU of vitamin D for adults. Several experts believe this intake level is inadequate for adults to maintain a optimal vitamin D status and a daily intake of close to 1000 IU of vitamin D is required to maintain health[38].

PROPOSED PROTECTIVE MECHANISMS FOR VITAMIN D IN CARDIOVASCULAR DISEASE

The mechanism for how vitamin D may protect against cardiovascular disease has not been fully elucidated. Proposed mechanisms include effects on the renin-angiotensin system, on glycemic control, inflammatory cytokines, direct effects on the vasculature and regulation of parathyroid hormone levels and calcium deposition in vascular smooth muscle[22,39,40]. Studies to examine these mechanisms have been conducted mainly in pre-clinical studies with very little information available from clinical trials.

Vitamin D as a negative regulator of renin

Pioneering work by Yan Chun Li at the University of Chicago has re-invigorated interest in vitamin D as an anti-hypertensive agent. His group clearly established that vitamin D receptor (VDR) knock-out mice have elevated blood pressure, cardiac hypertrophy and elevated activation of the renin-angiotensin-aldosterone system (RAAS) which can be reversed with an angiotensin converting enzyme inhibitor[41]. Furthermore, wild type mice given injections of $1,25(OH)_2D_3$ demonstrated suppression of renin mRNA expression[41]. Several novel vitamin D analogues have also been demonstrated to inhibit renin expression in vitro, possibly leading to the development of specific cardio-selective vitamin D compounds for the treatment of hypertension without calcemic effects[42]. In a follow-up study, Li and colleagues demonstrated that $1,25(OH)_2D$ inhibits renin gene expression by sequestering cAMP response element binding (CREB), a necessary factor for the transcription of renin mRNA[43]. These very intriguing observations have yet to be translated in rigorous randomized controlled trials of vitamin D or its analogues on hypertension and signaling of the RAAS.

Vitamin D as a factor in improving insulin sensitivity

The pancreas possesses the vitamin D receptor (VDR) and the 1-alpha-hydroxylase and thus has the vitamin D machinery for circulating 25(OH)D to be converted to $1,25(OH)_2D$ to work as a paracrine or autocrine hormone Early studies have suggested that vitamin D deficient rodents are not able to adequately secrete insulin compared to vitamin D sufficient controls[44]. Several small observational and case-control studies have been published to suggest that vitamin D deficiency is associated with insulin resistance or impaired insulin secretion[45,46]. Several studies including one published by Scragg et al demonstrated that lower vitamin D status was associated with increased risk of diabetes and better insulin sensitivity [47,48]. In a longitudinal study of Finnish men and women, a 40% reduction in risk of developing Type II diabetes was observed after 17 years of follow-up in those with 25(OH)D levels > 28 ng/mL at baseline[49]. One prospective study evaluated the effect of vitamin D supplementation (400 IU daily) on fasting glucose and found that subjects with impaired fasting glucose at baseline had less of a rise in fasting glucose concentrations over a 3 year period compared to subjects randomized to placebo[50]. Taken together, this early evidence suggests that vitamin D may have an important role in regulating glycemic control which may also contribute to a benefical effect on cardiovascular outcomes.

Vitamin D as a direct factor on cardiac tissues and the vasculature

A few in vitro and in vivo studies have evaluated the role of vitamin D acting directly on cardiac tissue, especially in response to injury. Rahman et al demonstrated that matrix metalloproteinases (MMP), proteins that contribute to aberrant cardiomyocyte remodeling in response to injury and atherosclerosis, were up-regulated in vitamin D receptor knockout mice[51]. Vitamin D receptor knock-out mice have impaired cardiac relaxation and contractility[52] and develop left ventricular hypertrophy[41,53].

Clinical studies have evaluated the role of vitamin D directly on the vasculature. A cross-sectional study of 52 subjects with ESRD demonstrated a significant positive correlation between vitamin D status and arterial compliance measured by brachial artery flow mediated dilation and a negative correlation between aortic pulse wave velocity, both findings indicating decreased vascular compliance[54]. Vitamin D (1,25-hydroxyvitamin D) inhibited pro-fibrotic markers in vitro using mesenchymal multipotent cells, suggesting that vitamin D may also have a direct effect on the vasculature in response to injury[55]. Diabetic patients who ingested a single large dose of vitamin D (100,000 IU) had significant improvement in endothelial function measured by flow mediated dilation and decrease in blood pressure[56]. Finally, a recent randomized controlled trial of vitamin D supplementation in subjects with heart failure

demonstrated significant reductions in inflammatory cytokines involved in the pathophysiology of heart failure[57].

CONCLUSION

Vitamin D insufficiency is very common in the United States and world-wide. Several recent epidemiologic studies have demonstrated a strong association between vitamin D insufficiency and risk of cardiovascular disease, risk of diabetes and metabolic syndrome. Several prospective studies have suggested that vitamin D deficiency predisposes individuals to increased risk of incident hypertension, ischemic heart disease, sudden cardiac death or heart failure. Initial randomized clinical trials of vitamin D in the treatment of hypertension have yielded mixed results; however, the study design of these trials limits definitive conclusions. No large randomized clinical trial using vitamin D or its analogues on cardiovascular endpoints have been published to date.

The potential for vitamin D to have a role in the prevention and/or treatment of cardiovascular disease has some biologic plausibility. Several studies have demonstrated that vitamin D receptor knockout mice have increased surrogate markers of cardiovascular disease including hypertension, left ventricular hypertrophy and increased proteinuria. One of the leading hypotheses for the protective effects of vitamin D is its negative regulation on the renin-angiotensin-aldosterone system. Other mechanisms may also include effects on cardiac remodeling, the vasculature, inflammatory markers and glycemic control.

The results of future trials should provide guidance on how to manage vitamin D status in clinical practice. There are currently no universal guidelines for the screening and treatment of vitamin D insufficiency. Furthermore, the adequate intake levels established by the Institutes of Medicine have been recognized to be inadequate and are currently in revision. In the meantime, it may be prudent to screen individuals who are at highest risk for vitamin D insufficiency (institutionalized elderly, osteoporotic individuals, chronically ill patients, African-American patients, especially those with cardiovascular disease[58]) and treat with vitamin D to a 25(OH)D level of 30 ng/mL. The current evidence does not strongly support screening for vitamin D deficiency in all patients with established CVD or who are at risk for CVD. For the general population, increasing vitamin D status with a daily supplement containing at least 1000 IU of may be sufficient, especially in areas with increased latitude from the equator or during the winter months.

Acknowledgments

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