

Vitamin D and Cardiovascular Disease

Carrie W. Nemerovski, Pharm.D., Michael P. Dorsch, Pharm.D., Robert U. Simpson, Ph.D.,
Henry G. Bone, M.D., Keith D. Aaronson, M.D., and Barry E. Bleske, Pharm.D., FCCP

The hormonal derivative of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]₂D) or calcitriol, has been implicated in many physiologic processes beyond calcium and phosphorus homeostasis, and likely plays a role in several chronic disease states, in particular, cardiovascular disease. Experimental data suggest that 1,25(OH)₂D affects cardiac muscle directly, controls parathyroid hormone secretion, regulates the renin-angiotensin-aldosterone system, and modulates the immune system. Because of these biologic effects, vitamin D deficiency has been associated with hypertension, several types of vascular diseases, and heart failure. We conducted a MEDLINE search of the English-language literature (1950–2008) to identify studies that examined these relationships; additional citations were obtained from the articles retrieved from the literature search. Treatment with vitamin D lowered blood pressure in patients with hypertension and modified the cytokine profile in patients with heart failure. Measurement of serum 25-hydroxyvitamin D concentration usually provides the best assessment of an individual's vitamin D status. Serum levels below 20 ng/ml represent vitamin D deficiency, and levels above 30 ng/ml are considered optimal. Although the observational data linking vitamin D status to cardiovascular disease appear robust, vitamin D supplementation is not recommended as routine treatment for heart disease until definitive prospective, randomized trials can be carried out to assess its effects. However, such supplementation is often appropriate for other reasons and may be beneficial to cardiovascular health in certain patients.

Key Words: cardiology, cardiovascular disease, heart failure, hypertension, vascular disease, vitamin D, 1,25-dihydroxyvitamin D, 1,25(OH)₂D, 25-hydroxyvitamin D, 25(OH)D.

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OUTLINE

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Vitamin D is a fat-soluble vitamin, and in conjunction with parathyroid hormone, its hormonal derivative 1,25-dihydroxyvitamin D (1,25[OH]₂D or calcitriol) is largely responsible for the regulation of calcium and phosphorus homeostasis. The best known pathologic conditions associated with vitamin D deficiency affect bone health. Severe vitamin D deficiency can result in hypocalcemia and hypophosphatemia, leading to rickets and osteomalacia, conditions characterized by inadequate bone mineralization.¹ To maintain adequate stores of this essential nutrient, humans obtain vitamin D

by three routes: sunlight exposure, dietary intake, and pharmaceutical supplementation. Vitamin D obtained from sunlight exposure is the result of the conversion of 7-dehydrocholesterol in the skin to vitamin D₃ through solar ultraviolet B radiation.² Dietary and pharmaceutical sources of vitamin D are available as either vitamin D₂ (ergocalciferol), mainly derived from plant sources, or vitamin D₃ (cholecalciferol), primarily from animal sources. Vitamin D obtained from any source is converted predominantly in the liver to 25-hydroxyvitamin D (25[OH]D).³ With relatively low biologic activity, 25(OH)D is the major circulating form of vitamin D in the body and is representative of total vitamin D stores.² The final activating step occurs primarily in the kidney to produce 1,25(OH)₂D, the biologically active form of vitamin D.² The physiologic effects of vitamin D are mediated by the interaction of 1,25(OH)₂D with the vitamin D receptor (Figure 1).^{2, 4, 5} Although the circulating 1,25(OH)₂D level regulates calcium absorption and bone homeostasis, it appears that local conversion of 25(OH)D to 1,25(OH)₂D is important for autocrine and paracrine signaling in many tissues.⁶

Whereas most experts agree that the circulating level of 25(OH)D represents the total vitamin D status of an individual, what constitutes the optimum level of this vitamin remains

From the Departments of Pharmacy Services (Drs. Nemerovski and Dorsch) and Internal Medicine, Division of Cardiology (Dr. Aaronson), University of Michigan Health System, Ann Arbor, Michigan; the Department of Clinical, Social, and Administrative Sciences, University of Michigan College of Pharmacy, Ann Arbor, Michigan (Drs. Nemerovski, Dorsch, and Bleske); the Departments of Pharmacology (Dr. Simpson) and Internal Medicine, Divisions of Metabolism, Endocrinology and Diabetes (Dr. Bone) and Cardiology (Dr. Aaronson), University of Michigan Medical School, Ann Arbor, Michigan; and the Michigan Bone and Mineral Clinic, P.C., Detroit, Michigan (Dr. Bone).

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Address reprint requests to Carrie W. Nemerovski, Pharm.D., 1500 East Medical Center Drive, UHB2D301 SPC 5008, Ann Arbor, MI 48109-5008.

controversial. Despite this debate, many authorities currently define vitamin D deficiency as a 25(OH)D level less than 20 ng/ml.^{2, 6, 7} More recently, some have defined 25(OH)D levels between 20 and 30 ng/ml as a relative insufficiency in vitamin D, whereas levels over 30 ng/ml are thought to represent sufficient vitamin D stores.^{2, 8, 9} The therapeutic index of vitamin D, while broad, can be exceeded. Vitamin D intoxication can be seen when 25(OH)D levels exceed 150 ng/ml and can result in severe hypercalcemia, hyperphosphatemia, and ultimately, renal impairment (Table 1).^{2, 6, 7}

Due to the fortification of numerous food products with vitamin D, the prevalence of rickets has been greatly reduced. However, minor deficiencies are often seen, and it is estimated that 1 billion people worldwide have either vitamin D deficiency or relative insufficiency.² Age, season in which the vitamin D status is assessed, end-organ function, and several other factors all contribute to a person's vitamin D status. Risk factors for vitamin D deficiency include the following^{2, 5, 10, 11}:

- Inadequate sunlight exposure
- Dark skin tone
- Advanced age
- Being institutionalized
- Decreased dietary intake of vitamin D
- Living in northern latitudes
- Malabsorption syndromes
- Drugs that accelerate metabolism of 1,25(OH)₂D (e.g., phenytoin, phenobarbital, corticosteroids)
- Chronic kidney disease
- Liver dysfunction
- Obesity

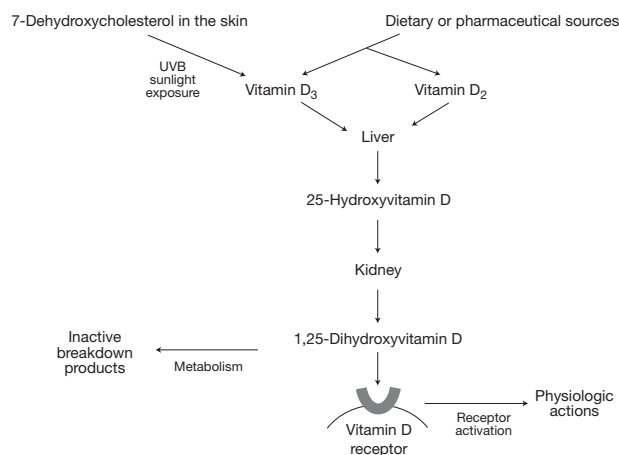


Figure 1. Vitamin D metabolism. UVB = ultraviolet B.

Table 1. Relationship Between Serum 25-Hydroxyvitamin D Concentration and Health^{2, 6, 7}

25-Hydroxyvitamin D Concentration (ng/ml)	Status	Health Consequence
< 15	Severe deficiency	Can lead to rickets and severe bone disease
< 20	Deficient	Inadequate bone health and osteoporosis
20–30	Relative insufficiency	Recently considered inadequate for optimal health status
> 30	Adequate stores	Optimal health status
> 150	Toxicity	Hypercalcemia, hyperphosphatemia, and renal impairment

Recently, vitamin D insufficiency has been associated with several chronic medical conditions such as osteoporosis, cancers, autoimmune diseases, and cardiovascular disease. The high prevalence of vitamin D deficiency combined with its potential to exacerbate disease have led to increased exploration of this relationship, particularly in the field of cardiovascular medicine. Thus, we conducted a MEDLINE search of the English-language literature (1950–2008) to identify studies that examined this relationship; additional citations were obtained from the articles retrieved from the literature search.

Pathophysiology of Vitamin D Deficiency in Cardiovascular Disease

The first studies to demonstrate a connection between cardiovascular homeostasis and vitamin D status used a rat model of vitamin D deficiency more than 20 years ago.^{12–14} These animal studies established a connection between vitamin D deficiency and cardiovascular dysfunction, including cardiac hypertrophy, fibrosis, hypertension, as well as alterations of serum calcium, parathyroid hormone, and renin levels. The studies supported a role for vitamin D in maintaining cardiovascular homeostasis through both a direct action of 1,25(OH)₂D on cardiomyocyte's vitamin D receptor and indirect actions on circulating hormones and calcium.

The first evidence that vitamin D deficiency could lead to human cardiovascular disease came from patients with end-stage renal disease (ESRD). The damaged kidney fails to convert 25(OH)D to 1,25(OH)₂D, resulting in a severe deficiency. In the absence of adequate 1,25(OH)₂D levels, secondary hyperparathyroidism develops resulting in elevated levels of circulating parathyroid hormone.¹⁵ Elevated levels of parathyroid hormone have been associated with increases in blood pressure and acute increases in cardiac contractility. The

sustained stress on myocardial tissue leads to cardiac hypertrophy, myocardial fibrosis, and heart failure (Figure 2).¹⁶ Administration of activated forms of vitamin D (1,25[OH]₂D or analogs) to patients with ESRD and secondary hyperparathyroidism has resulted in decreased left ventricular hypertrophy,¹⁷ along with a decrease in cardiovascular mortality.^{18, 19} Since elevations in parathyroid hormone levels are thought to be a primary cause of cardiac dysfunction, therapies aimed at decreasing circulating parathyroid hormone concentrations are often used in this patient population. Improvement in blood pressure and left ventricular hypertrophy regression after parathyroidectomy in patients with ESRD has been observed in some, but not all studies.^{17, 20, 21} The lack of consistent cardiovascular benefit observed after parathyroidectomy raises the following question: are long-term elevated levels of parathyroid hormone the sole cause of cardiac dysfunction seen in patients with ESRD? Based on these observations, it has been hypothesized that vitamin D metabolites not only regulate parathyroid hormone secretion, but also may have direct effects on cardiac function.

The vitamin D receptor is widely distributed throughout the body in several tissue types not involved in calcium metabolism such as lymphocytes, colonic cells, hepatocytes, and cardiac myocytes.²² The extensive expression of

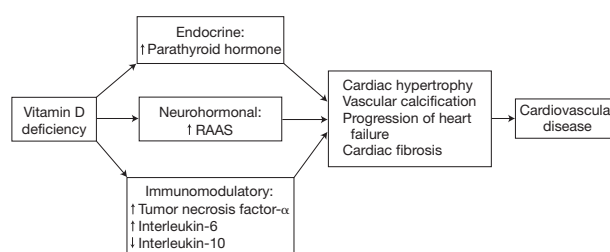


Figure 2. Cardiovascular pathophysiology of vitamin D deficiency. RAAS = renin-angiotensin-aldosterone system.

this receptor supports the notion that vitamin D plays a role in the endocrine system beyond the regulation of calcium homeostasis.⁴ Through interaction with the vitamin D receptor on the cardiac myocyte, $1,25(\text{OH})_2\text{D}$ regulates calcium influx into the cell, controls the amount of free cytosolic calcium available thus modifying contractility of the heart, and controls cell growth and proliferation.^{12-14, 23, 24} The direct physiologic consequences of the absence of the vitamin D receptor on cardiac function have been evaluated in several animal studies.²⁵⁻²⁷ In these studies, vitamin D receptor knockout mice were compared with their wild-type littermates at 12 months of life.^{25, 26} Histologic staining of cardiac tissue showed highly significant cellular hypertrophy in the vitamin D receptor knockout mice, and the heart:body weight ratio was significantly larger in vitamin D receptor knockout mice compared with that in wild-type mice. In addition to cardiac hypertrophy, cardiac fibrosis and collagen deposition were observed exclusively in the vitamin D receptor knockout mice.^{25, 26} Overall, these findings suggest an important role for the vitamin D receptor in cardiac physiology (Figure 2).

The vitamin D receptor knockout mouse has also provided evidence that vitamin D indirectly affects cardiac functioning because of its role as a negative regulator of the renin-angiotensin-aldosterone system (RAAS)^{27, 28} (Figure 2). One group of authors found that vitamin D receptor knockout mice had more than a 3-fold increase in renin messenger RNA (mRNA) expression and more than a 2.5-fold increase in plasma angiotensin II levels compared with wild-type mice.²⁸ Since $1,25(\text{OH})_2\text{D}$ regulates parathyroid hormone secretion and maintains calcium homeostasis, secondary hyperparathyroidism and hypocalcemia inevitably develop in vitamin D receptor knockout mice. The vitamin D receptor knockout mice in their study were evaluated early in life, before development of secondary hyperparathyroidism, and were supplemented with exogenous calcium to maintain adequate serum levels. Despite normal serum calcium and parathyroid hormone levels, vitamin D receptor knockout mice continued to produce elevated renin mRNA and plasma angiotensin II levels, suggesting that $1,25(\text{OH})_2\text{D}$ has a direct effect on the RAAS that is independent of calcium or parathyroid hormone.

In addition to RAAS activation, the upregulation of the immune system is often implicated in the pathophysiology of cardiovascular disease

(Figure 2). Immune system activation has been associated with atherosclerotic and valvular calcification, and plays a role in plaque instability and rupture.²⁹ Overproduction of inflammatory cytokines contributes to the development and progression of heart failure.³⁰ Experimental studies have suggested that vitamin D plays a role in the regulation of several important inflammatory and antiinflammatory cytokines.³¹⁻³³ In one study, a downregulation of inflammatory cytokine (interleukin [IL]-6 and tumor necrosis factor [TNF]- α) production was observed when activated monocytes were exposed to $1,25(\text{OH})_2\text{D}$.³² Conversely, in another study, the production of the antiinflammatory cytokine IL-10 significantly increased when dendritic cells were exposed to $1,25(\text{OH})_2\text{D}$ compared with control cells not so exposed.³¹ The aggregate data from these investigational studies suggest that the hormonal form of vitamin D plays an active and direct role in the regulation of several immunomodulatory cytokines, resulting in an overall downregulation of inflammation.

Vitamin D and Hypertension

The data from these experimental laboratory studies, particularly the association of vitamin D deficiency with RAAS activation, led to several small studies that attempted to correlate vitamin D levels with blood pressure in humans.³⁴⁻³⁶ In a small study conducted in 25 patients with hypertension, the authors found a significant inverse correlation between $25(\text{OH})\text{D}$ levels and systolic blood pressure, diastolic blood pressure, and calf vascular resistance, and a significant positive correlation between $25(\text{OH})\text{D}$ levels and calf blood flow.³⁴ A weaker, but still significant, inverse correlation was also noted between $1,25(\text{OH})_2\text{D}$ and systolic and diastolic blood pressure. Another study conducted in 100 normotensive men found a significant inverse correlation between serum levels of $1,25(\text{OH})_2\text{D}$ and systolic blood pressure; however, no significant correlation was noted between $1,25(\text{OH})_2\text{D}$ and diastolic blood pressure.³⁵ A third study did not detect any significant difference in $25(\text{OH})\text{D}$ levels when comparing hypertensive patients with matched controls.³⁶ In this study, hypertension was diagnosed based on one blood pressure reading, raising the possibility that several normotensive patients could have been placed in the hypertensive group.

Subsequently, large cross-sectional studies were

conducted to confirm these findings.^{37, 38} The third National Health and Nutrition Examination Survey (NHANES III) was a cross-sectional national survey representative of the noninstitutionalized U.S. population from 1988–1994. One group of authors analyzed survey participants in an attempt to define the correlation between blood pressure and vitamin D status.³⁷ Participants answered health information questionnaires and reported to mobile examination centers for blood pressure readings and blood sampling for determination of 25(OH)D level. A total of 12,644 patients were included in the analysis. Although all measurements were based on a single blood pressure reading, mean blood pressure varied inversely with serum 25(OH)D levels, and the association remained significant even after adjustment for age, sex, race-ethnicity, and physical activity. Conversely, a smaller cross-sectional survey conducted in Amsterdam that included 1205 patients failed to show an association between blood pressure and serum 25(OH)D levels.³⁸ Methods were similar to those used in the NHANES III analysis; however, patients treated with antihypertensive drugs were not excluded from the analysis. The lack of association between vitamin D levels and hypertension may be because only 10% of patients had vitamin D deficiency compared with over 20% of patients in the NHANES III analysis. The authors hypothesized that significant effects on blood pressure may be seen only in patients with lower levels of circulating vitamin D.

Among these five initial studies, an association between hypertension and vitamin D deficiency was observed in three studies, whereas no association was observed in two studies. Although the data from these observational studies are conflicting, the largest study (> 12,000 patients) did show a statistically significant association.³⁷

In addition to studying the association between hypertension and vitamin D deficiency, the risk of developing hypertension in patients with vitamin D deficiency was also studied in two prospective cohort studies that included more than 1800 patients.³⁹ In men from the Health Professionals' Follow-Up Study (HPFS) and women from the Nurses' Health Study (NHS I) without hypertension, the 25(OH)D level was measured during the study period. Participants were then followed for 4 years and evaluated for the development of hypertension. Individuals in each prospective cohort, evaluated separately or pooled together, had a greater risk of developing

hypertension if their 25(OH)D level was less than 15 ng/ml compared with those participants whose 25(OH)D level was greater than 30 ng/ml.

The associations seen between vitamin D deficiency and hypertension led to two prospective, randomized, controlled trials studying the effects of vitamin D supplementation on blood pressure.^{40, 41} In one of these studies, women older than 70 years who had 25(OH)D levels less than 20 ng/ml were randomly assigned to receive supplementation with calcium 1200 mg/day only or calcium 1200 mg/day plus vitamin D (cholecalciferol) 800 IU/day.⁴¹ Compared with calcium alone, treatment with cholecalciferol led to a significant reduction in systolic blood pressure and heart rate. Changes in diastolic blood pressure did not significantly differ between the groups. The reduction in systolic blood pressure was statistically significant ($p=0.02$) and appeared clinically significant as well, with mean \pm SD baseline systolic blood pressure of 144.1 ± 20.4 mm Hg declining to 131.0 ± 16.9 mm Hg after 8 weeks of treatment with vitamin D.

The other randomized trial was conducted in 34 patients with diabetes mellitus with a serum 25(OH)D level less than 20 ng/ml.⁴⁰ Patients were randomly assigned to receive a one-time dose of ergocalciferol 100,000 IU or placebo. The primary outcome of endothelial function assessed by flow-mediated vasodilation of the brachial artery in response to hyperemia was significantly improved in vitamin D–treated patients compared with the placebo group. In addition, vitamin D supplementation produced a significant decrease in systolic blood pressure that was not observed in the placebo group. Both randomized controlled trials achieved a significant reduction in systolic blood pressure with vitamin D supplementation even though the formulations and dosing regimens of vitamin D differed greatly between these two studies. However, each study was only conducted for 8 weeks, so it is unclear if the antihypertensive effect of vitamin D would be sustained over a longer period of time.

Table 2 summarizes the results of observational and randomized studies that evaluated the relationship between vitamin D and blood pressure.^{34–41}

Vitamin D and Vascular Disease

Since the activation of the RAAS and the immune system have been linked to vascular

Table 2. Studies of Vitamin D and Hypertension

Study Population	25(OH)D Level (ng/ml) ^a	Primary Outcome	Results
Observational studies			
Patients with HTN (n=25) ³⁴	17.8 ± 0.2	Correlate 25(OH)D levels with BP	Significant inverse correlation was noted between 25(OH)D level and SBP and DBP
Healthy men with no chronic diseases (n=100) ³⁵	25.3 ± 8.0	Correlate 1,25(OH) ₂ D levels with BP	Significant inverse correlation was noted between 1,25(OH) ₂ D level and SBP; no significant correlation was noted with DBP
Patients with HTN (n=186) and matched controls without HTN (n=186) ³⁶	26 ± 8 (HTN) 27 ± 11 (no HTN)	To compare mean vitamin D levels between patients with and those without HTN	No significant difference in vitamin D levels between patients with and those without HTN
Patients from NHANES III cohort (n=12,644) ³⁷	31.2 (males) 29.2 (females)	To compare BP between the highest quintile (≥ 34 ng/ml) and lowest quintile (≤ 16.2 ng/ml) of serum 25(OH)D concentrations	SBP and DBP were significantly higher in the lowest quintile compared with the highest quintile
Patients from the Longitudinal Aging Study (cross-sectional study) (n=1205) ³⁸	21.6	Use multiple linear regression to determine the association between 25(OH)D levels and SBP or DBP	No significant association was noted between serum 25(OH)D level and either SBP or DBP
Patients from the NHS I and HPFS prospective cohorts (n=1811) ³⁹	Not reported	To determine the RR of developing HTN in those with vitamin D deficiency (< 15 ng/ml) compared with those with sufficient vitamin D stores (≥ 30 ng/ml)	Increased risk of developing HTN over 4 yrs in both cohorts individually or combined when 25(OH)D level was < 15 ng/ml
Randomized studies			
148 women aged ≥ 70 yrs with serum 25(OH)D levels < 20 ng/ml (74 received calcium 1200 mg/day + vitamin D [cholecalciferol] 800 IU/day and 74 received calcium alone) ⁴¹	Baseline: 10.3 ± 5.4 (calcium + vitamin D) vs 9.8 ± 4.8 (calcium alone), p=NS	To compare SBP, DBP, and HR between patients who received calcium + vitamin D and those who received calcium alone	Mean SBP and HR were significantly reduced in the calcium + vitamin D group compared with the calcium alone group
34 patients with diabetes and serum 25(OH)D levels < 20 ng/ml (17 received vitamin D [ergocalciferol 100,000 IU x 1 dose] and 17 received placebo) ⁴⁰	Baseline: 16.1 ± 4.1 (vitamin D) vs 14.6 ± 3.4 (placebo), p=0.25	To compare FMD of the brachial artery in response to hyperemia in patients who received vitamin D with those who received placebo	Patients who received vitamin D had significant improvement in FMD and significantly decreased SBP compared with placebo-treated patients

25(OH)D = 25-hydroxyvitamin D; HTN = hypertension; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; 1,25(OH)₂D = 1,25-dihydroxyvitamin D; NHANES = National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; HPFS = Health Professionals' Follow-Up Study; RR = relative risk; CI = confidence interval; NS = not significant; HR = heart rate; FMD = flow-mediated vasodilation.

^aData are mean or mean ± SD.

disease, exploration of the relationship of vitamin D deficiency in humans to vascular disease was a logical next step. Subsequently, vitamin D deficiency was implicated in several types of vascular disease including peripheral artery disease (PAD), atherosclerosis, myocardial infarction, and ischemic stroke. A recent NHANES conducted from 2001–2004 was analyzed to determine the association between

25(OH)D levels and the prevalence of PAD.⁴² In this study, PAD was defined as an ankle brachial index of less than 0.9 and was seen in 406 of the 4839 patients evaluated. Patients with PAD had significantly lower mean serum 25(OH)D levels than participants without PAD, although the difference was numerically small and some may question its clinical significance. However, further analysis revealed a graded association

Table 2. (continued)

Statistical Significance
25(OH)D level and SBP: $r = -0.511$, $p=0.01$ 25(OH)D level and DBP: $r = -0.445$, $p=0.03$
1,25(OH) ₂ D level and SBP: $r = -0.24$, $p=0.016$ 1,25(OH) ₂ D level and DBP: $r = -0.19$, $p=0.06$
$p=0.20$
$p<0.05$ for SBP and DBP $p<0.05$ after adjustment for age, sex, race-ethnicity, and physical activity
$p=0.64$ for SBP $p=0.22$ for DBP $p>0.05$ after adjustment for multiple confounders
NHS I: RR 2.67 (95% CI 1.05–6.79) HPFS: RR 6.13 (95% CI 1.00–37.8) Pooled analysis: RR 3.18 (95% CI 1.39–7.29)
Change in SBP: $p=0.02$ Change in DBP: $p=0.10$ Change in HR: $p=0.02$
FMD: 2.35% vs 0.06%, $p=0.048$ Change in SBP: -7.3 vs $+6.6$ mm Hg, $p=0.001$

between lower 25(OH)D levels and a higher prevalence of PAD, suggesting that small differences in serum 25(OH)D level can greatly affect PAD risk. The relationship remained significant even after multivariable adjustment for age, sex, diabetes, cholesterol levels, statin use, blood pressure, and chronic kidney disease.⁴² More severe atherosclerosis, measured by carotid artery intimal medial thickness, was associated with lower vitamin D levels in a study conducted in 390 patients with diabetes.⁴³ Patients with vitamin D deficiency had significantly greater carotid artery intimal medial thickness than those

with sufficient vitamin D stores. This relationship remained significant after adjustment for age, sex, duration of diabetes, low-density lipoprotein cholesterol (LDL) concentration, drug therapy, and renal function. The authors also noted that patients with diabetes had significantly lower mean 25(OH)D levels compared with those of age-matched controls without diabetes. However, it was unclear if the vitamin D levels in the matched controls were obtained during the same season as those in the patients with diabetes.

A clear association between vitamin D status and the occurrence of acute myocardial infarction has not been rigorously established. One author actually found that patients who experienced an acute myocardial infarction reported a higher intake of vitamin D (dietary and supplementation) compared with matched controls.⁴⁴ This study did not, however, report serum vitamin D levels, so the true vitamin D status of these patients could not be assessed. Based on the concern that a higher vitamin D status could lead to an increased frequency of acute myocardial infarction, several subsequent small studies attempted to clarify these results.^{45–47} One study compared 25(OH)D levels between 15 patients with a diagnosis of acute myocardial infarction and 60 age-matched control patients; vitamin D levels did not differ significantly between groups.⁴⁶ In a study that compared 128 patients with either acute myocardial infarction or angina with 409 healthy control subjects, overall 25(OH)D levels were similar between groups.⁴⁵ However, 25(OH)D levels were significantly lower in the patients with heart disease compared with those in the controls in the spring and summer months.

Another group conducted the first prospective case-control study of vitamin D levels and the occurrence of acute myocardial infarction.⁴⁷ Participants in the Tromso Heart Study who were free of cardiovascular disease at the outset of the study were included. They were followed for 4 years, and the primary outcome of acute myocardial infarction occurred in 30 patients. Sixty controls matched for age and season of vitamin D level collection were compared with the 30 patients who experienced an acute myocardial infarction. No significant difference in mean 25(OH)D levels was noted between groups.

These older studies show no clear association between vitamin D levels and myocardial infarction, but they fail to account for LDL

concentrations, presence of diabetes, or previous cardiovascular disease—markers we now know are risk factors for development of a myocardial infarction.

Almost 30 years after the Tromso Heart Study, another group published the largest study to date attempting to define the relationship of vitamin D levels to the risk of acute myocardial infarction.⁴⁸ Men from the HPFS who provided a blood sample from 1993–1995 were evaluated. After exclusion of participants with a history of cardiovascular disease before 1994, 454 men experienced a nonfatal acute myocardial infarction or fatal coronary heart disease by 2004. Nine hundred matched controls without cardiovascular disease were randomly selected from study participants and were compared with the 454 participants who experienced an event. Plasma 25(OH)D levels were significantly lower in cases compared with controls, and men with deficient levels of 25(OH)D had a significantly elevated risk for acute myocardial infarction. This relative risk remained significant after adjustment for family history, diabetes, hypertension, race-ethnicity, body mass index, cholesterol levels, and renal function. Vitamin D deficiency emerged as an independent risk factor for nonfatal acute myocardial infarction or fatal coronary heart disease, and men with vitamin D levels of 30 ng/ml or higher had approximately half the risk, independent of other factors.

The association of vitamin D deficiency with all-type cardiovascular disease (defined as coronary artery disease, PAD, and cerebrovascular disease) has also been evaluated in several studies.^{49, 50} More than 400 patients with diabetes without renal or hepatic disease were evaluated in one study.⁴⁹ Serum 25(OH)D concentrations were measured at a single outpatient visit for all eligible patients. Patients with vitamin D deficiency (defined as < 20 ng/ml) had a higher prevalence of cardiovascular disease. Logistic regression analysis revealed that the association between vitamin D deficiency and cardiovascular disease remained statistically significant after adjustment for renal function, drug therapy, LDL concentrations, presence of metabolic syndrome, and hemoglobin A_{1c} concentrations.

In another study, 1739 participants from the Framingham Offspring cohort were prospectively evaluated to determine if lower vitamin D concentrations could predict the development of cardiovascular disease.⁵⁰ To be included in the analysis, participants had to have serum 25(OH)D levels measured between 1996 and 2001, and

those with known cardiovascular or kidney disease were excluded from the analysis. Participants were then followed for a median of 5.4 years after blood sample collection to determine the frequency of myocardial infarction, stroke, angina, transient ischemic attack, peripheral claudication, or heart failure. Multivariable Cox regression analysis revealed that vitamin D deficiency (< 15 ng/ml) was associated with an increased risk of cardiovascular events. This association retained statistical significance after adjustment for renal function, drug therapy, blood pressure, LDL concentrations, and other known cardiovascular risk factors. The 5-year rate of developing a cardiovascular event was twice as high in those with vitamin D deficiency as in those with greater vitamin D stores.

Vitamin D deficiency has not only been linked to several vascular diseases, but has also been associated with an increase in all-cause and cardiovascular mortality. The Ludwigshafen Risk and Cardiovascular Health (LURIC) cohort was evaluated to determine the relationship between vitamin D deficiency and mortality.⁵¹ Patients who were referred for coronary angiography were included in this prospective cohort study. Serum concentrations of 25(OH)D were measured at enrollment, and patients were then followed for a median of 7.7 years. Lower 25(OH)D and 1,25(OH)₂D levels were associated with a statistically significant increase in all-cause and cardiovascular mortality even after adjustment for multiple traditional cardiovascular risk factors. This inverse association with mortality was noted even in patients who had less than 20% stenosis on baseline angiogram. The authors concluded that a low 25(OH)D level can be considered a strong risk indicator for mortality.

These observational studies have shown a strong link between vitamin D deficiency and several types of vascular diseases, including PAD,⁴² increased carotid artery intimal medial thickness,⁴³ and myocardial infarction.⁴⁸ In addition, vitamin D deficiency has been associated with cardiovascular and all-cause mortality.^{51–53} Although these studies are primarily observational, their data support the hypotheses suggested by early experimental studies and provide evidence to conduct prospective randomized trials evaluating the role of vitamin D supplementation on preventing or treating vascular disease.

Only one study has evaluated the effect of vitamin D supplementation on cardiovascular

disease prevention.⁵⁴ In the Women's Health Initiative, more than 36,000 postmenopausal women were randomly assigned to receive calcium 500 mg plus vitamin D₃ (cholecalciferol) 200 IU twice/day or matching placebo. Patients were followed for a mean of 7.0 years, and the occurrence of cardiovascular events and death was determined for all patients. Occurrences of myocardial infarction, stroke, transient ischemic attack, confirmed angina, coronary artery bypass grafting or percutaneous coronary intervention, and cardiovascular death were similar between the two groups. The authors concluded that calcium plus vitamin D supplementation does not decrease the risk for coronary heart disease or stroke in postmenopausal women. This study, however, had several limitations that may have affected the results. Participants assigned to the calcium plus vitamin D group received a daily dose of only 400 IU of vitamin D, which may not be adequate for the prevention of cardiovascular diseases and is well below the recommended daily intake of 800 IU for postmenopausal women for the prevention of osteoporosis.^{2, 55} Women in the placebo group were permitted to take vitamin D supplements, which may have resulted in similar vitamin D intake in each group, nullifying the differences that might have been seen between the two groups. Finally, baseline 25(OH)D levels were not measured in this study. The benefit of supplementing only deficient individuals could not be assessed since treatment assignment was determined irrespective of vitamin D status. Large prospective trials assessing adequate doses of vitamin D supplementation in individuals with relatively low levels are needed to understand the role of vitamin D in the prevention of cardiovascular disease.

Table 3 summarizes the results of the observational and randomized studies that evaluated the relationship between vitamin D and vascular disease.^{42-51, 54}

Vitamin D and Heart Failure

The activation of the RAAS and the immune system associated with vitamin D deficiency has the potential to cause deleterious effects in patients with heart failure. The relationship between vitamin D levels and the frequency and severity of heart failure has been explored in several studies.⁵⁶⁻⁶² The authors of one study measured 25(OH)D levels in 25 African-American patients with heart failure.⁵⁸ They

divided patients into three groups: those with decompensated heart failure for 4 weeks or longer, those with decompensated heart failure for 1-2 weeks, and those with compensated heart failure. Mean 25(OH)D levels were compared among the groups. Although a trend toward lower 25(OH)D levels was noted in the most severely decompensated group, it did not reach statistical significance. A slightly larger study conducted with a similar methodology found that although mean 25(OH)D levels were similar among the three groups of patients with heart failure, they were significantly lower than the mean level of matched controls without heart failure.⁵⁷ The average creatinine clearance did not differ significantly between patients with heart failure and controls, and blood samples were obtained during the same season for patients with heart failure and controls.

Another group of authors enrolled 60 patients with systolic heart failure and found a significant positive correlation between 25(OH)D level and 6-minute walk test performance.⁵⁶ After multivariable logistic regression, lower vitamin D levels emerged as an independent predictor of poorer performance on the 6-minute walk test. Another study was conducted in 101 patients with heart failure who were undergoing evaluation for cardiac transplantation.⁵⁹ Among patients on the cardiac transplantation waiting list, those with more severe heart failure (those listed as United Network for Organ Sharing [UNOS] status 1) had significantly lower serum 25(OH)D concentrations than patients who were less ill (UNOS status 2). In addition, almost 25% of status 1 patients had severe vitamin D deficiency compared with less than 10% of status 2 patients.

In another study, 54 patients with New York Heart Association (NYHA) class II or greater heart failure with serum creatinine level less than 2 mg/dl were evaluated.⁶⁰ Twenty patients were younger than 50 years, and 34 were older than 50 years. A total of 34 elderly matched controls without heart failure were also evaluated. Serum 25(OH)D concentrations were significantly lower in patients with heart failure, regardless of age, compared with the elderly healthy controls. The authors also noted that elderly patients with heart failure had significantly higher levels of TNF- α compared with elderly controls. Most recently, 383 patients with end-stage heart failure awaiting cardiac transplantation were evaluated by the same authors.⁶¹ Patients were divided into two groups: those who were designated as an

Table 3. Studies of Vitamin D and Vascular Disease

Disease State, Study Population	25(OH)D Level (ng/ml) ^a	Primary Outcome	Results
Observational studies			
PAD	21.5 ± 0.6	To compare mean 25(OH)D	Patients with PAD had significantly lower
Patients from NHANES	(PAD)	levels between those with and	25(OH)D levels
2001–2004 cohort	24.6 ± 0.5	those without PAD	Lowest quintile of 25(OH)D (< 17.8 ng/ml)
(n=4839) ⁴²	(no PAD)		had a higher prevalence of PAD
			compared with the highest quintile of
			25(OH)D (≥ 29.2 ng/ml)
Atherosclerosis	19.3	To compare carotid intimal	Significantly larger carotid intimal medial
Patients with type 2		medial thickness between	thickness in patients with vitamin D
diabetes without		patients with vitamin D	deficiency compared with those
chronic liver or		deficiency and those with	without vitamin D deficiency
kidney disease		sufficient vitamin D stores	
(n=390) ⁴³			
MI	Not measured	To compare the average daily	Significantly higher average daily intake
150 patients who had an		intake of vitamin D among	of vitamin D in previous MI group than
MI, 88 with angina, and		patients who had a previous	in those without a previous MI
and 238 matched		MI with those who did not	No significant differences were noted
controls ⁴⁴		have a previous MI	between angina group and matched
			controls
MI	12.8 (MI)	To compare 25(OH)D levels	No significant differences in 25(OH)D
15 patients who had an	16.8 (controls	between patients who had an	levels were noted between groups
MI, 60 matched	aged 40–60 yrs)	MI and matched controls	
controls ⁴⁶	8.4 (controls		
	aged 60–80 yrs)		
MI	23.5 ± 10 (MI)	To compare 25(OH)D levels	25(OH)D levels were significantly lower
128 patients with chest	23.5 ± 9.6	between patients with chest	in patients with chest pain in the spring
pain (53 had an MI,	(angina)	pain and healthy controls in	and summer and not significantly
75 had angina), and	28.8 ± 12.3	each of the four seasons	different in fall and winter; overall, no
409 healthy controls ⁴⁵	(controls)		significant differences were noted
			between groups
MI	23.6 (MI)	To compare the mean	No significant difference in 25(OH)D
90 patients from the	25.4 (controls)	25(OH)D level between	level noted between groups over 4 yrs
Tromso Heart Study		participants who had an MI	of follow-up
prospective cohort		and those who did not	
(30 who had an MI,			
60 matched controls			
who did not) ⁴⁷			
MI	22.9 (MI)	To compare the mean 25(OH)D	Significantly lower 25(OH)D levels were
1354 men from the	24.5 (controls)	level between participants who	noted in those who had an MI compared
HPFS prospective		had an MI and those who did not	with those who did not have an MI
cohort (454 who had		To determine the RR of having an	Men with deficient levels of 25(OH)D
an MI, 900 matched		MI in patients with vitamin D	had a significantly elevated risk of MI
controls who did not) ⁴⁸		deficiency (< 15 ng/ml)	over 10 yrs
All-type CVD ^b	19.7	To compare the prevalence	Prevalence of CVD was greater among
Patients with type 2		of all-type CVD between	patients with vitamin D deficiency
diabetes without liver		patients with vitamin D	Logistic regression revealed a significant
or kidney disease		deficiency (< 20 ng/ml) and	association between vitamin D
(n=459) ⁴⁹		those without vitamin D	deficiency and prevalent CVD
		deficiency	
All-type CVD ^b	19.7	To determine the HR of	Rate of CVD development was twice as
1739 participants in		developing CVD in patients	high in those with vitamin D deficiency
the Framingham		with vitamin D deficiency	as in those without vitamin D deficiency
Offspring prospective		(< 15 ng/ml)	
cohort (120 developed			
CVD, 1619 did not) ⁵⁰			
All-type CVD ^b	17.3	To determine the HR of all-cause	All-cause and CV mortality increased
3258 participants in		and CV mortality in patients	significantly in patients within lowest
the LURIC prospective		within the lowest quartile of	quartile of vitamin D levels compared
cohort referred for		vitamin D levels compared with	with those in the highest quartile
coronary angiography ⁵¹		those in the highest quartile	over a median of 7.7 yrs

Table 3. (continued)

Statistical Significance
p<0.001, RR 2.18 (95% CI 1.50–3.16) Differences remained significant after multivariable adjustment
1.10 ± 0.15 vs 0.87 ± 0.14 mm, p=0.001 Differences in intimal medial thickness remained significant after multivariable adjustment
MI vs no MI: 31.3 vs 22.9 µg (men), p<0.001; 34.1 vs 20.7 µg (women), p<0.0025 Angina vs controls: p>0.05
p=NS
Patients with chest pain vs healthy controls: Spring: p<0.01 Summer: p<0.05 Fall: p=NS Winter: p=NS All seasons: p=NS p=NS
p=0.002
RR 2.42 (95% CI 1.53–3.84), p<0.001 RR remained significant after multivariable adjustment
24.4% vs. 35.5%, p=0.01 OR 1.7 (95% CI 1.1–2.6), p<0.01 OR remained significant after multivariable adjustment
HR 2.04 (95% CI 1.42–2.94), p<0.001 HR remained significant after multivariable adjustment
All-cause mortality: HR 3.33 (95% CI 2.66–4.16) CV mortality: HR 2.22 (95% CI 1.57–3.13) HR remained significant after multivariable adjustment

elective transplantation listing, and those who were designated as an urgent transplantation listing. Serum 1,25(OH)₂D concentrations were determined for all patients at the beginning of the study, and patients were then followed for 1 year to assess mortality and need for transplantation. After multivariable logistic regression, lower 1,25(OH)₂D levels were significantly associated with risk of initial urgent transplantation listing. In addition, Kaplan-Meier curves illustrated that a lower 1-year survival rate was noted in those patients with lower 1,25(OH)₂D concentrations.

Finally, the LURIC cohort of patients referred for coronary angiography, discussed earlier,⁵¹ was subsequently evaluated to determine the relationship between vitamin D deficiency and death due to heart failure or sudden cardiac death.⁶² This subsequent study evaluated 3299 Caucasian patients from the cohort and followed them for a median of 7.7 years.⁶² After adjustment for multiple traditional cardiovascular risk factors, patients with severe vitamin D deficiency (25[OH]D < 10 ng/ml) had a significantly increased risk for death due to heart failure and sudden cardiac death when compared with patients with optimal levels of vitamin D (25[OH]D ≥ 30 ng/ml). In addition, serum 25(OH)D concentrations inversely correlated with N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and NYHA class.

The aggregate data from the above-discussed seven studies suggest that patients with heart failure have lower serum vitamin D levels. In the only randomized trial evaluating vitamin D supplementation in patients with heart failure, a total of 123 ambulatory patients with NYHA class II or greater heart failure were randomly assigned to receive calcium 500 mg plus cholecalciferol 2000 IU/day or calcium 500 mg plus matching placebo each day for 9 months.⁶³ Patients with a serum creatinine level greater than 2 mg/dl were excluded. Survival rates at 15 months' follow-up and changes in biochemical markers at the end of the 9 months of treatment were compared between groups. Patients who received vitamin D supplementation had a significant decrease in TNF-α levels compared with patients receiving placebo, whose levels actually increased over time. Conversely, serum levels of the antiinflammatory cytokine IL-10 significantly increased in vitamin D-treated patients compared with patients receiving placebo, whose levels decreased. No significant differences in left ventricular ejection fraction (LVEF), C-reactive protein levels, or blood pressure were noted

Table 3. Studies of Vitamin D and Vascular Disease (continued)

Disease State, Study Population	25(OH)D Level (ng/ml) ^a	Primary Outcome	Results	Statistical Significance
Randomized study				
All-type CVD ^b	Not measured	To compare the occurrence of CVD between patients who received calcium + vitamin D vs those who received placebo	Calcium and vitamin D supplementation neither increased nor decreased the risk for CVD development over 7 years	p=NS
36,282 postmenopausal women in the WHI prospective cohort (18,176 received calcium 500 mg + vitamin D [cholecalciferol] 200 IU twice/day and 18,106 received matching placebo) ⁵⁴				

25(OH)D = 25-hydroxyvitamin D; PAD = peripheral artery disease; NHANES = National Health and Nutrition Examination Survey; MI = myocardial infarction; NS = not significant; HPFS = Health Professionals' Follow-Up Study; RR = relative risk; CI = confidence interval; CVD = cardiovascular disease; OR = odds ratio; HR = hazard ratio; LURIC = Ludwigshafen Risk and Cardiovascular Health cohort; CV = cardiovascular; WHI = Women's Health Initiative.

^aData are mean or mean \pm SD.

^bDefined as coronary artery disease, peripheral artery disease, and cerebrovascular disease.

between the two groups. Kaplan-Meier estimates of survival were not significantly different between groups. At study completion, vitamin D-treated patients had a mean 25(OH)D concentration of 42 ng/ml, which was a significant increase from baseline (14.4 ng/ml), but well below the toxic range (> 150 ng/ml). This study provides the first evidence that vitamin D supplementation can positively modify the cytokine profile of patients with heart failure, which is a research area of great interest. However, vitamin D supplementation was unable to improve survival or alternative markers of heart failure severity such as LVEF, or NT-proBNP or C-reactive protein levels. The lack of consistent benefit among all measured variables may relate to the size of the study population, dose of vitamin D, or the time between baseline and final measurements, all of which should be explored in future studies.

Table 4 summarizes the results of observational and randomized studies that evaluated the relationship between vitamin D and heart failure.⁵⁶⁻⁶³

Remaining Controversies for Future Evaluation

In most studies reviewed, a significant inverse correlation was found between vitamin D metabolite levels and cardiovascular disease. This relationship persisted when studied in a variety of specific cardiovascular disease states and in both small and large cohorts. However, most studies merely showed a correlation between vitamin D deficiency and cardiovascular disease, without proving causation. It is entirely

possible that patients with cardiovascular diseases are more debilitated, spend less time in the sunlight, and consequently have lower vitamin D levels.

To provide answers to this "chicken or the egg" debate, prospective trials evaluating the utility of vitamin D supplementation are necessary. Only a limited number of prospective, randomized, controlled trials designed to study the potential cardiovascular benefit of vitamin D supplementation exist, and analyses were not always adjusted for renal function, serum vitamin D levels were not always measured, the seasons in which vitamin D levels were obtained varied, and vitamin D intake for patients receiving placebo was not always controlled. Despite these limitations, an association between vitamin D deficiency and cardiovascular disease remains plausible and warrants further investigation.

Serum Vitamin D Level Threshold

Most studies showed a significant association between vitamin D deficiency and cardiovascular disease, but the serum level that defined vitamin D deficiency differed among studies. Only one study used an extremely low cutoff, a serum 25(OH)D level below 9 ng/ml, to define vitamin D deficiency,⁵⁹ whereas most studies used a level below 15 ng/ml^{39, 43, 48, 50} or 20 ng/ml.^{40, 41, 49} The two prospective trials showing a benefit with vitamin D supplementation enrolled patients only if their 25(OH)D level was less than 20 ng/ml,^{40, 41} and the third positive prospective study did not have a cutoff for eligibility, but mean 25(OH)D serum levels were 14.4 ng/ml

(range 11.5–22.1 ng/ml) in the vitamin D treatment group.⁶³ Several large prospective cohort studies established a lower risk of developing cardiovascular disease among patients with serum 25(OH)D levels above 30 ng/ml, a cutoff that has been suggested to distinguish vitamin D insufficiency from vitamin D sufficiency.^{39, 48, 51} Also, in each randomized controlled trial, vitamin D–treated patients had positive clinical outcomes and achieved mean 25(OH)D levels greater than 24 ng/ml and up to 42 ng/ml.^{40, 41, 63}

Based on the variety of cutoff values studied, it appears that levels less than 15 ng/ml were generally associated with a higher frequency of cardiovascular disease, and that risk was seen with 25(OH)D levels up to 20 ng/ml. Lower rates of disease were seen mainly in participants with levels above 30 ng/ml, but benefit, at least in patients with hypertension, was achieved by raising serum concentrations above 24 ng/ml. The cutoff values for vitamin D deficiency and cardiovascular disease risk suggested by these studies are in concordance with the latest definitions of vitamin D deficiency and insufficiency (Table 1). However, it may not be biologically reasonable to characterize serum 25(OH)D concentrations as either “deficient” or “sufficient,” but rather they might represent a continuous spectrum of cardiovascular disease risk.

Assessment of Vitamin D Status

What does seem clear from these data is that 25(OH)D concentration is a useful and appropriate marker of vitamin D status. Most studies used 25(OH)D exclusively, and those that also used 1,25(OH)₂D generally showed similar, but often weaker, correlations than were seen with 25(OH)D.^{34, 35, 51, 59, 61} Although 1,25(OH)₂D is the biologically active form of vitamin D, it is not the ideal marker of total body vitamin D stores. As a person becomes vitamin D deficient and serum calcium levels decrease, the body compensates by increasing parathyroid hormone secretion, which in turn promotes the renal production of 1,25(OH)₂D.⁷ Thus, despite total body vitamin D deficiency, 1,25(OH)₂D levels may appear normal. Eventually, the reduced availability of 25(OH)D will lead to a detectable decrease in serum 1,25(OH)₂D levels, but the first signs of vitamin D deficiency are best detected by the serum 25(OH)D level.⁷ In addition, although most 25(OH)D is converted to

1,25(OH)₂D in the kidney, it is recognized that many other tissues in the body (brain, colon, prostate, breast, immune cells, and others) have the capacity to convert 25(OH)D to 1,25(OH)₂D. These other tissue types rely on this local production of 1,25(OH)₂D to help control cell growth, differentiation, and activation.⁶ Therefore, for the body to maintain physiologic homeostasis, 25(OH)D levels must be adequate, regardless of 1,25(OH)₂D concentrations.

Another marker that may be considered for monitoring vitamin D status is parathyroid hormone level, since elevated levels are often implicated in many of these cardiovascular disease states.¹⁶ However, treatment of secondary hyperparathyroidism in these patients requires the administration of vitamin D, so evaluating the vitamin D status of an individual is more direct, whereas the role of parathyroid hormone level is confirmatory. Also, some adverse effects of vitamin D deficiency may occur in the absence of, or before, the development of secondary hyperparathyroidism.^{28, 61} Most data linking vitamin D to cardiovascular disease were obtained using this serum marker, and in the absence of renal insufficiency, 25(OH)D represents the main marker of the vitamin D status of an individual.

Vitamin D Supplementation

Along with the uncertainty surrounding serum vitamin D levels, the preferred formulation and dosage regimen for vitamin D supplementation have not been established. Cholecalciferol was used in two studies,^{41, 63} whereas ergocalciferol was used in another.⁴⁰ Large one-time doses have been used,⁴⁰ but smaller daily doses have also been studied.^{41, 63} In all of these studies showing positive clinical outcomes, serum concentrations of 25(OH)D, calcium, and phosphorus were measured before and after supplementation. Although vitamin D supplementation elevated these serum concentrations from baseline, elevations above the upper limit of the therapeutic range were not observed. Daily doses of at least 800 IU and up to 2000 IU appear safe through 15 months of follow-up. The large one-time dose appeared safe in one particular study,⁴⁰ but the timing of when a subsequent dose would be required was not established. The optimal dose required to achieve adequate vitamin D stores likely varies from person to person. Patients with decreased sun exposure, elevated levels of cutaneous melanin, or other risk factors for deficiency will likely require higher doses than

Table 4. Studies of Vitamin D and Heart Failure

Study Population	25(OH)D Level (ng/ml) ^a	Primary Outcome	Results
Observational studies			
25 African-Americans with HF: DHF for ≥ 4 wks in 11, DHF for 1–2 wks in 9, and 5 patients with CHF ⁵⁸	15.1 (DHF ≥ 4 wks) 20.3 (DHF 1–2 wks) 23.1 (CHF)	To compare 25(OH)D levels among the three HF groups	No significant differences in 25(OH)D levels were noted among the groups
40 African-Americans with HF (DHF for ≥ 4 wks in 15, DHF for 1–2 wks in 15, and 10 patients with CHF) and 9 controls without HF ⁵⁷	14 ± 1.0 (DHF ≥ 4 wks) 17 ± 4.0 (DHF 1–2 wks) 18 ± 4.0 (CHF) 37.7 ± 7.0 (controls)	To compare 25(OH)D levels among the three HF groups and control group	25(OH)D levels in the three HF groups were significantly lower compared with the control group
Outpatients aged ≥ 60 yrs with EF < 40% (n=60) ⁵⁶	26.7 ± 12.5	To correlate 6-min walk distance with 25(OH)D level	Significant positive correlation was noted between lower vitamin D levels and shorter 6-min walk distance
101 patients undergoing cardiac transplantation evaluation (61 UNOS status 1 and 40 UNOS status 2) ⁵⁹	21.0 ± 1.0	To compare 25(OH)D levels between UNOS status 1 and status 2 patients	Status 1 patients had significantly lower 25(OH)D and 1,25(OH) ₂ D levels than status 2 patients; 23% of status 1 patients had severe vitamin D deficiency (< 9 ng/ml) vs 8% of status 2 patients
54 patients with NYHA class ≥ II HF (20 aged < 50 yrs, 34 aged > 50 yrs) and 34 elderly controls without HF ⁶⁰	9.6 (young HF) 11.0 (elderly HF) 18.0 (elderly controls)	To compare 25(OH)D levels between younger HF patients and elderly controls and between elderly HF patients and elderly controls	Patients with HF, regardless of age, had significantly lower 25(OH)D levels than elderly controls without HF
383 patients with HF listed for cardiac transplantation (325 required elective listing and 58 required urgent listing) ⁶¹	14.0 ± 1.2 (elective listing) 9.3 ± 0.8 (urgent listing)	To compare 1,25(OH) ₂ D levels in those who required urgent transplantation listing with those who required elective listing To examine if 1,25(OH) ₂ D level predicted survival or need for transplantation at 1 yr	Patients in the urgent listing group had significantly lower 1,25(OH) ₂ D levels compared with patients in the elective listing group Kaplan-Meier estimates showed significantly higher rates of death or transplantation at 1 yr in patients with lower 1,25(OH) ₂ D levels
Patients in the LURIC prospective cohort referred for coronary angiography (n=3299) ⁶²	17.3	To determine the HR for death due to HF and SCD in patients with vitamin D deficiency compared with those with optimal levels of 25(OH)D	Risk of death due to HF and SCD was significantly higher in patients with severe vitamin D deficiency (< 10 ng/ml) vs those with optimal levels of 25(OH)D
Randomized study			
123 ambulatory patients with NYHA class ≥ II HF and S _{cr} < 2 mg/dl (61 received calcium 500 mg + vitamin D [cholecalciferol] 2000 IU/day and 62 received calcium 500 mg + matching placebo each day) ⁶³	Baseline: 14.4 (vitamin D) vs 15.3 (placebo), p=NS	To determine the survival and cytokine level differences between patients treated with vitamin D and those who received placebo	Kaplan-Meier estimates showed no significant differences in survival rates between groups during the 15-mo follow-up Statistically significant differences in TNF-α and IL-10 level changes were noted between groups

25(OH)D = 25-hydroxyvitamin D; HF = heart failure; DHF = decompensated heart failure; CHF = compensated heart failure; EF = ejection fraction; UNOS = United Network for Organ Sharing; LURIC = Ludwigshafen Risk and Cardiovascular Health cohort; NYHA = New York Heart Association; SCD = sudden cardiac death; TNF-α = tumor necrosis factor-α; IL = interleukin; S_{cr} = serum creatinine.

^aData are mean or mean ± SD.

those in whom these risk factors are absent. Serum vitamin D level measurements and a risk

factor assessment are needed to individualize vitamin D supplementation requirements.

Table 4. (continued)

Statistical Significance
p=NS
p<0.05
r = 0.24, p<0.05 Correlation remained significant after adjustment for age and sex
25(OH)D level: 19.0 vs 24.0 ng/ml, p≤0.01 1,25(OH) ₂ D level: 23.0 vs 29.0 ng/ml, p≤0.03
Young patients with HF vs control: p<0.001 Elderly patients with HF vs control: p<0.001
1,25(OH) ₂ D level: 17.4 vs 25.5 ng/ml, p<0.001
Survival rates: p<0.001 Kaplan-Meier estimates remained significant after multivariable adjustment
Death from HF: HR 4.13 (95% CI 1.77–9.62) SCD: HR 5.98 (95% CI 2.60–13.74) HR remained significant after multivariable adjustment
Survival rates: 85.7% vs 88.2%, p=0.84
Patients who received vitamin D vs placebo: Change in TNF-α levels: -2.0 vs +2.7, p=0.006 Change in IL-10 levels: +0.24 vs -0.20, p=0.042

Other Considerations

Since most studies found an association between vitamin D deficiency and cardiovascular disease risk, some might advocate for widespread

vitamin D supplementation. However, treatment strategies suggested solely by observational data may not be effective, and can be harmful. Several epidemiologic studies have shown an independent and graded association between cardiovascular disease risk and elevated homocysteine levels. Despite this observed correlation, supplementation with folic acid and B vitamins reduced homocysteine levels, but did not reduce the risk of major cardiovascular events.⁶⁴ Previous observational studies also suggested that hormone replacement therapy in postmenopausal women was associated with a reduction in the risk of cardiovascular disease. Based on the Women's Health Initiative, we now know that, depending on the age of the patient, estrogen and progestin replacement using a specific pharmaceutical product did not necessarily confer cardiovascular protection, and may actually increase risk of coronary heart disease, especially during the first year of supplementation.^{65, 66} Finally, dietary and pharmaceutical supplementation with antioxidants, such as vitamin E and vitamin C, has been associated with a reduced risk of coronary disease in epidemiologic and observational studies. However, supplementation with these antioxidants in the Women's Angiographic Vitamin and Estrogen (WAVE) trial⁶⁷ and the Heart Protection Study⁶⁸ resulted in no benefit.

More than 25 studies have examined the relationship between vitamin D levels and cardiovascular disease, and most have shown that lower vitamin D levels are associated with an increased risk of cardiovascular disease. None, however, showed an increased risk of cardiovascular disease with higher serum 25(OH)D levels. This evidence, along with the ability to measure serum 25(OH)D levels and prevent hypervitaminosis D, suggests that supplementation with vitamin D is unlikely to be harmful. In addition, several studies, not explicitly discussed in this review, evaluating the safety of vitamin D supplementation suggest that the tolerable upper level for vitamin D intake is likely 10–20 times higher than the current recommended daily intake.⁶⁹ From a cardiovascular perspective, however, because screening for deficiency, using pharmaceutical supplements, and monitoring for toxicities all consume health care dollars, widespread screening and supplementation should not be advocated until the benefits of vitamin D supplementation are borne out in large randomized controlled trials.

Recommendations for Vitamin D Supplementation

The strongest recommendation, based on the available data, is to conduct prospective, randomized, controlled trials evaluating the effects of vitamin D supplementation on the prevention and treatment of various cardiovascular diseases. The relevance of the large body of observational data can only be determined by the results of well-conducted prospective trials. Until the results of these future studies are available, the role of vitamin D or its metabolites in the management of heart disease will remain uncertain. Screening and supplementation should not be considered for every patient but may be valuable in certain populations. Patients with several risk factors for deficiency who have either difficult-to-control hypertension or heart failure and who have received maximum medical therapy but remain symptomatic may reasonably undergo assessment of their vitamin D status. Patients with serum 25(OH)D concentrations less than 20 ng/ml may be considered for supplementation.

The known benefits on bone health along with the relative safety, easy accessibility, and inexpensive nature of vitamin D supplements make it a reasonable option for an individual patient, especially in those for whom traditional drugs are inadequate. For patients at risk for osteoporosis, the choice for starting vitamin D (with calcium) for cardiovascular disease is perhaps easier. If vitamin D supplementation is implemented, daily doses of 800–2000 IU can be considered, with higher doses likely needed in patients with limited sunlight exposure or other risk factors for deficiency. As with all other drug therapies, appropriate monitoring for safety and efficacy must occur. Although no hypercalcemia, hyperphosphatemia, or hypervitaminosis D occurred in these limited number of studies, monitoring for these toxicities may be necessary, particularly when higher doses are used. Based on the half-life of 25(OH)D⁷⁰ and the follow-up used in these trials,^{40, 41, 63} serum calcium, phosphorus, and 25(OH)D levels could be measured within 6–15 weeks after initiation of vitamin D supplementation. Currently, not enough evidence is available to support long-term vitamin D supplementation specifically for the prevention of various cardiovascular diseases.

Conclusion

Experimental animal studies have shown that

vitamin D deficiency leads to increased secretion of parathyroid hormone and activation of the RAAS and immune system. A number of observational studies in humans have also linked vitamin D deficiency to cardiovascular disease. Despite this fairly large body of observational data, very few prospective, randomized, controlled trials have evaluated the benefit of vitamin D supplementation on cardiovascular health. A limited number of studies suggest that raising 25(OH)D levels may provide benefit to patients with heart failure or hypertension. When supplementation is used at studied doses, it appears safe and well tolerated. Vitamin D status assessment and supplementation should not be routine practice but may be considered in patients not adequately treated despite optimization of medical therapy. The question of whether or not vitamin D supplementation can prevent or treat cardiovascular diseases will be answered only after the completion of large randomized controlled trials.

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