Is Vitamin D Deficiency Associated With Heart Failure? A Review of Current Evidence

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Abstract
An estimated 1 billion people worldwide have deficient or insufficient levels of vitamin D. Even more alarming is the association of vitamin D deficiency with many types of diseases, particularly heart failure (HF). Hypovitaminosis D has been observed to be highly prevalent in the HF community with rates varying from approximately 80% to 95%. Higher rates of deficiency have been linked to winter months, in patients with protracted decompensated HF, darker skin pigmentation, and higher New York Heart Association (NYHA) classes. In fact, some data suggest vitamin D deficiency may even be an independent predictor of mortality in patients with HF. Traditionally obtained through UV exposure and activated in the liver and then the kidneys, vitamin D is classified as a vitamin but functions as a steroid hormone. The hormone acts through the vitamin D receptor (VDR), which is expressed in vascular smooth muscle cells, renal juxtaglomerular cells, and most interestingly, cardiac myocytes. Studies have shown that the association between vitamin D deficiency and HF often manifests in the structural components of cardiac myocytes and/or through alterations of the neurohormonal cascade. In addition, vitamin D may also act rapidly through intracellular nongenomic receptors that alter cardiac contractility. Unfortunately, prospective vitamin D supplementation trials show mixed results. In rat models, successful correction of deficiency was associated with reductions in ventricular hypertrophy. In humans, however, echocardiographic dimensions did not change significantly. These results bring into questions whether vitamin D is a risk factor for HF, a marker of HF disease severity, or has a true pathologic role. This article provides a thorough review of vitamin D deficiency etiology, prevalence, and possible pathophysiologic role in HF. Furthermore, we carefully review prospective trials on vitamin D therapy in HF. We believe more trials on vitamin D therapy in HF need to be conducted before any conclusions can be drawn.

Keywords
congestive heart failure, heart disease, cardiomyopathy, experimental and clinical heart failure

Introduction
An estimated 1 billion people worldwide have deficient or insufficient levels of vitamin D.1 On average, humans expose approximately 5% of their skin’s surface area to the sun, resulting in the production of approximately 14 ng/mL (35 nmol/L) of serum vitamin D (25-dihydroxyvitamin D [25-OH D]).2,3 Use of sunscreen, increasing time spent indoors, darker pigmentation, age, extreme latitude, and seasonal variation all contribute to decreased skin synthesis of vitamin D, resulting in vitamin deficiency.1,4-6 Vitamin D deficiency is characterized by serum 25-OH D levels as deficient, insufficient, hypovitaminosis, adequate, and toxic (Table 1).2,7,8 In this review, the term deficiency will be used to describe patients with 25-OH D concentrations that are <40 ng/mL (<100 nmol/L). Specific values will be mentioned when appropriate.

Vitamin D is obtained through diet, sunlight exposure, and nutritional supplements. There are natural and fortified sources of dietary vitamin D. Multiple types of fish salmon, mackerel, tuna, cod, sardines, as well as shiitake mushrooms and egg yolk are naturally enriched with vitamin D.1,5,9 Foods fortified in vitamin D (D2 or D3), cereal, juice, milk, cheese, butter, and margarine, contain up to half the daily recommended dose of the vitamin.9 Despite dietary intake, if one is not consuming supplemental tablets of vitamin D, the primary source remains sunlight exposure.

The implications of vitamin D deficiency extend far beyond the skeletal system of the human body. Vitamin D receptors (VDRs) have been identified within the cardiovascular (CV) system on vascular smooth muscle cells (VSMCs), renal juxtaglomerular cells, and cardiac myocytes.10-13 It is, therefore, no
statistical significance. Interestingly, sub-group analysis of hypertensive and nonhypertensive participants showed that an increased risk of CV events was associated with vitamin D deficiency only for the hypertensive group; unfortunately, a formal test for interaction was of borderline significance ($P = .08$). In addition, the development of HTN in vitamin D deficient patients may partially account for the increased CV risk.\textsuperscript{20} Non-hypertensive vitamin D deficient individuals did not have an increased risk of CV events.\textsuperscript{20} Furthermore, the Framingham Offspring cohort was a completely white population, making it difficult to generalize the data to the AA population, who have a higher prevalence of vitamin D deficiency.\textsuperscript{31}

Both the NHANES studies and the Framingham Offspring cohort do not specify HF etiology or severity in their analyses. Alsafwah et al\textsuperscript{28} conducted a small cross-sectional study on African American patients with HF, in Tennessee, with depressed ejection fraction (EF) <35\%. Heart failure was due to idiopathic dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (iCM). The patients were divided into 4 groups: (a) hospitalized decompensated HF patients with EF <35\%, (b) outpatient compensated HF patients with EF <35\%, (c) out-patients with heart disease without HF (HDNHF), and (d) healthy volunteers. The hospitalized group was further divided into those with protracted HF (≥4 weeks) and short duration HF (1-2 weeks). In all, 102 patients in total were studied; serum 25-OHD levels were drawn within the first 48 hours of hospitalization in all admitted patients. For analysis, serum 25-OH D levels <30 ng/mL were considered vitamin D deficient. Ninety-six percent of the participants in the protracted decompensated HF group that were hospitalized had deficient vitamin D (13.9 ± 1.3; 7-31 ng/mL); 90\% of participants in the hospitalized decompensated compensated HF patients with a shorter duration of HF were deficient (15.1 ± 2.6; 7-54 ng/mL); 95\% of outpatient compensated HF patients were deficient (16.9 ± 2.2; 7-43 ng/mL); 100\% in the HDNHF group were deficient (15.1 ± 1.8; 7-30 ng/mL); and only 33\% of healthy AA volunteers were deficient (36.6 ± 6.8; 5-71 ng/mL).\textsuperscript{28} Sample sizes of the latter 3 groups were all <20 patients, and between-groups analysis was not performed to assess the statistical significance of these differences. The degree of deficiency mirrors the findings of the NHANES study (98\% prevalence) in AA cohort.

Alsafwah et al also observed a similar trend with elevated serum parathyroid (PTH) levels (65 pg/mL), a sign of secondary hyperparathyroidism (SHPTH). In all, 100\% of protracted HF patients had elevated PTH, compared with 67\% of patients with shorter duration HF, 11\% of compensated outpatient HF patients, 12\% of HDNHF patients, and 0\% of healthy controls.\textsuperscript{28} While medications such as furosemide can alter calcium excretion, thereby disrupting serum calcium homeostasis and triggering secondary SHPTH, these findings suggest that SHPTH may play a role in the vitamin D deficient patient with a decompensating heart.\textsuperscript{28,32}

Further exploration of the association of HF severity to vitamin D deficiency was conducted by Pilz et al.\textsuperscript{19} Prior to undergoing angiography, serum 25-OH D levels in caucasian patients were measured. Using analysis of variance (ANOVA), the author showed that a greater proportion of New York Heart Association (NYHA) class 3 and class 4 patients had severe vitamin D deficiency (<10 ng/mL) as compared to moderate (10-20 ng/mL), mild (20-30 ng/mL), or adequate (>30 ng/mL) vitamin D deficiency ($P < .001$ for each class). Inversely, more patients with NYHA class 1 HF had no vitamin D insufficiency (>30 ng/mL) compared to patients with mild, moderate, or severe vitamin D deficiency ($P < .001$). Unfortunately, these associations did not maintain their statistical significance after multivariable adjustments. The association between NYHA class and hypovitaminosis was primarily confounded by physical exercise level. At angiography, ventriculography was used to further categorize EF as "normal," "minimally impaired," "moderately impaired," or "severely impaired." Similar to findings by NYHA class, more patients with "moderately" and "severely" impaired left ventricular (LV) function had severe vitamin D deficiency (<10 ng/mL) compared to patients with normal serum vitamin D levels (>30 ng/mL; $P < .001$). This association remained statistically significant after adjusting for the same confounders.\textsuperscript{19} Pilz et al continued to follow this original study population to prospectively assess mortality related to SCD and HF.\textsuperscript{19} After a median follow-up time of 7.7 years, 15\% of all deaths were attributed to HF. An unadjusted HR (with 95\% CI) of 4.13 (1.77-9.62) was found for death due to HF in the group with severe vitamin D deficiency compared to the group with normal range. This ratio remained statistically significant after controlling for possible confounders.\textsuperscript{19} This study confirmed the findings of the earlier Framingham Offspring cohort and strengthened the association between severity of HF and severity of vitamin D deficiency.

In regard to the type of HF, Ameri et al studied HF caused by hypertensive disease and CAD and found no difference in 25-OH D concentrations in patients with diastolic or systolic HF. The authors proceeded to analyze echocardiographic parameters in a subset of the study population. They compared end diastolic systolic diameter (EDD/ESD) and end diastolic/systolic volume (EDV/ESV) in HF patients with severe (<10 ng/mL) and moderate-to-normal vitamin D deficiency. Seventy-five percent of these patients had diastolic HF and the remaining had systolic HF. The patients with severe vitamin deficiency had significantly longer EDD and ESD as well as significantly larger EDV and ESV. Moreover, fractional shortening was significantly lower in the severely deficient group.\textsuperscript{33} These findings suggest an association between LV dysfunction and severity of vitamin D deficiency.

All of the above data is suggestive of a correlation between CVD, in specific HF, and serum 25-OH D levels as the primary marker of vitamin D deficiency, even though calcitriol (1,25-OH D) is the biologically active form. The former is regarded a better indicator of vitamin status in patients without kidney disease due to its longer biological half-life and higher circulating concentrations, and also because it reflects endogenous and exogenous sources of the vitamin.\textsuperscript{20} 1,25-OH D production and levels are tightly regulated by the kidneys, plasma PTH, calcium, and phosphorous; however, in a deficient state, renal synthesis may become dependent on the
Hypertrophy has been well documented in the literature. The system has been shown to act systemically and in an autocrine–paracrine fashion. Kong et al showed that VDR-KO mice had markedly increased blood pressure, which was also associated with renin overstimulation. They demonstrated that vitamin D may repress renin expression independent of angiotensin II (ANGII) feedback. Based on these findings, Xiang et al sought out to investigate whether the RAS system or actions mediated through the VDR was responsible for cardiac hypertrophy seen in VDR-KO mice. They confirmed that VDR-KO mice had elevated systemic and cardiac renin levels that were associated with increased blood pressure and increased myocyte size. The investigators subsequently treated VDR-KO and WT mice with a 2-week course of captopril and noted that both groups developed increased renin levels, which is indicative of successful treatment. However, the VDR-KO group had a significant decline in heart weight compared to WT. This suggests that hypertrophy in the absence of vitamin D is mediated by ANGII; however, until a head-to-head study in mice is conducted to compare the effects of vitamin D supplementation and ace inhibitors on cardiac hypertrophy, definitive conclusions are difficult to draw.

Pathologic hypertrophy, as described above, helps maintain cardiac output. Once this system is exhausted, further adverse remodeling occurs that alters cardiac functioning. This occurs primarily in the form of dilatation and impaired contractility. Rahman et al, in an extension of the study described above, looked at ECM gene expression. They studied matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) since previous studies had demonstrated the effect of dysregulation of these genes in the failing heart. Matrix metalloproteinases 2 and 9, gelatinase proteins that break down type IV collagen (the major structural component of basement membranes), were isolated from the failing hearts of patients with ischemic and DCM. Differential expression of these proteins is regulated by TIMPs-1 and -3. Rahman et al showed that compared to WT mice, the VDR-KO mice had increased expression of MMP-2 and MMP-9 as well as decreased expression of TIMPs-1 and -3 ($P < .05$). These findings suggest that a lack of VDR activation results in a proteolytic environment within the myocardium. This environment may proceed to disrupt the structural integrity of tissues, leading to LV dilatation and impaired cardiac function.
and overall survival.\(^69\) Patients treated with vitamin D did not show a significant reduction in TNF-\(\alpha\) (\(P = .8\)), however, the control group showed a 12\% increase in TNF-\(\alpha\) (\(P = .01\)). The difference between the 2 groups was calculated to be statistically significant (\(P = .006\)). Interleukin 10, an anti-inflammatory cytokine, showed an increase by 43\% in the treatment group (\(P = .03\)) and a nonsignificant 22\% reduction in the placebo group (\(P = .5\)). The difference between the 2 groups was calculated to be statistically significant (\(P = .04\)). Parathyroid fell by 14\% in the treatment group (\(P = .03\)) but showed a nonsignificant decrease of 11\% in the placebo group (\(P = .09\)). The difference between the 2 groups was calculated to be statistically significant (\(P = .007\)). Natriuretic peptide (BNP) was not significantly affected by treatment.\(^69\) Because TNF-\(\alpha\) is a risk factor for CHF and IL-10 is an anti-inflammatory cytokine, this study suggests that vitamin D deficiency treatment is associated with a reduction in the inflammatory state in patients with HF. The significance of this observed change in inflammatory state is questionable. Schleithoff et al also studied LVEF and LVEDD, in the study described above and showed both treatment and placebo groups showed improvements in both LVEF/LVEDD; however, the extent of change from baseline did not differ significantly between study groups.\(^69\) While the study may have been affected by a high dropout rate, these findings suggest that vitamin D is merely a marker of HF rather than a role player in the pathogenic cascade.

Another prospective double-blinded study conducted by Witham et al raises similar questions. The study was done on elderly patients with systolic HF (>70 years old) with NYHA class II or III. A total of 105 patients had serum 25-OH D levels <20 ng/mL and were randomized to either placebo or Ergocalciferol 100 000 IU once every 10 weeks, for 2 doses. The 6-minute walk test was used as the primary outcome measure as vitamin D is thought to enhance both muscle reactions to sway and muscle strength.\(^26\) In addition, the investigators assessed quality of life using the Minnesota Living with Heart Failure (MLWHF) scoring system and measured other CV and inflammatory markers. After 10 and 20 weeks of ergocalciferol therapy, the investigators found no significant differences between the change in 6-minute walk test of the treatment group and the change in 6-minute walk test of the placebo group. Furthermore, no significant changes in TNF-\(\alpha\), renin, or aldosterone levels were seen. Interestingly, the investigators showed a paradoxically small, but significant, worsening in the change of the MLWHF score at 20 weeks between the 2 groups (\(P = .03\)).\(^72\) These findings suggest that systolic HF symptoms do not change with vitamin D deficiency treatment. While this is in contrast to the beneficial effect of vitamin D deficiency correction observed in SHHF rats, it is possible that vitamin D therapy is only effective in diastolic or HTN-induced HF and not in systolic HF.

**Possibility of Type of Vitamin D Supplement Affecting Outcomes**

Lastly, it is noteworthy to mention that patients in the above 2 studies may not have reached sufficient serum 25-OH D levels at the end of either study (based on the reported means).\(^69\)\(^,\)\(^72\) This is important since better outcomes occur at 25-OH D levels >40 ng/mL, when PTH is maximally suppressed.\(^2\)

One theory is that target 25-OH D concentrations may have not been achieved due to the dosing regimen of vitamin D. While Ergocalciferol 100 000 IU is considered a high dose of vitamin D, it was administered every 10 weeks, averaging to less than 2000 IU/d. For maintenance therapy, the Institute of Medicine currently recommends vitamin D intake of 200 IU/d for adults 19 to 50, 400 IU/d for adults ages 51 to 70, and 600 IU/d for adults ages 71+. However, in order to reach circulating levels of 25-OH D that exceed 40 ng/mL (100 nmol/L), the total vitamin D supply from dietary and environmental sources must be 4000 IU/d.\(^2\) Both human studies described here used smaller doses.

Lastly, the rat models described above utilized calcitriol, the biologically active form of vitamin D, in their respective treatment arms. In order to become biologically active, both ergocalciferol and cholecalciferol need to undergo 1 and 2 hydroxylation steps, respectively. Since 1-\(\alpha\)-hydroxylase has also been locally isolated in cardiac muscle, it is possible that injured myocardium contains ineffective enzyme activity, therefore resulting in less than ideal levels of active serum calcitriol.

**Conclusion**

In conclusion, our current understanding about vitamin D deficiency and HF is evolving. Epidemiologic studies show an 80\% to 96\% prevalence of vitamin D deficiency in HF, with increasing severity of HF associated with increasing severity of vitamin D deficiency. A pathophysiologic role has been suggested in rat models that associates hypertrophy and HTN with vitamin D deficiency. Prospective studies on vitamin D correction show positive results in rat models, but this finding has not been demonstrated in human trials. While this may be due to study design, it is also possible that vitamin D plays a major role in diastolic HF, plays a role in end-stage HF, or that vitamin D is merely a risk factor or predictor in HF. Most importantly, further studies need to be conducted before a final conclusion can be reached.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

**Funding**

The author(s) received no financial support for the research and/or authorship of this article.

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