# The role of vitamin D in chronic heart failure

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**Purpose of review**
Despite advanced medical and device-based therapies, congestive heart failure (CHF) remains a major medical problem, associated with significant morbidity and mortality. Vitamin D deficiency is prevalent in CHF and is associated with poor outcomes. In this manuscript we review the evidence linking vitamin D deficiency and CHF and discuss potential mechanisms involved, as well the clinical data on vitamin D supplementation in CHF patients.

**Recent findings**
A clear relationship has been established between Vitamin D deficiency and increased mortality and morbidity in CHF. However, the mechanism involved is not clearly understood. Recent clinical and experimental evidence have identified the renin–angiotensin–aldosterone system and inflammatory cytokines as likely mediators that can lead to poor clinical outcomes via the cardiorenal syndrome. Clinical data on vitamin D supplementation also remain unestablished, with potential clinical benefits recently reported in patients with vitamin D deficiency. Nonetheless, large-scale randomized clinical trials are lacking.

**Summary**
Vitamin D is an emerging agent with tremendous potential and may represent a novel target for therapy in CHF. Further studies are needed to identify the mechanism(s) involved in the pathophysiology as well as to adequately examine the role of Vitamin D measurement and supplementation in patients with CHF.

**Keywords**
cardiorenal syndrome, congestive heart failure, renin–angiotensin–aldosterone system, vitamin D

## INTRODUCTION

Congestive heart failure (CHF) is a major medical problem in the western world, associated with significant morbidity and mortality, hospitalizations and increasing healthcare costs [1]. With an aging population, increasing prevalence of comorbidities such as diabetes and sleep apnea, and improved management of coronary artery disease, the number of patients living with ventricular dysfunction has increased, resulting in a significant increase in CHF patients over the last few years [2]. CHF is a progressive condition, involving the activation of various neurohormonal systems such as the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, which in the long term are responsible for pathological cardiac remodeling and disease progression [3]. Despite the significant advances over the last 2 decades with medical and device therapy, the 1-year mortality rate from CHF remains very high, between 10 and 35% [4], necessitating novel targets and treatment options. One of the novel concepts that have emerged recently is the potential role of Vitamin D in various cardiovascular disorders, including CHF [5▪▪,6].

Vitamin D has traditionally been regarded as a mediator of calcium and phosphorus homeostasis, and thus a major regular of bone mineralization. However, experimental and epidemiological evidence has highlighted that Vitamin D deficiency plays an important role in various cardiovascular diseases [5▪▪,7], such as CHF, as well as various non-cardiac conditions such as glucose and insulin regulation [8,9] and inflammatory diseases such as inflammatory bowel disease [10], asthma and chronic obstructive pulmonary disease [11,12]. Despite this clinical relationship, the mechanism by which Vitamin D may exert its beneficial effect is still undetermined. The present manuscript

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## KEY POINTS

- Vitamin D deficiency is a poor prognostic marker in patients with CHF.
- Adverse clinical outcomes associated with vitamin D deficiency are likely multifactorial, involving the RAAS and various systemic inflammatory pathways.
- Vitamin D is an exciting and emerging agent, with tremendous potential; however, a tremendous amount of work is needed before we can fully elucidate its potential clinical benefit in patients with CHF.

reviews the evidence supporting the link between Vitamin D and CHF and discusses the potential mechanisms through which Vitamin D may exert its cardio-protective effects.

## VITAMIN D

Vitamin D is a collection of fat-soluble steroids, commonly referring to two different compounds, $D_2$ and $D_3$, ergocalciferol and cholecalciferol, respectively. Plants and invertebrates manufacture Vitamin $D_2$, whereas mammals largely produce $D_3$. In humans, Vitamin D is obtained via endogenous production or from dietary intake, with the latter accounting for nearly 10–20% of our total supply [13]. Cholecalciferol is produced from its precursor 7-dehydrocholesterol, in the skin, after exposure to ultraviolet B spectrum of sunlight. In its original state, Vitamin $D_3$ is inactive and requires two separate hydroxylation reactions to become biologically active. The first step occurs in the liver, yielding 25-hydroxyvitamin D, (25[OH] D); the second step occurs in the kidney, wherein the active form of vitamin D, calcitriol, 1,25-hydroxyvitamin D (1,25 [$OH_2$] D), is produced (Fig. 1). Calcitriol exerts its biological effects via the Vitamin D receptor (VDR), a member of the intracellular, steroid hormone receptor super family. Upon activation, VDR acts upon the nuclei of target cells and regulates gene transcription and protein synthesis [14].

The major action of calcitriol is to maintain skeletal calcium balance via calcium absorption within the intestinal tract, promoting osteoclast production and function, and by regulating the secretion of parathyroid hormone, which is also an important regulator of calcium homeostasis. However, over the last several years, the biological influence of Vitamin D has been significantly expanded beyond just calcium regulation. VDR has been isolated from a number of different tissues not traditionally involved in calcium homeostasis, such as the myocardium [15,16] and fibroblasts [15].

## VITAMIN D AND CARDIOVASCULAR DISEASE

Vitamin D deficiency is a prevalent and preventable condition. It is estimated to affect over 1 billion individuals worldwide [13]. Table 1 represents the cut points for defining Vitamin D status [17].

Early cross-sectional studies reported a significant inverse relationship between calcitriol levels and SBP [18,19]. Since then, low vitamin D levels have also been linked with increased coronary artery calcification [20,21] and increased risk of myocardial infarction [22]. One of the earliest prospective studies to validate the relationship between Vitamin D deficiency and cardiovascular disease was by Wang *et al.* [23], in which, after adjustments for conventional risk factors, Vitamin D deficiency was associated with a significant increase in incidence of cardiovascular disease. This relationship was confirmed by a larger subsequent prospective study that showed an increased risk of myocardial infarction with Vitamin D deficiency [24].

Experimental studies have also been helpful in strengthening this relationship. VDR has been isolated in both animal [15] and human heart tissue [16], whereas experimental animals with nonfunctional VDR and/or defects in the enzymatic pathway for the production of vitamin D develop hypertension and pathological remodeling and fibrosis, as evident in humans with CHF [25,26]. Together, the clinical and laboratory evidence available clearly indicates the regulatory role of the Vitamin D signaling system within the cardiovascular system and, more importantly, highlights the link between vitamin D deficiency and increased cardiac disorder.

## VITAMIN D AND CHRONIC HEART FAILURE

CHF is associated with a high prevalence of vitamin D deficiency, while low circulating levels of vitamin D have been associated with poor clinical events in a wide range of patient populations.

### Vitamin D deficiency in congestive heart failure

One of the earliest reports was by Brunvand *et al.* [27], who reported a case of an infant with severe vitamin D deficiency, hypocalcemia and severe myocardial dysfunction and CHF. Since then, numerous reports have highlighted the relationship between Vitamin D deficiency and CHF [28,29]. Shane *et al.* [28] demonstrated a high prevalence of Vitamin D deficiency in patients with CHF, as well as inverse correlation between serum levels of vitamin D and worsening left ventricular function and disease severity. Zittermann *et al.* [29] demonstrated lower circulating levels of 25(OH)D and

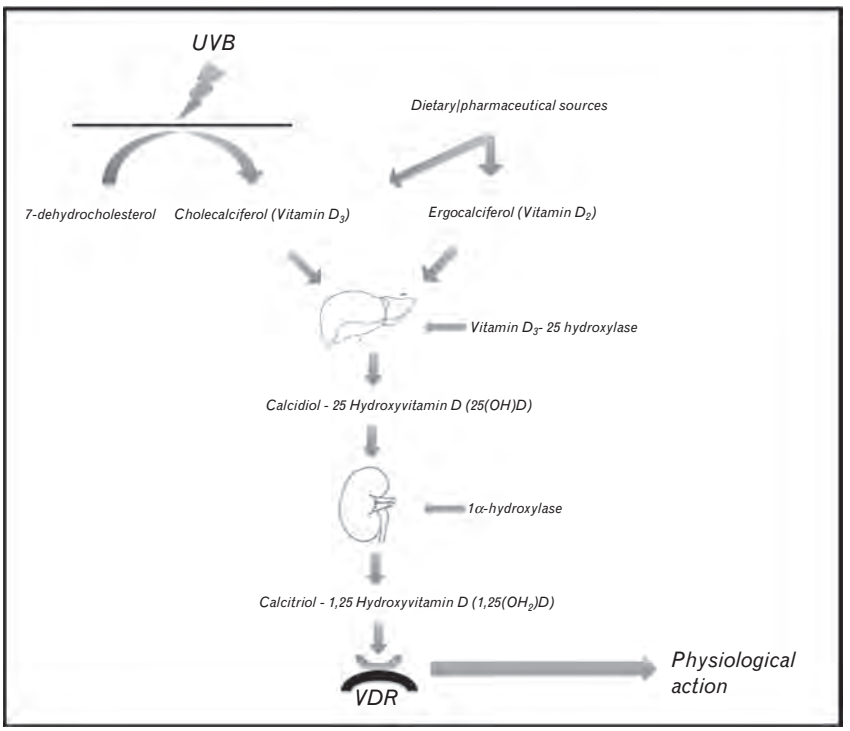


**FIGURE 1.** The process of vitamin D production in the body and the activation of the vitamin D receptor. UVB, ultra-violet B; VDR, vitamin D receptor.

calcitriol in patients with mild CHF [at least New York Heart Association (NYHA) 2] when compared with controls. Moreover, this relationship was present even in younger patients (<50 years), suggesting that the relationship between CHF and vitamin D deficiency is independent of age. An inverse relationship between low levels of 25(OH)D and N-terminal proatrial natriuretic peptide (NT-proANP) levels was also noted. Later on, in a 2008 cross-sectional prospective study, Zittermann *et al.* [30] demonstrated a higher prevalence of vitamin D deficiency in patients on the urgent cardiac transplant list as compared with those on the elective list. Lower circulating vitamin D levels were associated with higher adverse events, defined as death or transplantation.

**Table 1. Stages of vitamin D status according to circulating 25 hydroxy-vitamin D concentrations [17]**

| Serum 25 (OH) vitamin D (nmol/l) | Vitamin D status |
|---|---|
| 0–25 | Deficiency |
| >25–50 | Insufficiency |
| >50–70 | Hypovitaminosis D |
| >70–250 | Adequacy |
| >25 | Toxicity |

Adapted from [17].

Within the last year, there have been two large studies that have further strengthened the relationship between vitamin D deficiency and CHF. First, Liu *et al.* [31▪▪] reported that, among 548 patients, lower 25(OH)D levels were associated with higher levels of brain natriuretic peptide (BNP) and higher plasma renin activity, as well as increased CHF hospitalization and overall higher incidence of all-cause mortality. A low 25(OH)D was identified as an independent risk factor for CHF hospitalization and mortality. Gotsman *et al.* [32▪▪] reported a high prevalence of 25(OH)D deficiency in CHF patients as compared with controls. The authors reported that fewer than 9% of patients with CHF had optimal levels of 25(OH)D, highlighting the significant burden of vitamin D deficiency within a country with plenty of sun exposure, such as Israel. Taken together, these studies clearly demonstrate that there is high prevalence of vitamin D deficiency in CHF patients and that vitamin D deficiency is associated with more severe disease and higher rates of adverse outcomes.

## Vitamin D supplementation in congestive heart failure

The potential benefit of Vitamin D supplementation in patients with CHF has been an area of significant research interest, but thus, far the emerging data

from mostly small studies have been incongruent. Animal models of CHF treated with calcitriol have reported a reduction in heart weights and better overall cardiac function after 13 weeks of treatment [33,34]. Schleithoff *et al.* [35] were the first to look at the potential benefits of Vitamin D supplementation in ambulatory patients with NYHA class II or higher symptoms. Nine months of cholecalciferol therapy improved the inflammatory status by decreasing tumor necrosis factor α (TNFα) and increasing interleukin 10 (IL-10), although this difference did not result in improved ventricular function or survival benefit. Witham *et al.* also failed to demonstrate a benefit with vitamin D supplementation in elderly patients with systolic heart failure, although the treatment was associated with a significant reduction in BNP levels at 10 weeks [36]. One of the limitations of this study may have been the dosing of ergocalciferol. The drug was administered twice, 100 000 IU, once at baseline and again at 10 weeks for a total dose of 200 000 IU, resulting in a near 200% increase in circulating levels of 25(OH)D, with an average value of 40 nmol/l, which was still in the deficient range and may explain the lack of clinical benefit within the treatment arm. More recently, in pediatric CHF patients (~60% dilated cardiomyopathy), daily vitamin D supplementation with 25 μg of cholecalciferol (1000 IU) resulted in significant improvement in left ventricular end diastolic and systolic diameters, left ventricular ejection fraction and myocardial performance index, together with reduction in inflammatory cytokines [37]. Gotsman *et al.* [32▪▪] confirmed that vitamin D supplementation (between 800 and 1000 IU per day) in patients with CHF and low 25(OH)D levels was associated with a significant reduction in mortality, independent of the baseline 25(OH)D levels. These studies highlight a possible benefit for vitamin D supplementation in patients with CHF. More large-scale randomized, multicenter clinical trials are needed before routine vitamin D supplementation can be recommended as part of clinical care of CHF patients.

## Pathophysiology of Vitamin D deficiency in congestive heart failure

Despite the emerging evidence demonstrating the relationship between Vitamin D and CHF, the exact mechanism by which vitamin D deficiency leads to poor clinical outcome has not been clearly established. One of the potential mechanisms is via the cardiorenal syndrome (CRS) and worsening renal function. The cardiovascular and renal systems are interrelated, and as such the impairment of one system can induce pathological processes within the other, which in turn accelerates the progressive failure of both. This interrelationship serves as the pathophysiological basis of the clinical entity called the CRS [38▪]. The progression of CRS involves neurohormonal overactivation, specifically the RAAS and the sympathetic nervous system, as well as systemic inflammation, which over time can disturb electrolyte and fluid regulation, cause endothelial dysfunction, and cause both left ventricular remodeling and fibrosis along with renal fibrosis and failure [39,40]. These changes set up a vicious cycle wherein, in response to further deterioration of cardiovascular and renal systems, more neurohormonal activation and inflammatory cytokines are released, resulting in further systemic dysfunction until organ failure occurs (Fig. 2).

There is emerging evidence suggesting that Vitamin D can be an important regulator of the progression of CRS. First, within the chronic kidney disease (CKD) population, similarly to that of CHF patients, the prevalence of vitamin D deficiency is high, and, similarly to those patients with CHF, it is also associated with increased cardiovascular events [41]. The dysregulation of Vitamin D metabolism, due to reduced 1α hydroxylase activity and the depletion of vitamin D binding proteins secondary to proteinuria, are responsible for vitamin D deficiency in CKD patients [42], and, given the high prevalence of CKD within CHF patients, these changes can also be prevalent in the latter group. The close relationship between CHF and CKD, and the high prevalence of vitamin D deficiency in both conditions, highlight the potential importance of vitamin D in the pathophysiology of CRS. The 'VITAL Study' has, thus far, provided some indirect evidence linking CRS with Vitamin D. In this study, the VDR agonist paricalcitol significantly reduced proteinuria (surrogate for adverse cardiac events [43] and hospitalization [44]) in patients with diabetic nephropathy [45].

Other evidence supporting a role of Vitamin D in the pathogenesis of CRS is reported involvement of the RAAS and inflammatory cytokines, both of which are regulated by the Vitamin D system, in the progression of CRS. The RAAS has been well described as being involved in the pathophysiology of CHF and various forms of renal disorders, and the blockade of this system serves as the corner stone of medical management of CHF and various forms of CKD such as proteinuria [46,47]. The association between vitamin D and the activated RAAS was suggested from observations in VDR knockout mice, wherein renin mRNA and protein and circulating angiotensin II levels were elevated, compared with wild-type mice [48]. These changes were

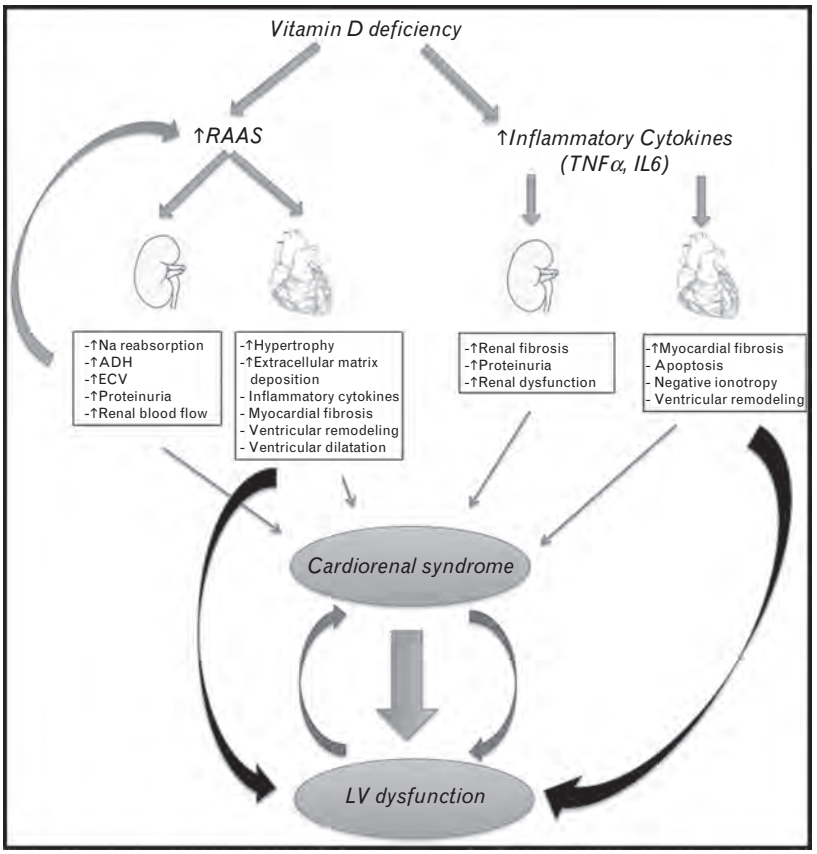


**FIGURE 2.** The proposed pathway through which vitamin D deficiency could result in more severe left ventricular dysfunction and poor clinical outcome in patients with congestive heart failure. ADH, antidiuretic hormone; CHF, congestive heart failure; ECV, extra-cellular volume; IL, interleukin; LV, left ventricle; Na, sodium; RAAS, renin–angiotensin–aldosterone system; TNF, tumor necrosis factor.

counterbalanced with the addition of an angiotensin converting enzyme inhibitor, captopril, or an angiotensin II receptor blocker, losartan [49]. Overactivation of the RAAS has also been reported in CHF patients with Vitamin D deficiency [31▪▪] as well as those without [50–53].

Vitamin D deficiency has also been linked to increased production and release of inflammatory cytokines, which can have a direct negative effect on the myocardium or indirectly affect other vital organs. Directly they can cause myocardial apoptosis, hypertrophy, fibrosis, left ventricular remodeling, negative ionotropic effects [54–56], as well as increased renal fibrosis and renal failure [57,58]. In-vitro studies suggest that Vitamin D suppresses proinflammatory cytokines such as TNFα and IL-6, while upregulating antiinflammatory cytokines such as IL-10 [59]. Animal studies using VDR knockout mice have also demonstrated that lack of Vitamin D signaling is associated with increased myocardial matrix metalloproteinases (MMP) expression and activity that results in tissue remodeling, increased collagen deposition and fibrosis [60,61]. TNFα is an important regulator of MMP activity and the blockade of its downstream effects has been associated with improved cardiac and renal outcomes [62,63]. In animal models of pressure overload induced heart failure, the VDR agonist paricalcitol has been shown to significantly reduce myocardial fibrosis, which was associated with preserved cardiac performance [64]. Increased myocardial fibrosis and remodeling/hypertrophy can serve as a substrate for increased risk of ventricular arrhythmias, which can in part be responsible for the reported increased risk of sudden cardiac death associated with Vitamin D deficiency [65–67]. Thus, worsening clinical outcomes in CHF patients with vitamin D deficiency can be in part related to a proinflammatory state, which can either directly affect cardiac function or indirectly affect other organ systems, and thus result in overall poor clinical course.

## CONCLUSION

Research over the last few years has greatly advanced our understanding of the cardiovascular effects of vitamin D. The evidence for the cardioprotective and renoprotective effects of Vitamin D is actively increasing; however, the mechanism through which this protective effect is carried out is not fully established. The current emerging evidence suggests that the mechanism of action is likely multifactorial, involving neurohormonal systems like the RAAS, as well as inflammatory cytokines such as TNFα and ILs, which together can lead to poor clinical outcomes by directly exerting a negative effect on the heart as well as indirectly by acting on other organ systems such as the kidneys via CRS. A thorough understanding of this mechanism will allow the development of therapeutic strategies and novel agents and/or newer vitamin D analog drugs for management of these conditions. In addition to identifying the mechanism involved, the potential clinical benefits of vitamin D supplementation in patients with cardiac and renal disease have also not been adequately addressed. Small, nonrandomized clinical studies to date have been inconsistent with respect to clinical benefits, and as such large randomized clinical trials will be essential to answer this question. Despite the pharmaceutical arsenal and devices currently available in the management of CHF, its prevalence continues to grow, it is still associated with significant morbidity and mortality, and it is still associated with a significant financial burden. Vitamin D is an exciting and emerging agent with tremendous potential and may represent a novel target for therapy in CHF.

### Acknowledgements

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### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 266).

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