



The role of vitamin D in cardiovascular disease and COVID-19

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Accepted: 10 July 2021 / Published online: 2 March 2022

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Abstract

Patients with pre-existing cardiovascular disease (CVD) are at high risk for adverse outcomes with coronavirus disease 2019 (COVID-19). Further, COVID-19 infection is associated with numerous cardiovascular (CV) complications including arrhythmia, myocardial injury, cardiomyopathy, and thrombotic events. Increased susceptibility to COVID-19 and CV complications related to COVID-19 may be in part related to immune dysregulation and inflammation associated with CV disease which is exacerbated with viral infection. Vitamin D plays a major role in immune function and exerts anti-inflammatory effects, which may prove important in the context of CVD and COVID-19. To date, studies have shown minimal benefit for vitamin D supplementation in patients with COVID-19, though there are no studies specific to patients with CVD and related complications. Further, given that vitamin D has important protective effects on the CV system, including augmentation of myocardial contractility and anti-thrombotic effects, it is unknown if supplementation with vitamin D can mitigate CVD complications associated with COVID-19.

Keywords Vitamin D · Coronavirus · COVID-19 · Coagulopathy

Abbreviations

COVID-19	Coronavirus disease 2019
CVD	Cardiovascular disease
CV	Cardiovascular
ICU	Intensive care unit
CHF	Congestive heart failure
HFrEF	Heart failure with reduced ejection fraction
EF	Ejection fraction

1 Introduction

The coronavirus disease of 2019 (COVID-19) is associated with devastating morbidity and mortality around the world. Demonstrated by numerous multinational studies, patients with cardiovascular disease (CVD) and related cardiovascular (CV) risk factors are at especially high risk for adverse outcomes with COVID-19 [1, 2]. Additionally, COVID-19 has been associated with a number of CV complications

including arrhythmia, myocardial injury, cardiomyopathy, and thrombotic events [1, 3]. While the exact pathophysiologic mechanisms that underlie the high risk interaction between COVID-19 and pre-existing CVD have not been completely elucidated, the high inflammatory burden associated with both disease states is thought to play a major contributing role [4]. As such, anti-inflammatory and immune-modulating agents remain a major focus of research in COVID-19 therapeutics. Given the important role of vitamin D in CV function and homeostasis, as well as its effects on immune regulation and inflammation, its potential role to mitigate the adverse outcomes in patients with CVD and COVID-19 is important to consider.

2 Vitamin D and inflammation: impact on COVID-19 and cardiovascular complications

In addition to its well-known role in mineral metabolism, vitamin D signaling helps regulate immunity and the immune-mediated inflammatory response [5]. Specifically, vitamin D promotes transcription of proteins such as cathelicidin and β -defensin 2 both of which have antimicrobial properties and aid in clearance of respiratory pathogens [5–7]. Relevant specifically to viral infection, vitamin D

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promotes autophagy that enhances viral clearance and tempers the inflammatory response [5, 6]. As such, vitamin D supplementation in viral infection has been extensively studied. In a large meta-analysis including 25 RCTs and 11,321 patients (age 0–95), daily or weekly supplementation with vitamin D reduced risk for development of acute respiratory infections (adjusted OR 0.88, 95% CI 0.81–0.96) [8]. Importantly, the protective effects were greatest among those with pre-existing vitamin D deficiency (< 25 nmol/L).

As such, several studies have implicated vitamin D deficiency as a potential risk factor for COVID-19 and related complications and mortality [9–11]. Interestingly, one group postulated vitamin D deficiency as one potential mechanism for increased susceptibility to COVID-19 among elderly, black and minority populations, in whom vitamin D deficiency is most common [11]. However, in 2 large observational studies of over 300,000 United Kingdom Biobank participants, vitamin D levels were not related to susceptibility to or mortality from COVID-19 infection [11, 12].

To date, there are few randomized controlled trials designed to study the impact of vitamin D supplementation on outcomes in COVID-19. One multicenter, double-blind placebo-controlled trial enrolled 240 patients hospitalized in Brazil with COVID-19 from June–August 2020 [13]. Patients were randomized to a single high-dose of vitamin D (200,000 IU) versus placebo. The primary outcome of this study was hospital length of stay. Compared to placebo, individuals who received vitamin D supplementation did not have a shorter length of stay (HR for discharge 1.07, 95% CI 0.82–1.39). Notably, in-hospital mortality, intensive care unit (ICU) admission, mechanical ventilation requirement, and duration of mechanical ventilation also did not differ by treatment arm. Importantly, 13.5% of patients in this cohort had pre-existing CVD, 52.7% had pre-existing hypertension, and 35.4% had pre-existing diabetes. A smaller-scale single-center pilot study in Spain randomized 76 patients hospitalized with COVID-19 to vitamin D supplementation (0.532 mg on day 1, 0.266 on day 3 and 7) versus placebo, both in combination with best available therapy, and found less ICU admissions among those patients who received vitamin D supplementation (multivariate OR 0.03 (95% CI 0.003–0.25) [14]. Notably, only 3.9% of the cohort had pre-existing CVD while 34.2% had pre-existing hypertension and 10.5% had pre-existing diabetes. Additionally, another small-scale study of 40 patients with known vitamin D deficiency and asymptomatic to mildly symptomatic COVID-19 infection were randomized to vitamin D supplementation (60,000 IU for 7 days) versus placebo [15]. Individuals who received supplementation were more likely to clear COVID-19 infection (62.5% participants in the intervention group and 20.8% participants in the control arm, $p < 0.018$) by RT-PCR assay and had lower levels of fibrinogen at follow up. Levels of other inflammatory markers did not differ

by supplementation status and clinical outcomes were not examined. Overall, the majority of the data to date do not support vitamin D supplementation to prevent adverse outcomes in COVID-19, though notably no adverse events occurred in any trial with vitamin D supplementation.

It is important to note that no prospective studies to date have solely focused on vitamin D supplementation in COVID-19 patients with pre-existing CVD. Patients with pre-existing CVD have at baseline heightened inflammation and impaired immunity, which may explain an increased susceptibility to severe COVID-19 infection and adverse outcomes [16, 17]. Further, many of the CV complications associated with COVID-19 are least partly mediated by inflammation, including arrhythmia, myocarditis, acute coronary syndrome, thromboembolic disease and heart failure [1]. Therefore, there is a need for effective treatment regimens to impact the immune dysregulation and inflammatory response associated with COVID-19 in patients with CV disease. Vitamin D may be considered as a potential adjunctive therapeutic agent in this context and further studies are warranted.

3 Vitamin D and COVID-19-associated cardiomyopathy

Vitamin D is a precursor of the biologically active steroid hormone 1–25-dihydroxy vitamin D (1,25)OH, which is activated via a series of hydroxylation reactions occurring in the liver and kidney, respectively [18, 19]. Receptors for the activated form of vitamin D are present throughout the cardiovascular system, including in the myocardium, where binding and activation leads to numerous protective CV effects [19]. After binding to receptors on the myocardium, vitamin D imparts antihypertrophic effects, regulates calcium flux and thereby augments myocardial contractility [20, 21]. In accordance, numerous observational studies have shown an association between vitamin D deficiency and congestive heart failure (CHF) [22–25]. Due to this association, one study randomized 229 patients with heart failure with reduced ejection fraction (HFrEF) to 1 year of vitamin D supplementation (4000 IU daily) versus placebo [22]. While there was no difference in the primary endpoint in improvement in 6-minute walk distance at one year, individuals randomized to receive vitamin D supplementation experienced significant improvement in cardiac function as measured by ejection fraction (EF) as well as reversal of left ventricular remodeling. In another study of 101 patients with HFrEF, patients were randomized to 6 weeks of vitamin D supplementation (2000 IU daily) versus placebo [26]. In patients who received vitamin D supplementation, plasma renin activity was lower compared to control. Given the association of RAAS activation with heart failure, this study

offers potential mechanistic insights into the protective role of vitamin D in cardiomyopathy. Further, in a trial of 5,292 patients without history of CVD, incident CHF was lower among those patients who received vitamin D supplementation for 3 years (800 IU/d) compared to those who did not (HR 0.75, 95% CI 0.58–0.97) [27]. Interestingly, however, the same investigators completed a meta-analysis of 21 trials including 13,033 patients in which there was no association between vitamin D supplementation and CHF, possibly due to heterogeneity between studies [27].

While the etiology of cardiomyopathy in the setting of COVID-19 may be multifactorial, potentially due stress, myocarditis, or worsening of underlying pre-existing cardiomyopathy, the role of vitamin D supplementation is important to consider [1]. Further, given poor outcomes associated with pre-existing heart failure in COVID-19, monitoring vitamin D and ensuring replete levels during the COVID-19 pandemic may prove important in this population [28]. At this time, however, there is insufficient data to recommend vitamin D supplementation for patients with heart failure and COVID-19.

4 Vitamin D and COVID-19-associated thrombotic complications

There are also vitamin D receptors throughout the vasculature, where binding of activated vitamin D to its receptor imparts anti-atherosclerotic and anti-thrombotic effects [19]. These effects include inhibition of foam cell formation, stimulation of endothelial nitric oxide production, downregulation of pro-thrombotic tissue factors, promotion of vascular repair, and modulation of vascular calcification [19]. In accordance, there have been several observational studies that demonstrate an association between vitamin D deficiency and adverse atherosclerotic and thrombotic events. In an analysis of the Framingham Offspring Study including 1739 participants, individuals with a vitamin D level < 15 ng/mL had significantly increased risk for coronary events, cerebrovascular events, and claudication compared to those with the highest levels of circulating vitamin D (HR 1.62, 95% CI 1.11–2.36, $p=0.01$) [29]. In a large meta-analysis of 24 prospective studies (65,994 patients), there was an inverse, dose-dependent association between circulating vitamin D levels and risk for CVD complications, including acute coronary syndrome and stroke [30]. Other large meta-analyses have reported similar results though all noting significant heterogeneity in studies [31, 32].

There are very few randomized trials designed to study the causal relationship between vitamin D and atherosclerotic and thrombotic CV events. One study randomized 25,871 patients to receive vitamin D supplementation

(2000 IU daily) and studied the incidence of myocardial infarction, stroke, or death from CV causes [33]. In this analysis, supplementation with vitamin D did not result in a lower incidence of adverse CV outcomes compared to placebo. However, given the high inflammatory state associated with COVID-19 and the potential for major CV events such as acute coronary syndrome and stroke, the potential impact of vitamin D deficiency and the potential role for supplementation during the acute illness phase is an important area for investigation.

In contrast to the conflicting data for the association between vitamin D status and thrombotic events such as myocardial infarction and/or stroke, numerous studies have demonstrated an association between vitamin D deficiency and venous thromboembolism [34–37]. In a randomized trial of 220 patients with hypercoagulability due to underlying malignancy, those randomized to chemotherapy plus vitamin D supplementation versus chemotherapy plus placebo had significantly less thrombotic events (1 (6%) versus 8 (8%), $p=0.01$) [38]. Notably, both venous and arterial thromboembolic events were less frequent in the supplemented arm. Interestingly, other studies have shown that patients with greater sun exposure, the main source of vitamin D in humans, have 30% lower risk for development of venous thromboembolism compared to those without such exposure [39]. Given the association between COVID-19 and thromboembolic complications, through mechanisms of excessive inflammation, platelet activation, endothelial dysfunction, and stasis, the role for preventative therapies is an area of intense investigation [3]. While there a strong focus on discovering optimal anticoagulation strategies in patients hospitalized with COVID-19, vitamin D supplementation may be an important therapeutic option or adjunctive agent in this setting [40].

5 Vitamin D deficiency and CV risk factors: impact on risk for COVID-19

Vitamin D deficiency has also been associated with CV risk factors such as hypertension, diabetes, obesity, and dyslipidemia in many observational studies [41–46]. While causal relationships have been established in the few randomized studies designed to address these associations, the discrepancy between the observational and investigational data have led to the idea as vitamin D deficiency as a marker for poor overall health [44, 47]. One hypothesis is that heightened inflammation may confound the relationship between vitamin D deficiency and CV risk factors and disease [47]. Given that both of these entities confer worse prognosis with COVID-19, there may be a role for assessment of vitamin D status as a surrogate marker of

risk for severity of illness or development of complications among patients with pre-existing CV disease.

6 Conclusions

Given the anti-inflammatory function of vitamin D, in addition to its important role in CV function, further investigation into the impact of vitamin D supplementation in patients with COVID-19 and pre-existing CV disease is warranted. Specifically, the role of vitamin D to prevent cardiomyopathy and/or thromboembolic complications associated with COVID-19 may be an interesting area of investigation. Additionally, given the association of vitamin D deficiency with CV risk factors and related chronic illness, vitamin D deficiency may be a risk factor for poor outcomes in COVID-19 among those with pre-existing CV disease.

Declarations

Conflicts of interest Dr. Madhavan reports institutional grant support by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center. Dr. Gupta received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation and from the Ben C. Martin Law Firm for work related to an inferior vena cava filter litigation; received consulting fees from Edward Lifesciences; and holds equity in the healthcare telecardiology startup Heartbeat Health.

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