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MECHANISMS IN ENDOCRINOLOGY

Vitamin D and COVID-19

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Abstract

The SARS-CoV-2 virus responsible for the COVID-19 pandemic has generated an explosion of interest both in the mechanisms of infection leading to dissemination and expression of this disease, and in potential risk factors that may have a mechanistic basis for disease propagation or control. Vitamin D has emerged as a factor that may be involved in these two areas. The focus of this article is to apply our current understanding of vitamin D as a facilitator of immunocompetence both with regard to innate and adaptive immunity and to consider how this may relate to COVID-19 disease. There are also intriguing potential links to vitamin D as a factor in the cytokine storm that portends some of the most serious consequences of SARS-CoV-2 infection, such as the acute respiratory distress syndrome. Moreover, cardiac and coagulopathic features of COVID-19 disease deserve attention as they may also be related to vitamin D. Finally, we review the current clinical data associating vitamin D with SARS-CoV-2 infection, a putative clinical link that at this time must still be considered hypothetical.

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Invited Author's profile

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Introduction

At the time of this writing, SARS-CoV-2, the virus causing the COVID-19 pandemic had infected over 15 million people and had caused over 400 000 deaths worldwide (1). In the United States, one of the countries hardest hit by the pandemic, there have been over 4 million people infected and over 140 000 deaths. Undoubtedly, these numbers will grow greatly in the months to come. The search for risk factors predisposing to adverse outcomes of this disease has focused upon age, obesity, diabetes, hypertension, ethnicity, and other factors (2, 3, 4, 5, 6, 7). Recently, vitamin D inadequacy has emerged as another potential risk factor (8, 9, 10). In view of current interest in vitamin D as a potential factor in the COVID-19 pandemic, we review what is known about the role of vitamin D as a facilitator of immunocompetence regarding innate and adaptive immunity. We also summarize current information implicating vitamin D as a factor in the cytokine storm that portends some of the most serious consequences of COVID-19 disease. A discussion of possible involvement of vitamin D in the cardiac and coagulopathic features of COVID-19 disease is followed by a review of the available clinical data associating vitamin D with SARS-CoV-2, a putative clinical link that, at this time, must still be considered hypothetical.

Vitamin D as a regulator of the immune response

A major initial observation linking vitamin D to the immune system was the appreciation that antigen-presenting cells such as macrophages and dendritic cells synthesise the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$) from its precursor 25-hydroxyvitamin D (25-OHD) via the enzyme 1α-hydroxylase (CYP27B1). This property of macrophages and dendritic cells was initially considered to be a pathological response in association with immune disorders, such as sarcoidosis, tuberculosis, and other granulomatous diseases (11). However, subsequent studies showed that the expression of CYP27B1 and synthesis of 1,25 $(OH)_2D$ are a fundamental feature in the normal development of antigen-presenting cells (12, 13). These seminal observations provided a mechanism by which macrophages and dendritic cells could be influenced by vitamin D. Accompanying these observations is the finding that epithelia, the main barrier between the environment and the body, also express CYP27B1. In general, the epithelia are the first responders to invading pathogens sounding the alarm, as it were, via their own innate immune system to activate dendritic cells and macrophages and to recruit neutrophils and T cells to the site of infection. In the setting of vitamin D deficiency, immune responses would be impaired because less 25-OHD would be available for synthesis of 1,25 $(OH)_2D$ leading to impairment of innate immune function (14). This localized, intracrine, mechanism is now considered a cornerstone of the interaction between vitamin D and the immune system. It is quite distinct from the endocrine actions of vitamin D concerned with regulating mineral homeostasis. Conventional skeletal and calcium regulating effects of vitamin D are driven by circulating 1,25 $(OH)_2D$ synthesized primarily by the kidneys. In this conventional setting, 1,25 $(OH)_2D$ is under the regulation not only by its precursor, 25-OHD but also by parathyroid hormone and fibroblast growth factor 23 (15). In contrast, vitamin D's role in immune response mechanisms appears to be regulated primarily by availability of 25-OHD, induction of CYP27B1 by the invading pathogens and, ultimately, by stimulation of 1,25 $(OH)_2D$ in target tissues of the immune system.

Vitamin D as a regulator of the innate immune response

Antimicrobial actions of vitamin D and the innate immune response

An antimicrobial role for 1,25 $(OH)_2D$ was initially described almost 30 years ago (16). However, the relevance of this antimicrobial property of vitamin D was appreciated only later in studies of the intracellular synthesis of 1,25 $(OH)_2D$ as a mechanism for promoting antibacterial responses to *Mycobacterium tuberculosis*. Local, intracellular synthesis of 1,25 $(OH)_2D$ by monocytes/macrophages promotes the expression of the antimicrobial protein cathelicidin and enhances intracellular killing of *M. tuberculosis*. (17). Similar processes occur in epithelia and are an important component of the barrier function that these tissues display. Specifically, the 1,25 $(OH)_2D$–vitamin D receptor complex acts on the cathelicidin gene promoter vitamin D response elements to enhance transcription of cathelicidin (18). Although the antimicrobial function of cathelicidin is crucial, this protein has a number of other functions including the induction of a variety of proinflammatory cytokines, stimulation of the chemotaxis of neutrophils, monocytes, macrophages, and T cells into the site of infection, and promotion of the clearance of respiratory pathogens by

inducing apoptosis and autophagy of infected epithelial cells (19, 20). The induction of cathelicidin by1,25 $(OH)_2D$ is observed only in higher primates, and, thus, it appears that the ability of vitamin D to promote cathelicidin synthesis is a recent evolutionary development (21). The ability of macrophages to produce cathelicidin correlated well with the serum 25-OHD concentration (17, 22). These observations provided a plausible explanation for the reported high prevalence of tuberculosis and various other respiratory disorders in individuals with vitamin D deficiency (23).

In addition to cathelicidin, vitamin D influences another innate antibacterial element, β-defensin2 (18). β-Defensin2, such as cathelicidin, contributes to host defense by stimulating the expression of antiviral cytokines and chemokines involved in the recruitment of monocytes/macrophages, natural killer cells, neutrophils, T cells (24). Cellular production of cathelcidin and β-defensin2 depends on the vitamin D receptor and CYP27B1 the expressions of which are enhanced following interaction of pathogens with membrane PRRs, such as toll-like receptor 2 and toll-like receptor 4. Another important intracellular pattern recognition receptor, stimulated by 1,25 $(OH)_2D$, is nucleotide-binding oligomerization domain-containing protein 2 (NOD2) which enhances β-defensin2 expression (25). Yet another mechanism by which vitamin D can serve an antimicrobial function relates to cellular iron metabolism. Bacteria depend upon intracellular iron for survival. In the course of infection, hepcidin, which restricts the transcellular export of iron through ferroportin is induced, thus increasing cellular iron levels (26). 1,25 $(OH)_2D$ is a potent suppressor of hepcidin, and therefore acts to enhance ferroportin and reduce intracellular iron, thereby providing another mechanism for suppression of bacterial growth (27). Ultimately, the ability of vitamin D to promote antimicrobial, innate immune function is closely linked to phagocytosis, and subsequent enhanced bacterial killing via the induction of autophagy (28). Similar considerations pertain to viral clearance as described below. A model for integration of antimicrobial responses to vitamin D, as it relates to *M tb* is shown in Fig. 1.

Importantly, vitamin D may have broader antimicrobial actions beyond those described in Fig. 1, including the generation of nitric oxide (29) and superoxide (30). In addition to enhancing monocyte/macrophage antimicrobial functions, vitamin D promotes the killing of pneumococcus by stimulating neutrophils via a range of mechanisms that included upregulation

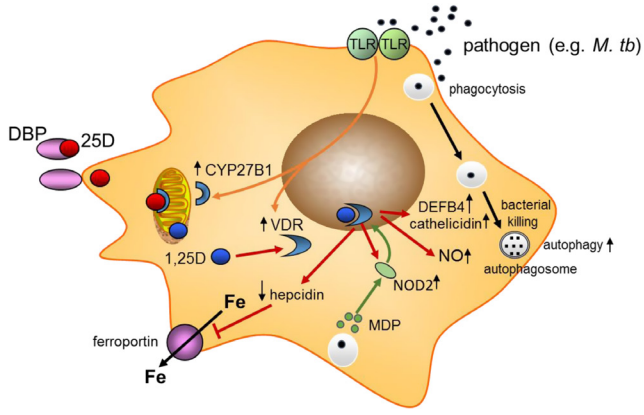

Figure 1

Antimicrobial actions of vitamin D. Schematic showing possible macrophage responses to microbial infection. Pattern recognition receptors such as toll-like receptors (TLR) signal responses to pathogens. This includes transcriptional induction of 1α-hydroxylase (CYP27B1) and the vitamin D receptor (VDR). Serum 25-hydroxyvitamin D (25-OHD) bound to vitamin D binding protein (DBP) allows intracellular access of free 25-OHD for conversion to 1,25 $(OH)_2D$, which then bind to VDR. Transcriptional responses to 1,25 $(OH)_2D$ (shown with red arrows) include induction of cathelicidin and β-defensin 2 (DEFB4), NOD2, and nitric oxide (NO). Intracellular iron (Fe) is exported via ferroportin which is targeted for degradation by hepcidin. The bacterial cell wall product muramyl dipeptide binds to NOD2.

of toll-like receptor 2, NOD2, and cathelicidin together with enhanced antimicrobial human neutrophil peptide (HNP1–3) production (31). Even beyond monocytes, macrophages, and neutrophils, which collectively illustrate the importance of vitamin D in supporting a range of innate antibacterial responses, vitamin D can promote antimicrobial function outside the immune system. For example, within the gastrointestinal tract, vitamin D promotes the expression of gap junction proteins that maintain barrier integrity thereby preventing tissue ingress by bacteria from the gut microbiome (32). Similar barrier integrity effects of vitamin D have also been observed for the epithelial cells of the lung (33), along with stimulation of antimicrobial proteins by lung epithelial cells (34, 35).

Antiviral actions of vitamin D and the innate immune response

Although studies of vitamin D and innate immune activity have focused primarily on antibacterial

mechanisms, as noted and illustrated in Fig. 1, vitamin D can also promote antiviral immunity, which is of great importance in any discussion for its role in COVID-19 infection. This involves a number of mechanisms that overlap with antibacterial responses, such as the induction of cathelicidin and defensins, which can block viral entry into cells as well as suppress viral replication (36, 37). Another property of vitamin D relevant both to antibacterial and antiviral mechanisms are promoting autophagy (38, 39). Autophagy is a fundamental biological process that maintains cellular homeostasis via intracellular membrane encapsulation of damaged organelles and misfolded proteins. Autophagy is also an essential mechanism by which cells deal with viruses. Autophagic encapsulation of viral particles packages them for lysosomal degradation and subsequent antigen-presentation and adaptive antiviral immune responses (40). Thus, autophagy facilitates, but does not guarantee, a hostile cellular antiviral environment.

Induction of autophagy is a key cellular response to vitamin D, with both 25-OHD and 1,25 $(OH)_2D$ enhancing expression of the autophagy marker LC3 (28, 41). Within the innate immune response, vitamin D enhances autophagy by mechanisms similar to the response prompted by antibacterial proteins (42). Thus, autophagy may be sensitive to changes in serum 25-OHD levels. The specific mechanisms by which vitamin D promotes autophagy involves downregulating the mTOR pathway, which inhibits autophagy (43), and by promoting Beclin 1 and PI3KC3, key enzyme drivers of autophagy (44). Upregulation of intracellular Ca and NO by vitamin D also stimulates PI3KC3 activity to promote autophagy (45) (Fig. 2). Beyond the immediate regulation of pathways associated with autophagy induction, vitamin D may also stimulate the formation of autophagosomes to facilitate viral clearance indirectly through induction of cathelicidin expression, which in turn stimulates key autophagy factors such as Beclin 1 (28). In considering the effects of vitamin D on autophagy, it is important to recognize that these actions are closely linked to apoptosis, which may aid viral replication. Therefore vitamin D may play a crucial role in maintaining appropriate balance between autophagy and apoptosis to maximize antiviral responses to infection (46). Vitamin D-induced autophagy decreases HIV-1 infection (47, 48), influenza A (49), rotavirus (50), and hepatitis C (51), but wider virus- and target cell-specific antiviral responses to vitamin D have been reviewed in detail elsewhere (46).

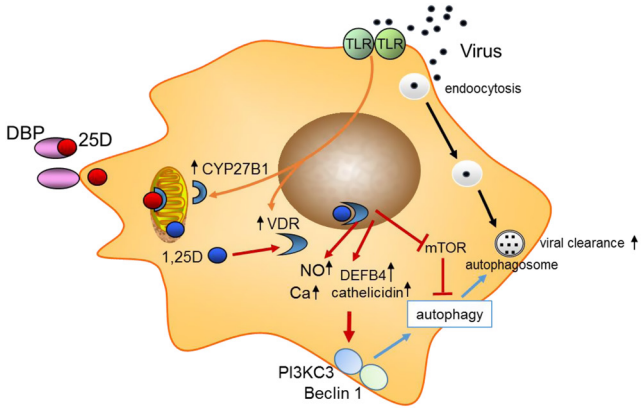

Figure 2

Autophagy and antivirobial actions of vitamin D. Schematic showing possible macrophage responses to viral infection. This includes transcriptional induction of 1α-hydroxylase (CYP27B1) and the vitamin D receptor (VDR). Serum 25-hydroxyvitamin D (25-OHD) bound to vitamin D binding protein (DBP) allows intracellular access of free 25-OHD for conversion to 1,25 $(OH)_2D$, which then bind to VDR. Transcriptional responses to 1,25 $(OH)_2D$ (shown with red arrows) include induction of cathelicidin and β-defensin 2 (DEFB4), nitric oxide (NO) and intracellular calcium (Ca).

Vitamin D as a regulator of the adaptive immune response

The adaptive immune response is initiated by cells specialized in antigen presentation, such as dendritic cells and macrophages, which in turn activate the cells responsible for subsequent antigen recognition, T and B lymphocytes. These cells are capable of a wide repertoire of responses that ultimately determine the nature and duration of the immune response. Activation of T and B cells occurs after a priming period in tissues of the body, such as lymph nodes, that are typically distant from the site of the initial exposure to the antigenic substance. This period is marked by proliferation of the activated T and B cells accompanied by post-translational modifications of immunoglobulin production that enable the cellular response to adapt specifically to the antigen presented. The type of T cell activated, CD4 or CD8, or within the helper T cell class Th1, Th2, Th17, Treg, is dependent on the context of the antigen presented by which cell and in what environment. Systemic factors such as vitamin D influence this process. 1,25$(OH)_2D$, in general, exerts an inhibitory, anti-inflammatory, action on the adaptive immune system. When airway dendritic cells are activated

by a virus, for example, they migrate to lymph nodes where they gain enhanced ability to present antigen for activation of T cells (52). As noted previously, this activation and maturation of dendritic cells includes increased CYP27B1 expression but also a decrease in the vitamin D receptor (21). 1,25$(OH)_2$D decreases the maturation of dendritic cells, decreasing their ability to present antigen and to activate T cells (53). Treatment of dendritic cells with 1,25$(OH)_2$D can also induce regulatory T cells (Treg) cells (54, 55). Treg cells are critical for the induction of immune tolerance (56) and likely play a key role in preventing the cytokine storm associated with severe respiratory disease caused by viral infections (57).

The vitamin D receptor as a regulator of both innate and adaptive immunity

Both innate and adaptive immune responses can vary according to different polymorphisms found in many steps of the vitamin D pathway. One of the most studied of these polymorphisms is that related to the vitamin D receptor. By meta-analysis, variability in risk for enveloped virus infection was dependent on the presence of alleles defined by *FokI*. The majority studies included in this meta-analysis focused on Respiratory Syncytial Virus infection. The recessive genotype TT of *FokI* increases susceptibility as compared to CT+CC genotypes. The T allele reduces the ability of vitamin D receptor complex to bind to gene elements responsive to vitamin D and, according to this meta-analysis, it was consistently associated with higher susceptibility to Respiratory Syncytial Virus infections. Moreover, the worldwide distribution of the T allele overlaps the incidence of Respiratory Syncytial Virus infection, reinforcing the association between vitamin D and immune response against enveloped viruses such as Respiratory Syncytial Virus (58).

The lung as a host for vitamin D-associated immune defense mechanisms

The lungs are a major target for SARS-CoV-2 and related viruses and, thus, are of major interest in understanding the host immune response to them. The respiratory tract has a large surface area (approximately 70 m^2) in contact with the environment. Thus, it provides a major site for invasion by pathogenic organisms, against which it must defend. The defense mechanism is composed of both innate and adaptive immunity. Activation of the innate immune system drives the induction of the long-term adaptive immune system (59). The principal cells involved are the airway epithelia, alveolar macrophages, and dendritic cells. These cells all express CYP27B1 and therefore have the potential to synthesize 1,25 $(OH)_2$D. Expression of CYP27B1 is constitutive in airway epithelial cells (60), but is induced in alveolar macrophages by toll-like receptor (TLR) ligands (e.g. lipopeptide from *M. tuberculosis*), interferonγ (IFNγ), and LPS (61, 62), and in dendritic cells by TNFα, IFNγ, polyI:C, and LPS (63, 64, 65). Moreover, these cells all express pattern recognition receptors (PRRs) of which TLRs are a major component and by which viral RNAs are recognized (66).

Proposed mechanisms for antibacterial and antiviral actions of vitamin D have been derived essentially from *in vitro* and *ex vivo* studies, but they have also been used as a rationale for *in vivo* analysis of the antimicrobial actions of vitamin D. Experiments using animal models have been limited because key antimicrobial responses to vitamin D such as cathelicidin induction appear to be restricted to primates (21). As outlined earlier, vitamin D deficiency in humans is linked to mycobacterial diseases, such as tuberculosis (67). However, over the last 10 years, vitamin D deficiency has also been linked to a wide range of common infectious disease, such as sepsis, pneumonia, and MRSA as well as viral infections such as influenza, hepatitis C and human immunodeficiency virus type 1 (HIV-1) (68). Other viral infections putatively linked to vitamin D include EBS, VZV, CMV, HIV, HCV, HBV, HPV, and Dengue (46). A causal link between low serum 25-OHD and impaired antibacterial and antiviral immunity via the mechanisms outlined in Figs 1 and 2, is plausible given the impact that this will have on intracrine generation of 1,25 $(OH)_2$D and subsequent vitamin D receptor-mediated responses by cells within the immune system and barrier tissue sites.

Although 25-OHD is an important component of antimicrobial responses to vitamin D via its local conversion to 1,25 $(OH)_2$D, it is also noteworthy as a circulating lipophilic molecule bound to vitamin D binding protein (69). Thus, the ability of 25-OHD to access target immune cells, such as macrophages and dendritic cells and the epithelia of the lung and skin, is limited by its binding to vitamin D binding protein. Indeed, studies have shown that in fact, it is the relatively small unbound or 'free' fraction of 25-OHD that is acquired by immune cells to drive intracrine induction of antimicrobial responses (70). This suggests that in considering the impact of vitamin D on antimicrobial immune responses, it is important not only to assess the level of 25-OHD but

also the associated concentration of vitamin D binding protein. It is also possible that infection and associated inflammatory immune responses lead, in turn, to altered vitamin D metabolism, so that low serum 25-OHD could also be a consequence of infectious disease.

Cytokine storm and vitamin D

One of the devastating pathophysiological aspects of SARS-CoV-2 infection is the so-called pulmonary cytokine storm, a major cause of morbidity and mortality. The cytokine storm results from dysregulation of the innate immune system with an outpouring of proinflammatory cytokines and chemokines, leading to abnormal activation of the adaptive immune pathway. The serious damage caused by coronaviruses such as SARS-COV-2 is due to their infection of both the upper and lower airways with rapid virus replication, massive inflammatory cell infiltration producing a huge increase in proinflammatory cytokines and chemokines leading to acute respiratory distress syndrome (71). The initial infection of the airway epithelium leads to rapid viral replication (72, 73) complicated by a virus-induced delayed increase in class 1 interferon (IFNα/β) expression in dendritic cells that would normally block viral replication and enhance viral clearance by CD8 T cells (74). The delayed expression of class 1 interferon subsequently increases recruitment of proinflammatory cells, contributing to the problem. These infected airway epithelial cells then secrete a number of proinflammatory cytokines/chemokines that further dysregulate the innate immune response and attract the influx of inflammatory cells including neutrophils, monocytes and macrophages while sensitizing T cells to apoptosis (75). The consequences include a breakdown in the microvascular and alveolar epithelial barrier from apoptosis of the lung epithelium and endothelium, resulting in vascular leakage and alveolar edema. The T cell response required for viral clearance is blunted (76), and their role in dampening the cytokine storm is reduced.

A potential role for vitamin D in modulating these pathophysiological aspects of the cytokine storm is noteworthy. Airway epithelia constitutively express both CYP27B1, $1,25(OH)_2D$, and the vitamin D receptor. Furthermore, pulmonary alveolar macrophages are induced to express both CYP27B1 and the vitamin D receptor by pathogens such as viruses and cytokines released from infected cells. Although not demonstrated for coronaviruses, such as SARS-CoV-2, for other viruses and other respiratory pathogens, activation of innate immunity leading to increased local $1,25(OH)_2D$ production has been shown to enhance viral neutralization and clearance while modulating the subsequent proinflammatory response. Whether this sequence of events will be the case for SARS-CoV-2 remains to be seen.

Summary of molecular features that could link vitamin D to COVID-19 infection

The innate immune system is the first line of defense against invading pathogens, such as viruses. It is prebuilt, relying on constitutive expression of pattern recognition receptors like TLRs to identify such pathogens. $1,25(OH)_2D$ enhances that defense by inducing antimicrobial peptides such as cathelicidin that lead to viral destruction and clearance by several mechanisms, helps recruit neutrophils, monocytes/macrophages, and dendritic cells which further the killing and clearance of these pathogens, and initiates the adaptive immune response. While beneficial acutely, chronic activation of the innate immune response is not necessarily beneficial, and can result in a cytokine storm. $1,25(OH)_2D$ works to curtail this chronic innate immune response through a number of mechanisms including down regulation of TLRs and direction inhibition of TNF/NFκB and IFNγ signaling pathways. The adaptive immune system provides a more specific response, but takes longer to develop, although once developed provides a powerful response against invading organisms. However, this response if not controlled can also be destructive. Vitamin D, via its active metabolite $1,25(OH)_2D$, regulates adaptive immunity by limiting the maturation of dendritic cells, limiting their ability to present antigen to T cells, and shifting the T cell profile from the proinflammatory Th1 and Th17 subsets to Th2 and Treg subsets, which inhibit the proinflammatory processes. Although these results come from studies with a variety of pathogens, viral and bacterial, the relevance of these protective actions on SARS-CoV-2 merits further investigation.

Vitamin D and the cardiovascular system in COVID-19

COVID-19 has been associated with cardiovascular sequelae, including myocardial injury, type 1 myocardial infarction, acute coronary syndromes, acute cor pulmonale, cardiomyopathy, arrhythmias, thrombotic complications, and cardiogenic shock (77, 78, 79). Myocardial injury,

with the elevation of cardiac biomarkers as well as electrocardiographic or echocardiographic changes, is common, reported in 20–30% of hospitalized patients with COVID-19 (80, 81). Cardiomyopathy has been reported in 7–33% of critically ill COVID-19 patients (82, 83, 84). Cardiac arrhythmias, including new onset atrial fibrillation and atrial flutter, heart block, and ventricular arrhythmias have been reported in 17% of hospitalized patients, and 44% of patients in the ICU setting (85).

Preclinical evidence suggests that vitamin D may protect against atherosclerosis, a substrate for deleterious myocardial events, by inhibiting the transformation of macrophages to foam cells and by increasing cholesterol efflux (86, 87). 1,25 $(OH)_2$D-induced production of vascular endothelial growth factor in vascular smooth muscle cells has been proposed to promote endothelial repair (88). Anti-inflammatory actions such as reduced NFκB and interleukin 6 expression in endothelial cells, reduced thrombogenicity – through the downregulation of tissue factor (F3) and upregulation of thrombomodulin expression in endothelial cells and macrophages, and increased endothelial nitric oxide production are some of the other possible antiatherosclerotic mechanisms of vitamin D (88). The effects of vitamin D on vascular calcification, however, can be 'double-edged' because both deficiency and excess vitamin D has been associated with vascular calcification, a key component of atherosclerotic cardiovascular disease (88).

While no direct causal evidence for a role of vitamin D deficiency in SARS-CoV-2-related heart disease is available, extrapolation of evidence from prior animal and human studies permits speculation of several plausible mechanisms. The rather widespread presence of CYP27B1 includes cells of the cardiovascular system (89, 90). Furthermore, the vitamin D receptor for 1,25 $(OH)_2$D is expressed in the heart and blood vessels (84, 86). In mice models in which the CYP27B1 or the vitamin D receptor has been knocked out systemically, myocardial hypertrophy with overexpression of the renin–angiotensin–aldosterone system (RAAS), hypertension, increased thrombogenicity, and progression of atherosclerosis have been reported (89, 91). The proposed overexpression of the RAAS system, fits these sequelae of vitamin D deficiency in animal models. The various cardiovascular risk factors that have been correlated with higher mortality from COVID-19 are also more evident in experimental and clinical studies of vitamin D deficiency (92, 93, 94, 95, 96, 97, 98). Such risk factors for cardiovascular disease in COVID-19 disease, which are linked to vitamin D deficiency include hypertension (99), diabetes (100), obesity (101) and chronic kidney disease (102). In particular, vitamin D deficiency may predispose to hypertension by upregulation of the RAAS, and increasing vascular resistance and vasoconstriction (103, 104, 105). In mice with endothelial-specific knockout of the vitamin D receptor gene, vascular function is significantly altered, with increased sensitivity to angiotensin-2 compared with control mice (106). It is possible that this is further exacerbated by SARS-CoV-2 infection, in which viral binding with cellular entry receptor ACE2 leads to dysregulation of the RAAS in favour of angiotensin-2 (107, 108, 109).

Activation of the vitamin D receptor also modulates myocardial contractility, likely by regulating calcium flux (110). Several meta-analyses of prospective clinical studies have consistently shown that low 25-OHD serum concentrations indicate an increased risk of overall cardiovascular events and cardiovascular mortality (111, 112, 113, 114, 115, 116). While a majority of the randomized controlled trials examining effects of vitamin D supplementation have not shown benefit, the VINDICATE study demonstrated beneficial effects for improvement in left ventricular rejection fraction and reversal of left ventricular remodeling in patients with chronic heart failure who received vitamin D (117).

Patients with COVID-19 are also at risk for a number of thrombotic complications (118), which may be due to a number of direct and indirect effects of SARS-CoV-2 infection. Several reports have suggested elevated rates of both arterial and venous thrombotic events in patients with COVID-19 (119, 120, 121, 122, 123) and significant coagulopathy is related to poor prognosis in COVID-19 patients (118, 121). While the mechanisms which lead to these events have yet to be fully elucidated, it is plausible that vitamin D levels may be a contributing risk factor. The vitamin D receptor is expressed ubiquitously in blood vessels (90). The possible interaction between inflammatory and hemostatic pathways and vitamin D status is supported by both preclinical and clinical data. Mice in which the vitamin D receptor has been knocked out demonstrate enhanced platelet aggregation, downregulation of antithrombin and thrombomodulin gene expression, and upregulation of tissue factor expression (124). Other studies have suggested that 1,25 $(OH)_2$D can downregulate proinflammatory signaling and promote inhibition of tissue factor activity, thus reducing a prothrombotic milieu (125). In addition, a limited number of clinical reports, antedating the COVID-19 era suggest a link between the development of vitamin D deficiency and incident thrombotic events, including

deep venous thrombosis and cerebrovascular events (126, 127, 128). This may be especially true in patients who are critically ill and require intensive care, among whom low 25-OHD levels have been reported in up to 80% in the pre-COVID-19 era (129, 130). However, it remains unclear whether vitamin D supplementation in such patients has an effect on outcomes (131).

Given the relationship between vitamin D and the RAAS, inflammatory and hemostatic pathways, all of which have been implicated in the development of cardiovascular complications from SARS-CoV-2 infection, further studies evaluating the role of vitamin D in COVID-19-related cardiovascular and thrombotic events may prove critical to gaining insights into both mechanism and therapeutics.

Clinical data linking vitamin D to pulmonary infections

Historically and well before the sun was linked to vitamin D metabolism and activation, it occupied a central position in popular lore as a source of life. The Hindu prayer Surya Namascar is based on the myth of Samba, the son of Krishna, who was cured of leprosy by praying to Surya, a solar deity (132). Until the beginning of the last century, sanatoriums to treat tuberculosis were commonly located in sunny places, where sunbathing was part of the treatment. Interestingly, cod liver oil was used to treat tuberculosis in the 19th century, even before knowing that it was extremely rich in vitamin D (133). Recognition that the vitamin D precursor in the skin is thermoactivated by sunlight has been known only for the past 100 years (134). So intense is the activation of the vitamin D pathway by macrophages and other immune-oriented cells that $1,25(OH)_2D$-dependent hypercalcemia can occur in patients with granulomatous diseases, such as tuberculosis or other granulomatous diseases (135). However, the enticing historical backdrop to vitamin D as a therapeutic for tuberculosis has not met with general consensus (136). Nevertheless, a recent meta-analysis evaluating the effects of vitamin D supplementation on different outcomes in 1787 patients with pulmonary tuberculosis demonstrated some benefits and concluded that this supplementation should be considered as an adjuvant therapy, together with antibiotics (137).

The link between vitamin D and viral infections arose from the observation of the seasonality of vitamin D with lower levels in the winter and concomitant increases in influenza. Conversely, in summer, serum levels of 25-OHD increase and influenza virtually disappears, except during pandemics. Even in pandemics, most deaths occur during cold months (138).

Lower 25-OHD concentrations are associated with a higher risk for infections, especially from the respiratory tract (139). Seeking a link to acute respiratory infections, Sabetta *et al*. measured monthly 25-OHD concentrations in 198 healthy adults and followed them during fall and winter (140). Individuals with 25-OHD concentrations ≥38 ng/mL had a two-fold lower risk of viral acute respiratory infections and faster recovery, compared to those with lower concentrations ($P < 0.0001$). Other studies have also found an association between lower levels of 25-OHD and higher risk of acute respiratory infections but with different thresholds. Nevertheless, they are consistent in showing that the lower the 25-OHD concentration, the greater the risk for acute respiratory infections. Generally, higher-risk occurred at 25-OHD concentrations below 20 ng/mL, but in a retrospective study of 14 108 individuals from the National Health and Nutrition Examination Survey, levels <30 ng/mL were associated with 58% higher odds of acute respiratory infections (141, 142, 143).

Recently, Martineau *et al*. reported the effects of Vitamin D supplementation to prevent acute respiratory infections (144). This meta-analysis included 25 randomized double-blind placebo-controlled trials with individual data from 10 933 patients across the lifespan. Vitamin D supplementation decreased risk of respiratory tract infections by 12%. A stronger protective effect was observed in those with baseline levels of 25-OHD <10 ng/mL compared with those with a baseline levels > 10 ng/mL. This protective effect was much more evident in those receiving daily or weekly doses of vitamin D in contrast to those receiving bolus doses. When combining the daily and weekly doses, the protective effect was more evident at baseline concentrations <10 ng/mL but also at baseline levels ≥10 ng/mL.

Clinical data linking Vitamin D to COVID-19 infection

In a small study ($n=20$) of hospitalized COVID-19 patients, vitamin D insufficiency (defined as levels of 25-OHD < 30 ng/mL) was present in 75% of the overall cohort and in 85% of those who required ICU care ($n=13$) (145). Additionally, an analysis of COVID-19 severity based on survey vitamin D status in Europe suggested that countries with highest rate of vitamin D deficiency are associated with highest rates of infection and death (146).

Furthermore, a preliminary study from the United States has found a strong correlation of vitamin D deficiency with mortality and other aspects of poorer outcome (147).

Recently, Ilie *et al*. observed a significant negative correlation between historical mean25-OHD concentrations per European country with COVID-19 mortality and number of cases (148). Following similar reasoning, Marik *et al*. observed a higher fatality rate for COVID-19 for Northern (>40°N latitude) vs Southern states (6.0% vs 3.5%, $P < 0.001$) in the US (149). Very recently, Gennari *et al*. reports lower levels of 25-OHD levels among patients hospitalized with COVID-19 in Italy (150). In the aggregate, these data suggest a potential deleterious effect of vitamin D deficiency on risk and outcome in COVID-19 disease.

D'Avolio *et al*. investigated retrospectively 25-OHD concentrations in 107 patients who were tested for COVID-19 by nasopharyngeal swab from March 1 to April 14, 2020, in a single hospital from Switzerland (151). The median 25-OHD level was 22.2 ng/mL, similar to the median of a control cohort from the same period in 2019 (24.6 ng/mL). In the 27 individuals with PCR positivity for SARS-COVID-2, the median 25-OHD was 11.1 ng/mL while in those who were PCR negative, the median was 24.6 ng/mL; $P < 0.004$. This relationship, however, was not found by Hastie *et al*. using UK biobank data (152). They investigated 449 individuals with confirmed COVID-19 infection who had 25-OHD concentrations obtained 10 years before. The initial inverse association disappeared after adjustment for confounders. Male sex, poorer health status, socioeconomic deprivation, age, BMI, and ethnicity were predictive factors for COVID-19 in a multivariable logistic regression. Curiously, they could also not find any association of this viral infection with diabetes, blood pressures, or smoking. Grant *et al*. have provided evidence that vitamin D supplementation might be associated with reduce risk of COVID-19 infections and deaths (153).

It is intriguing that, Italy and Spain, which have been heavily affected by COVID-19 are among the European Countries with the highest prevalence of hypovitaminosis D (142). In a sampling of 700 Italian women, 60-80 years old, 25-OHD levels were reported to be lower than 12 ng/mL in 76% (154). Moreover, prevalence of hypovitaminosis D was reported in up to 32% of healthy postmenopausal women in winter and more than 80% in institutionalized individuals (155). Diabetes and obesity, recognized risk factors for the disease or for its severity, are characterized by poor vitamin D status and elevated vitamin D requirements (154, 156). In the vast majority of hospitalized elderly Italian subjects, hypovitaminosis D was present with more than half showing severe vitamin D deficiency. Lack of vitamin D also correlated with inflammatory parameters (157).

Endogenous levels of 25-OHD are dependent, to variable extent on sun irradiation, particularly in those countries where foods are not fortified in vitamin D. Low vitamin D status could potentially be a mechanistic link between age, comorbidities and increased susceptibility to complications and mortality due to COVID-19 at least in some countries (9, 148). However, in Italy, vitamin D is predominantly prescribed to post-menopausal women with osteoporosis and for this reason, it can be hypothesized that older men are, at least in part, more vulnerable to the most serious consequences of the infection on this basis (153, 158)

The available clinical data, in brief, are still very preliminary with regard to vitamin D status and COVID-19 disease. Many reports, to date, have been published without rigorous peer-review, are retrospective, and only associative. Caution is, therefore necessary in interpreting the data. Nevertheless, recent publications consistently show a higher prevalence of vitamin D deficiency in patients presenting with severe forms of COVID-19 (153). In addition, putative mechanisms underlying vitamin D's role in immunity and non-skeletal actions, would provide support for the hypothesis advanced that vitamin D deficiency is a risk factor for the disease and/or its adverse outcome. Clearly, there are other factors to consider that include not only established risk factors (159, 160, 161) but also local public health measures that are taken to control the spread of the SARS-CoV-2 virus.

An increasing number of clinical trials are being registered to investigate the effect of vitamin D supplementation or 25-OHD levels on various COVID-19 outcomes (159). Until the results of these trials are known, a prudent, general health measure is to ensure vitamin D sufficiency. For most individuals worldwide, this recommendation comes with the need for vitamin D supplementation in order to maintain adequate circulating levels of 25-OHD.

Conclusions

The pervasive actions of vitamin D on many organ systems have raised many possible interactions between it and the mechanisms by which the SARS-CoV-2 virus infects human beings. While the data are far from conclusive in attributing a role for vitamin D in influencing the risk and

outcome of this disease, it is nevertheless also clear that more research would be timely and revealing.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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