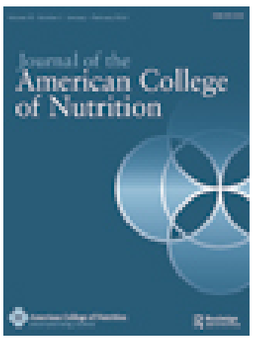

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REVIEW

Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects

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ABSTRACT

Vitamin D deficiency (VDD) partly explains geographical differences in COVID-19 susceptibility, severity, and mortality. VDD among African-Americans, diabetics, hypertensive, and aged populations possibly explain the higher death rate, aggravated by cocooning. Vitamin D is pleiotropic, mediating bone metabolism, calcium homeostasis, and immune functions, whereas VDD is associated with inflammatory reactions and immune dysfunction, predisposing individuals to severe infections. Vitamin D modulates innate and adaptive immunity via the expression of genes that code antimicrobial peptides (AMPs). And the expression of cluster of differentiation (CD)14, the co-receptor for epidermal toll-like receptor (TLR)4. AMPs stimulate TLR2 in macrophages, increasing the conversion of vitamin D into its active form by cytochrome P450 27B1. Antiviral properties of vitamin D-induced AMPs can shift the polarization of the adaptive immune response from helper T cells (Th)1 to the more regulatory Th2 responses that suppress immune over-reactivity by preventing cytokine storm, which is already demonstrated during the Spanish flu episode. Vitamin D induces antiviral effects by both direct and indirect mechanisms via AMPs, immunomodulation, the interplay between major cellular and viral elements, induction of autophagy and apoptosis, variation of genetic and epigenetic factors. The crosstalk between vitamin D and intracellular signaling pathways may operate as a primary regulatory action on viral gene transcription. VDD may increase the likelihood of infection with enveloped viruses, including retrovirus, hepatitis, and dengue. Global data correlates severe VDD with COVID-19 associated coagulopathy, disrupted immune response and mortality, reduced platelet count, and prolonged prothrombin time, suggesting benefits from supplementation.

KEY TEACHING POINTS

- Vitamin D induces antiviral effects by direct and indirect mechanisms via AMPs, immunomodulation, induction of autophagy, etc.
- Epidemiology of VDD partly explains geographical differences in COVID-19 susceptibility, severity, and mortality.
- Global data correlates severe VDD with COVID-19 associated coagulopathy, disrupted immune response and mortality, reduced platelet count, and prolonged prothrombin time, together suggesting benefits from supplementation.
- Many clinical trials are underway globally to delineate the role of vitamin D in both prevention and treatment of COVID-19.

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Coronavirus; COVID-19; immunity; pandemic; SARS-CoV-2; vitamin D

Introduction

Pneumonia of idiopathic nature identified in Wuhan, China, was initially reported on December 31, 2019 to the World Health Organization (WHO) (1), which was declared a Public Health Emergency of International Concern on January 30, 2020. On February 11, 2020, the WHO announced the name 'COVID-19' for the new coronavirus disease of 2019. COVID-19, an emerging infectious disease (EID) infected by multiple strains of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, which has spread alarmingly throughout the globe (1). By March 11, 2020, WHO has reached an assessment that

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COVID-19 can be considered a pandemic because of the alarming spread and severity, as well as by the disturbing levels of health-systems inaction (2). Currently, the pandemic has spread over 216 countries and territories, dramatically impacting global health and economies. As of July 31, 2020, globally, there were 17.3 million confirmed cases for COVID-19, including 0.67 million deaths with a case-fatality rate (CFR) of 3.9% (3). Among WHO regions, the Americas and Europe have the highest confirmed cases. Ten most affected countries are the United States of America (USA), Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Iran, and the United Kingdom (UK) (4). However, the mortality rate of COVID-19 varies significantly across countries. For instance, CFR has been higher in UK (15.2%), Italy (14.2%), France (13.6%), Mexico (11.1%) and Spain (10%) than in Brazil (3.5%), USA (3.4%), India (2.2%), Russia (1.7%) and South Africa (1.6%), as of today (3). Although reasons behind the disparities are not clearly understood, different explanations have been proposed, such as multiple strains of the virus, variations in COVID-19 testing methods, differences in quality and access to the healthcare and preventive strategies (5,6). More importantly, demographic features of the affected population, including the proportion of geriatrics, nutritional status, comorbidities, and socioeconomic status, also influence the CFR.

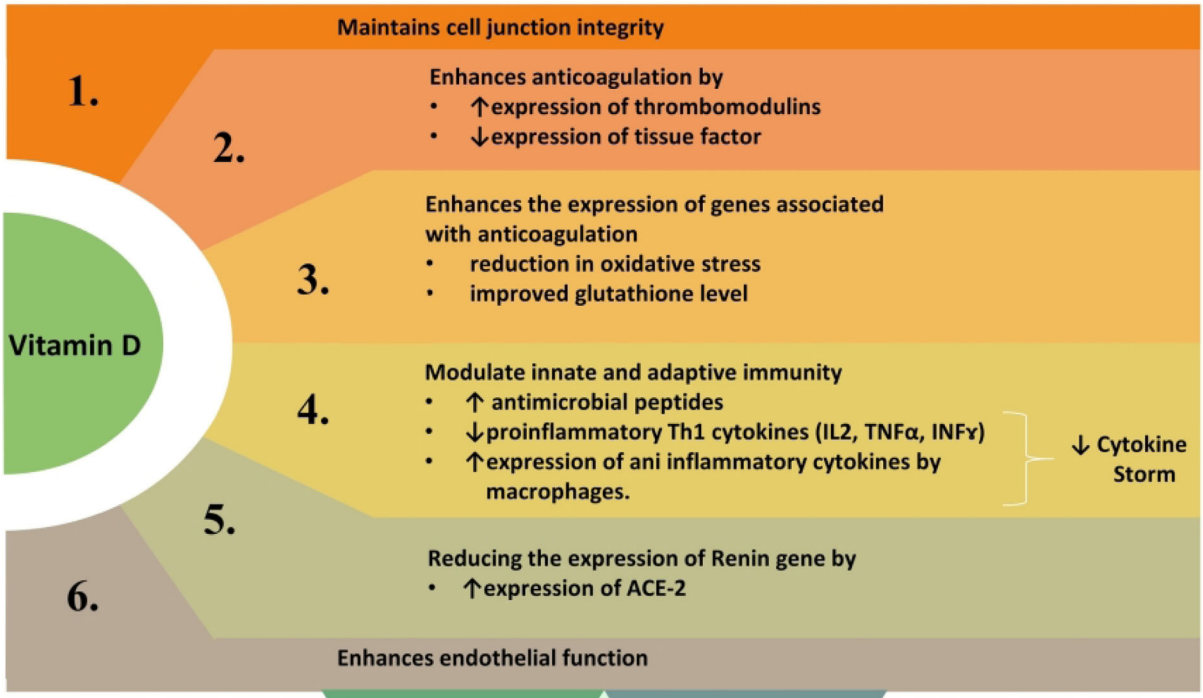
The majority of the individuals infected with the SARS-CoV-2 virus have mild-moderate respiratory disorders that resolve without any specific therapy. Meanwhile, the elderly and those with cardiac disease, hypertension, diabetes, chronic lung disorders, and cancer are highly susceptible to severe COVID-19 (1). Most importantly, the current pandemic is particularly severe, with higher case fatality in individuals with non-communicable diseases (NCDs). A meta-analysis of 30 retrospective studies with 53,000 confirmed COVID-19 patients reported a pooled incidence of 20.2% severity and 3.1% mortality (7). Old age, cardiovascular problems, hypertension, and diabetes were identified as independent risk factors for mortality. Additionally, the report suggested that c-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer along with reduced lymphocytes and platelets to be significantly related to severe COVID-19. On the other hand, the immune system in certain patients may help overcome COVID-19 better than others. Time series analysis of the number of confirmed, dead, and recovered cases will reveal the pattern of impact on various populations (5), explain the role of the immune system in COVID-19, and help develop specific therapy for viral infections. Without specific vaccines and drugs for SARS-CoV-2, we need to evolve strategies to control the spread of COVID-19 and decrease mortality. This review will discuss the possibilities of employing vitamin D as a preventive and ameliorative measure for COVID-19 via its pleiotropic effects (Figure 1).

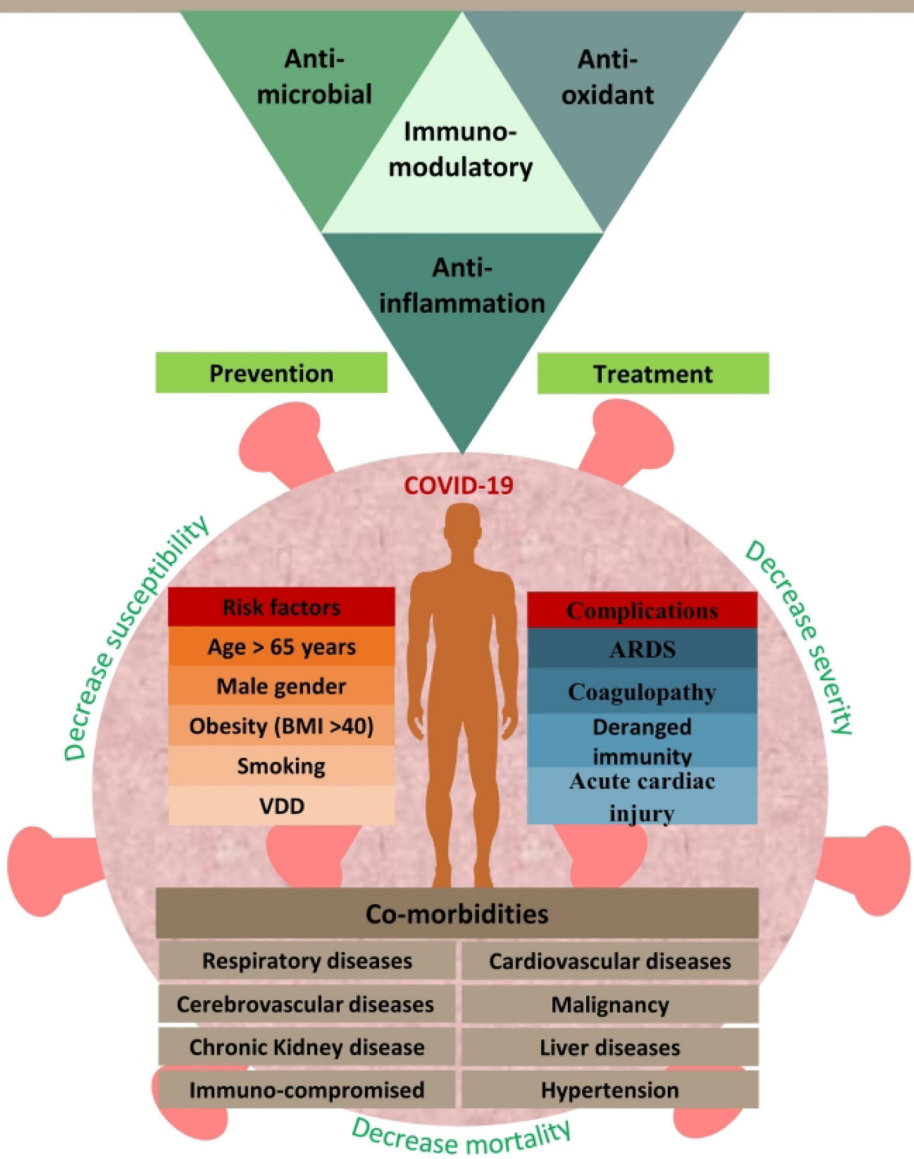
Vitamin D and immunity

Vitamin D, also called the sunshine vitamin, is a steroid hormone that exists in different forms. While 25-hydroxyvitamin D is the primary circulating form, the biologically active form is 1,25-dihydroxyvitamin D (8). Vitamin D mediates several physiological processes, including bone and extra-skeletal metabolism, cardiovascular and calcium homeostasis, and, most importantly, immune functions (9). On the other hand, vitamin D deficiency (VDD) is associated with inflammatory reactions and immune dysfunction, predisposing individuals to severe infection (10). A recent meta-analysis established that severe VDD is independently related to a higher risk of mortality in adult sepsis patients (11). Similarly, a multicentre study concluded that VDD at the time of initiation of critical care is a potential predictor of all-cause mortality in severe cases (12).

Evidence is mounting on vitamin D's mediatory role in the immune response to infection. The biologically active form of vitamin D modulates innate and adaptive immunity via genes regulated by the vitamin D receptor (VDR), a transcription factor (Figure 2). An *in vitro* study using human cell lines revealed around 15 genes operating as major mediators of vitamin D's action in both innate and adaptive immunity (13). Therefore, vitamin D may be considered for combating viral infections in both clinical and preclinical studies (14). Vitamin D acts by binding to the VDR, a nuclear receptor, which dimerizes with an isoform of the retinoid X receptor (RXR), whereupon the VDR-RXR heterodimers bind to vitamin D response elements (VDRE) on the promoter regions of target genes (14). VDRE then promotes the transcription of antimicrobial peptides (AMPs) such as human cathelicidin (human cationic antimicrobial protein; hCAP18) and human β-defensin-2 (hBD-2). AMPs are endogenously synthesized molecules found on mucosal and epithelial layers of multicellular organisms that offer the first-line defense against infections (bacterial and viral). AMPs also possess immunomodulatory functions. Defensins and cathelicidins constitute the two major families of AMPs. Defensins consist of six α- and two β- subclasses. hCAP18/LL-37 is the only type of cathelicidins in humans (15). Additionally, VDR-RXR heterodimers can also displace the nuclear factors of activated T lymphocytes (T cells), thereby suppressing cytokine-related genes in humans (16).

Critical to the innate immune response in humans and other mammals are the toll-like receptors (TLRs) located on epithelial cells, macrophages, polymorphonuclear cells, and monocytes (17,18). Pathogen surfaces have characteristic molecular features called pathogen-associated molecular patterns (PAMP). TLRs recognize the PAMPs, in addition to viral proteins and nucleic acids. TLR2 also identifies the lipopolysaccharides of microbes. In a rat mast cell model, TLRs upon recognizing and binding to targets, get activated, and secrete cytokines that stimulate the expression of AMPs and reactive oxygen species (ROS) (19). VDR stimulation affects many TLRs and vice versa. Vitamin D's active form induces the expression of the cluster of differentiation (CD)-14, which is the co-receptor for TLR4 in both epidermal keratinocytes and monocytes. Stimulation of TLR2 in macrophages by AMPs increases the local expression of cytochrome P450 27B1 (CYP27B1), converting vitamin D into its active form, demonstrating the pleiotropic actions of


Maintains cell junction integrity
1.
2.
Enhances anticoagulation by
• ↑expression of thrombomodulins
• ↓expression of tissue factor
Vitamin D
3.
Enhances the expression of genes associated with anticoagulation
• reduction in oxidative stress
• improved glutathione level
4.
Modulate innate and adaptive immunity
• ↑ antimicrobial peptides
• ↓proinflammatory Th1 cytokines (IL2, TNFα, INFɤ)
• ↑expression of ani inflammatory cytokines by macrophages.
↓ Cytokine Storm
5.
Reducing the expression of Renin gene by
• ↑expression of ACE-2
6.
Enhances endothelial function


Anti-microbial
Immuno-modulatory
Anti-oxidant
Anti-inflammation
Prevention
Treatment
COVID-19
Decrease susceptibility
Decrease severity
Risk factors
Age > 65 years
Male gender
Obesity (BMI >40)
Smoking
VDD
Complications
ARDS
Coagulopathy
Deranged immunity
Acute cardiac injury
Co-morbidities
Respiratory diseases
Cardiovascular diseases
Cerebrovascular diseases
Malignancy
Chronic Kidney disease
Liver diseases
Immuno-compromised
Hypertension
Decrease mortality

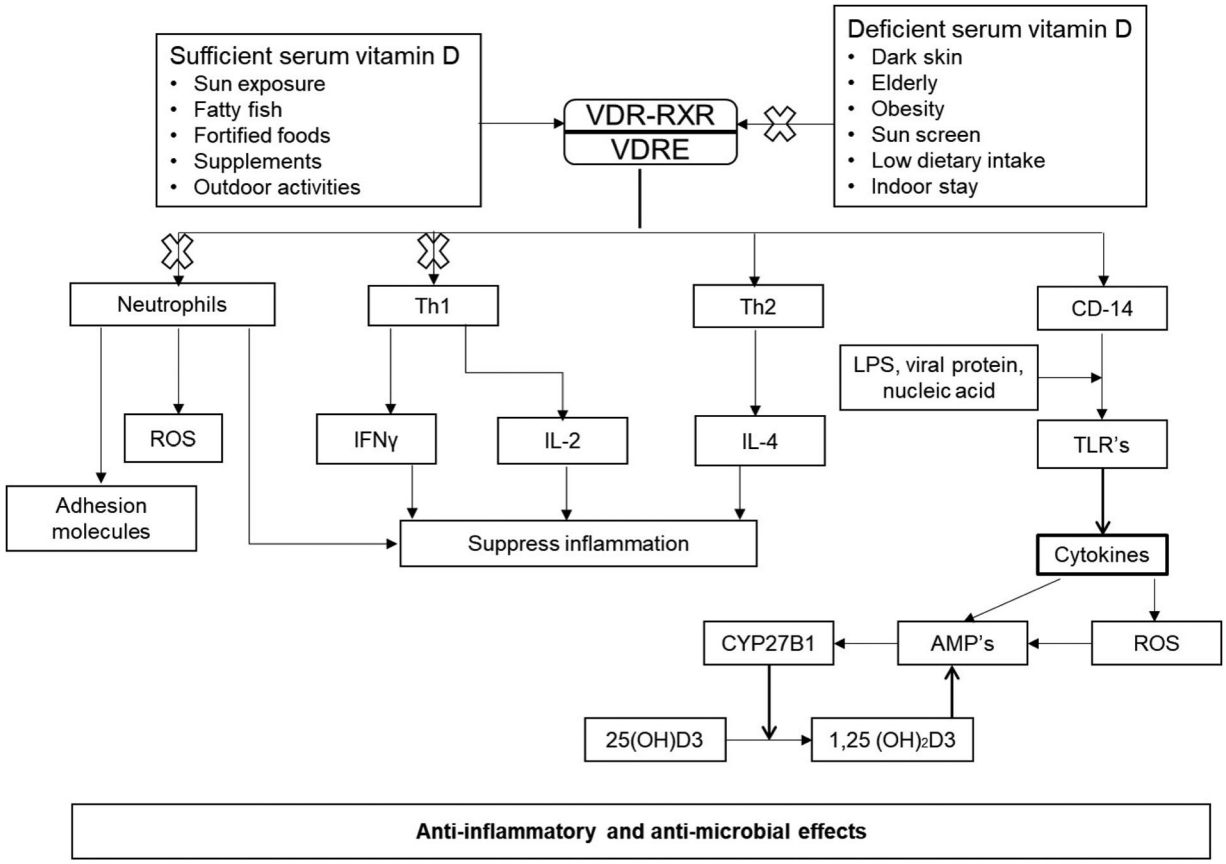


Figure 2. Overview of immune modulatory mechanism of Vitamin D. VDR-RXR: Vitamin D receptor-retinoid X receptor; Th1: Helper T cells type 1; Th2: Helper T cells type 2; VDRE: Vitamin D response elements; CD-14: Cluster of differentiation-14; ROS: Reactive oxygen species; IFNγ: Interferon-gamma; IL-2: Interleukin-2; IL-4: Interleukin-4; TLRs: Toll-like receptors; CYP27B1: Cytochrome P450 27B1; AMPs: Antimicrobial peptides; 25(OH)D3: 25-hydroxyvitamin D; $1,25(OH)_2D3$: 1,25-dihydroxyvitamin D.

vitamin D on human immunity (20). Certain AMPs related to TLRs exhibit antiviral properties, and their expression is influenced by the serum levels of vitamin D. hBD-2 is modestly upregulated by vitamin D and may add to antiviral effects as a chemoattractant for monocytes and neutrophils. Conversely, in monocytes, activation by vitamin D alone is not sufficient to induce gene expression. Activated TLR1/2 induce hCAP18, which is vigorously upregulated by the active form of vitamin D (20). While most of the hCAP18 are stored in neutrophil granules for discharge at the pathogen invasion sites, several other types of immune cells including B lymphocyte (B cells), monocytes and natural killer (NK) cells express and release hCAP18 into the blood from the epithelia of the digestive tract, respiratory tract, urinary tract, epithelial tract, conjunctiva, cornea, and skin. Both clinical and preclinical experimental studies have shown that at the cellular level, expression of CYP27B1 in keratinocytes and macrophages induce hCAP18 expression, which is impaired in the absence of vitamin D, VDR, or CYP27B1 (14,15). On the other hand, hCAP18 demonstrates anti-bacterial effects, including membrane disruption, and antiviral effects *in vitro* (21).

Vitamin D suppresses helper T cells (Th)1 proliferation, suppressing the production of interferon-gamma (IFNγ), and interleukin (IL)-2. A decrease in circulating cytokines will suppress antigen presentation by dendritic cells, and decrease T lymphocyte recruitment and proliferation. Vitamin D improves the expression of Th2 associated cytokines, such as IL-4, shifting the polarization of the adaptive immune response from Th1 to the more regulatory Th2 responses (14,15,17,20).

Another important aspect of vitamin D is its antioxidant potential. U937 monocyte cell lines demonstrated vitamin D's *in vitro* antioxidant effects via increasing glutathione (GSH) formation (22), mediated by the upregulation of glutamate-cysteine ligase catalytic subunit (GCLC) and glutathione reductase (GR), which regenerate GSH from glutathione disulfide (GSSG), the oxidized form. GSH scavenges ROS, thereby reducing intracellular ROS after vitamin D supplementation. The decreased oxidative stress inhibits the release of proinflammatory cytokines from monocytes, namely monocyte chemoattractant protein-1 (MCP-1) and IL-8. On the other hand, an *in vitro* study showed that GSH deficiency per se produces oxidative damage and reduces vitamin D regulatory gene expression levels (23). Moreover,

Figure 1. Proposed pleiotropic effects of vitamin D for the prevention and treatment of COVID-19. Th1: Helper T cells type 1, IL-2: Interleukin-2; TNF-α: Tumor necrosis factor-alpha; IFNγ: Interferon-gamma; ACE-2: Angiotensin-converting enzyme; BMI: Body mass index; ARDS: Acute respiratory distress syndrome; VDD: vitamin D deficiency.

GSH deficiency decreases the body's ability to fight infections by impairing the activity of specialized immune cells (24). Jain et al. demonstrated that a rise in GSH, after co-administration of vitamin D with L-cysteine (a precursor of GSH), profoundly decreased oxidative stress in a mouse model of VDD (25). L-cysteine also increases GSH levels via upregulating the expression of vitamin D binding protein (DBP), vitamin D 25-hydroxylase, and VDR, thereby improving vitamin D status and reducing inflammation in diabetic rats (26). Another study found significantly lower levels of anti-inflammatory biomarkers hydrogen sulfide (H_2S) and cyclic adenosine monophosphate (cAMP) and higher levels of oxidative stress in African-Americans with diabetes (27). On the other hand, in high-glucose treated U937 monocytes, vitamin D supplementation, *in vitro*, upregulates cystathionase, formation of H_2S, and cAMP synthesis and decrease ROS.

Vitamin D and viral infections

Decades of investigations on vitamin D's pleiotropism have demonstrated interactions between VDD and a variety of infections, including viral infections. A large-scale meta-analysis of 25 randomized controlled trials (RCTs) with 11,321 human subjects showed that vitamin D supplements are protective in acute respiratory tract infections (28). Vitamin D exhibits its antiviral effects by both direct and indirect mechanisms such as induction of AMPs, immunomodulation, the interplay between major cellular and viral elements, induction of autophagy and apoptosis, and variation of genetic and epigenetic factors. The crosstalk between vitamin D and intracellular signaling pathways may operate as a primary regulatory action on viral gene transcription (29).

Antimicrobial and antiviral effects of vitamin D are attributed to the induction of AMPs such as hCAP18 and hBDs. These AMPs provide direct antimicrobial actions and pleiotropic effects such as induction of immune modulation to pathogen-associated stimuli (30). Research on innate immunity has demonstrated that vitamin D produces intracrine induction of antimicrobial effects, critical for the response of monocytes/macrophages against infection. hCAP18 shows antimicrobial effects by interacting with formyl peptide receptor-like 1(FPRL1) and recruiting T cells, monocytes, and neutrophils to the site of infection. Besides, hCAP18 participates in innate immunity by transactivating epidermal growth factor receptor (EGFR) at the surface of the airway epithelium. Moreover, an *in vitro* study demonstrated hCAP18 can enhance the respiratory microbial clearance via induction of apoptosis of the infected human epithelial tissues by depolarizing the mitochondrial membrane and enhancing the secretion of mitochondrial cytochrome c into the cytosol (31). Direct antiviral actions of hBDs can interrupt the viral membrane, interfere with its glycoproteins, inhibit viral replication, and downregulate viral receptors. During human viral infections, hBD indirectly regulates immune cell migration to the infection site (32).

The potent antiviral effect of AMPs has been steadily gaining prominence. Indeed, potential antiviral effects of hCAP18 and hBD have been amply demonstrated against multiple viral infections such as human immunodeficiency virus (HIV)-1, vaccinia virus, herpes simplex virus (HSV)-1 and 2, influenza virus (IFV), rhinovirus (RV), adenovirus (AV) and hepatitis C virus (HCV), etc. A recent clinical trial showed that mega-doses of vitamin D as adjuvant therapy attenuated immune activation and exhaustion caused by antiretroviral treatment for HIV (33). An *in vitro* study reported a repressive effect of vitamin D on RV replication, possibly by induction of the hCAP18 in primary bronchial epithelial cells from cystic fibrosis patients (34). Vitamin D supplementation has already demonstrated reduced the risk of infection and mortality in influenza and COVID-19 in humans (35). A meta-analysis reported lower serum vitamin D in chronic hepatitis B virus (HBV) patients. Vitamin D levels were inversely correlated with HBV loads (36). Mounting evidence shows that VDD is a risk factor for HCV infections, while vitamin D supplements prevent liver disease progression and enhance response to therapy in HCV patients (37). Likewise, a meta-analysis reported that VDD might increase the likelihood of infection with enveloped viruses, including retrovirus, hepatitis, dengue, and respiratory syncytial virus, etc (38).

Vitamin D deficiency and COVID-19 disease

VDD can, at least partly, explain geographical differences in morbidity and mortality associated with COVID-19. Indeed, VDD is counted as a risk factor for severity. An observational study found that the risk of severe COVID-19 to be 17.3% among patients with severe VDD, whereas it was only 14.6% in patients with normal levels of vitamin D, amounting to a difference of 15.6% (5). Interestingly, VDD and COVID-19 severity match similar prevalence patterns such as advanced age, male gender, obesity, diabetes, hypertension, ethnic minorities, and nursing home residents (39). Aging can weaken the innate immunity, increasing chances for severe COVID-19. The diminished immune response in the elderly may increase the viral load, whereas a shortage in memory B cells may be attributed to exaggeration of adaptive immunity induced by elevated cytokines (5). Nearly 76% of African-Americans have VDD, almost twice the American adult population (40). The variation in DBP levels may be responsible for the observed racial differences in total vitamin D levels and VDD manifestations. DBP gene polymorphism in blacks has been attributed to low DBP levels (41). Blacks accounted for 52% of COVID-19 cases and 58% of COVID-19 related mortality in the USA (42). Spatial modeling of New York City, ZIP code-level testing showed that African-Americans are five times more likely to contract COVID-19 (43). The report also says that population and spatial patterns of COVID-19 differ by race, age, physical environment, and health status. Indeed, such disparities are more obvious within different counties in the USA. For example, in Milwaukee County in Wisconsin, 73% of COVID-19 deaths occurred in blacks, who constitute only

26% of the population (42). Similarly, in Louisiana, blacks account for 70% mortality but constitute only 32% of the population (44). Similar to VDD, GSH deficiency is also prevalent in African-Americans (45). A preclinical study demonstrated that GSH deficiency and the related oxidative stress can epigenetically modify vitamin D regulatory genes, thereby suppressing gene expression, diminishing vitamin D synthesis, and secondary VDD (46). Jain et al. reported that reduced levels of L-cysteine and GSH correlates with decreased DBP and vitamin D levels in patients with type 2 diabetes (47). Robust evidence from clinical and preclinical research shows a positive correlation between serum GSH and vitamin D status (46–48). Considering these findings, researchers suggested that vitamin D and L-cysteine co-administration may reduce VDD and COVID-19 deaths in African-Americans (49). Another hypothesis is endogenous GSH deficiency and resultant VDD as the most likely cause of COVID-19 severity and mortality (50).

VDD is common in Europe, with 30 to 60% in Western, Southern, and Eastern Europe, but <20% in Northern Europe (51). The mean concentration of vitamin D in 20 European countries correlated with the corresponding mortality rate. People with below-average vitamin D levels are more prone to COVID-19 mortality (52). Vitamin D levels are very low among the elderly, particularly in Spain, Italy, and Switzerland, the most vulnerable cohorts for COVID-19, justifying the greater severity of COVID-19 in these countries than Nordic countries. Lower vitamin D levels in Southern European nations are possibly linked to reduced exposure to sunlight and higher skin pigmentation. Further, Nordic countries employ vitamin D supplementation by fortification of dairy products and cod liver oil (51). Cocooning or indoor confinement also raises the risk for VDD on account of diminished exposure to ultraviolet B (UVB) light (53,54). Interestingly, the entire cluster of asymptomatic COVID-19 cases could be traced to a single shelter for the homeless in Boston (55). Although the homeless have poorer health and nutritional status, compromising immunity, they have good exposure to sunlight, the primary source (up to 90%) of vitamin D.

Global data have revealed a strong connection between severe VDD and COVID-19 mortality (5). A study found VDD among 84.6% of COVID-19 patients in intensive care units of a tertiary care facility in New Orleans, USA (39). VDD potentially worsens COVID-19 severity by a prothrombotic action and derangement of the immune response. COVID-19 associated coagulopathy (CAC) is emerging as a key indicator of survival after COVID-19. The American Society of Hematology recommends routine prophylaxis for deep vein thrombosis (DVT) for all COVID-19 patients (56). COVID-19 increases coagulopathy with elevated D-dimer levels, reduced platelet count, and prolonged prothrombin time (PT) (57). A meta-analysis also reported that low platelet count is linked to a higher risk of severe COVID-19 and mortality (58). The role of CAC is further confirmed by the presence of microvascular clots in multiple organs of hospitalized COVID-19 patients. This comprises of DVT/pulmonary emboli, acute renal failure, cerebrovascular, and cardiovascular ischemic events. Another hallmark feature is lymphocytopenia, resulting from a deranged immune response, possibly mediated by a massive influx of the inflammatory cells into various organs, including the central nervous system (CNS), suggesting an autoimmune component in the pathology. The increased incidence of stroke and reports of loss of smell and taste sensitivity suggests CNS involvement. Reports suggest an association between vitamin D status and severe COVID-19 based on the strong connection between VDD and CRP (5). Inflammatory cells convert vitamin D to its active form and thereby express VDR, implicating an inverse relation between CRP and vitamin D. CRPs protect the arteries, cells, and tissues from the damage induced by an autoimmune response, infection, etc.

Both preclinical and clinical evidence showed that VDD is associated with both hypertension (59) and diabetes (60), risk factors of COVID-19 fatality (7). A mounting concern is that the association with hypertension is confounded by antihypertensive drugs, namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). ACEIs and ARBs cause a two-fold increase in the severity and mortality of patients with COVID-19 (61), explaining the molecular mechanism of angiotensin-converting enzyme 2 (ACE2) compared with previous coronavirus infections. An *in vitro* study has demonstrated that ACE2 is a membrane-bound aminopeptidase with a profound role in the cardiovascular and immune systems and ubiquitous in the epithelia of the human lung and small intestine (62). ACE2 is related to cardiac function and the pathophysiology of hypertension and diabetes. ACE2 inversely modulates the renin-angiotensin system (RAS), whereas ACE2 participates in the harmonizing mechanism for ACE, which positively modulates the RAS. The respiratory tract is the foremost site of coronavirus infection and related morbidity. SARS-CoV-2 infects host cells via ACE2 receptors, resulting in COVID-19 associated pneumonia and cardiovascular problems. An *in vitro* study using human and animal cell lines exhibited the route of entry of the SARS-CoV-2 virus is via ACE2 receptors in the lung epithelium (63). Replication of previous coronaviruses downregulates ACE2. Therefore, RAS will be dysregulated because it depends on counterbalancing ACE and ACE2. Thus ACE2 depletion leads to RAS overactivation, causing a cytokine storm, leading to acute respiratory distress syndrome (ARDS). VDD is strongly associated with 90% of ARDS patients with poor outcomes, such as the extended duration of mechanical ventilation (64). Besides, the chronic VDD promotes lung fibrosis via activation of the RAS. A chronic VDD model in mice could induce RAS stimulating activation, stimulating the expression of profibrotic factors that aggravate the fibrotic cascade (65). Indeed, RAS's profibrotic effect is independent of elevated blood pressure.

Vitamin D and COVID-19 pathology: emerging evidence

There are multiple clinical reports citing evidence for an association between vitamin D status and COVID-19, but

Table 1. Studies on association of vitamin D with COVID-19 patients.

Sl.no.	Author, Year	Study title	Objectives	Method	Key findings
1.	Daneshkhah (2020) (5)	The Possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients	Vitamin D in inflammatory response associated with severe COVID-19	Global databases and literature	Reduces fatality and severity by suppressing cytokine storm
2.	Lau et al. (2020) (39)	Vitamin D insufficiency (VDI) is prevalent in severe COVID-19	Serum vitamin D levels in COVID-19 patients in ICU in New Orleans	Retrospective analysis of a tertiary care hospital database (n = 20)	75% patients had VDI, with significant progression and severity of COVID-19
3.	Ilie et al. (2020) (52)	The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality	Mean vitamin D levels with COVID-19 cases and mortality in 20 European countries	Global databases and literature	A negative correlation between the vitamin D and COVID-19 cases and mortality
4.	Moozhipurath et al. (2020) (54)	Evidence of protective role of ultraviolet-B (UVB) radiation in reducing COVID-19 deaths	UVB rays and morbidity associated with COVID-19	Global databases of 152 countries with fixed-effect log-linear regression model	A unit increase in ultraviolet index (UVI) can ameliorate the COVID-19 deaths by 1.2% and case-fatality rate (CFR) by 1%
5.	Glicio (2020) (66)	Vitamin D level of mild and severe elderly cases of COVID-19: a preliminary report	Serum vitamin D levels and immune response within the lungs	Retrospective analysis of 2 tertiary hospital databases in South-Asian (n = 176)	80% of the patients had vitamin D deficiency (VDD), with 92% have severe infection
6.	Raharusuna et al. (2020) (67)	Patterns of COVID-19 mortality and vitamin D: an Indonesian study	COVID-19 mortality with serum vitamin D levels	Retrospective analysis of Indonesian Government hospital databases with two cohorts: active and expired (n = 780)	Vitamin D status is strongly associated with COVID-19 mortality, with an increased risk in older and male cases with comorbidity
7.	D'Avolio et al. (2020) (68)	25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2	Serum vitamin D levels in COVID-19 patients of Switzerland	Retrospective analysis of COVID-19 positive (n = 20) and negative (n = 80) cases	A significantly lower levels of serum vitamin D in COVID-19 positive cases
8.	Laird et al., (2020) (69)	Vitamin D and inflammation: potential implication for severity of COVID-19	Influence of vitamin D levels on COVID-19 morbidity and mortality of 12 European regions	Global databases and literature	Regions with lower mean vitamin D levels had more cases and mortality rate
9.	Meltzer et al. (2020) (70)	Association of vitamin D deficiency and treatment with COVID-19 incidence	VDD and its effect on COVID-19	Retrospective analysis of a university hospital database in Chicago (n = 489)	VDD that is not sufficiently treated is associated with COVID-19 risk
10.	Alipio (2020) (71)	Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (Covid-2019)	Serum vitamin D levels and clinical outcomes of COVID-19	Retrospective analysis of 3 hospital databases in South-Asian (n = 212)	Vitamin D could improve the outcomes, with increasing odds ratio of mild outcome when the level increases
11.	Herwig et al. (2020) (72)	Sedeprovid, a novel vitamin D based substance, plus AlphaH℗ lead to complete recovery from COVID-19 within 48 h after application in a 7-mo old baby, a 1.5-year-old toddler and three further adults	Sedeprovid and AlphaH℗ on COVID-9 outcomes	Prospective study with positive patients (n = 5) with symptoms	The symptoms significantly subsided in 24 hours and completely recovered from COVID-19 within 48 h
12.	Sun et al. (2020) (73)	Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019	Association of serum calcium levels with disease severity and prognosis in COVID-19 patients	Retrospective analysis of a hospital database in Wuhan (n = 241)	Hypocalcemia was associated with disease severity and poor prognosis in COVID-19 patients. A positive correlation was identified between serum calcium and vitamin D levels
13.	Lansiaux et al. (2020) (74)	Covid-19 and vit-D: disease mortality negatively correlates with sunlight exposure	Correlation between sunlight exposure and SARS-CoV-2 infection	Cross-sectional study French databases (n= 64,553,275)	Sunlight could have a protective effect against COVID −19 mortality
14.	Hastie et al. (2020) (75)	Vitamin D concentrations and COVID-19 infection in UK biobank	Influence of vitamin D status with risk of COVID-19	Retrospective analysis of UK biobank database (n = 348,598)	No evidence of susceptibility to COVID-19 infection

VDI: Vitamin D insufficiency; UVB: Ultraviolet-B; UVI: Ultraviolet index; CFR: Case-fatality rate; VDD: Vitamin D deficiency.

they are all based on retrospective data. We have identified 13 such key clinical studies that support this presumption (5,39,52,54,66–74) and one that contradicts (75) (Table 1). Most of these studies suggest a link between VDD and increased susceptibility to SARS-CoV-2 infection while underlining the importance of restoring vitamin D levels to

normal (66,67). These findings are significant because vitamin D boosts cellular immunity, regulates the adaptive immune response, and enhances antioxidant-related gene expression. Therefore, several researchers suggest vitamin D supplements as a preventive and curative measure for COVID-19 (35,68). Moreover, mandatory cocooning could decrease physical activity and the consequent deconditioning of muscles. Therefore, optimizing vitamin D levels with supplements will help regain muscle health and strength, a clear advantage in COVID-19 (69). Meltzer et al. found that untreated VDD may heighten the risk of COVID-19 (70), suggesting that prioritizing interventions to rectify VDD could decrease COVID-19. Such intervention should include both the general population and sub-populations at higher risk of VDD with or without COVID-19. Certain studies imply that vitamin D can rebalance the RAS. Thus, vitamin D can attenuate lung injury by modulating the RAS and blocking the cascade of Ang-2-Tie-2-MLC kinase and suppressing the renin gene's expression *in vitro* (76).

Many have demonstrated the association between vitamin D status and COVID-19 outcomes. For example, a multinomial logistic regression by Alipio, using the databases from three hospitals in South-Asian countries (71), suggests that vitamin D supplementation improves the clinical outcomes of COVID-19 patients. A transnational sensitivity analysis recommends that vitamin D may affect the adaptive average of the time-adjusted case mortality ratio (5), possibly by attenuating COVID-19-related mortality and severity by suppressing the cytokine storm. This could be due to vitamin D's ability to enhance innate immunity and repress adaptive immunity.

The potent role of vitamin D in suppressing the cytokine storm was well documented during the 1918–1919 influenza pandemic (77). Furthermore, vitamin D's boosting immune reaction in flu and during the previous coronavirus outbreak has been well-established. A Pan-European study revealed a negative correlation between the mean concentration of vitamin D, the number of COVID-19 cases, and related fatality (52). Davies et al. constructed two models for analyzing global COVID-19 data and verified the factors that govern causal inference models, concluding a high level of confidence in a causal role for vitamin D in COVID-19 (78).

Certain clinical studies have reported the effect of vitamin D related intervention on COVID-19 treatment outcomes. Moozhipurath et al. demonstrated a profound inverse association between UVB and COVID-19 deaths, suggesting the evidence of the protective effect of the radiation in alleviating COVID-19 related mortality (54). Similarly, previous studies have indicated the protective role of UVB in human health. UVB is a prime source of vitamin D, which boosts immunity and reduces susceptibility to severe infections and related mortality. Herwig et al. published a case series of intervention with a novel water-soluble transport form of vitamin D_3 plus an oral supplement comprising of natural compounds alpha-ketoglutarate, vitamin C, 5 - hydroxymethylfurfural and carnosine with total recovery from COVID-19 within two days in both pediatric and adult patients (72). Currently, multiple intervention studies with vitamin D are registered in clinical trial registries around the world. We found 19 RCTs and eight prospective observational studies on vitamin D in trial registries of the USA, India, and China (Table 2).

Recommendation of vitamin D use

Several public health agencies have revised the recommendation of nutritional supplements, especially for vitamin D. Since COVID-19 pandemic has potentially exacerbated VDD (because of mandatory indoor confinement and the associated UVB exposure deficit), vitamin D supplementation, the UK recommends at least 400 international unit (IU) vitamin D daily to the general population (79). The USA and European Union recommend 600 IU for the general population and 800 IU for those over 70 years (51,80). The Irish Longitudinal Study on Ageing (TILDA) recommends 400 IU during winter for the general population, but 600 to 800 IU for those confined indoor and 800 to1000 IU for over 70 years (53). Several reports propose higher doses of vitamin D to tackle COVID-19. A review by Grant et al. suggested vitamin D_3 10,000 IU per day for a few weeks to promptly increase vitamin D levels (above 40–60 ng/mL), followed by a daily dose of 5000 IU to ameliorate COVID-19 risk (35). On the other hand, those already infected with COVID-19 might benefit from mega-doses of vitamin D_3. Ebadi and Montano-Loza proposed a loading dose of 1,00,000 IU in week 1, and 50,000 IU for weeks 2 and 3 (81). Meanwhile, another review suggested a loading dose of 200,000 to 3,00,000 IU a week to alleviate the risk and severity of COVID-19 (82). In this era of precision medicine, prescribing vitamin D should be target-specific, because different ethnic groups are affected differently with VDD. We suggest a personalized vitamin D dosage regimen, based on nutrigenomics research.

Conflicting evidence

The immune-modulatory actions of vitamin D in viral infections are highly complex and vary with nature and strains of the virus and the type of immune response employed. Researchers across the globe have identified 200 genetic mutations and multiple strains of the SARS-CoV-2, some of which are more virulent than others. Furthermore, vitamin D's anti-influenza action seems to be transient, ranging from differentially modulated antiviral immune responses to regulation of viral pathogenesis. UK Biobank study found conflicting evidence on vitamin D supplementation in COVID-19, suggesting that vitamin D supplements may not be effective (75). Additionally, they found no evidence to back a potential role for vitamin D levels to link susceptibility to COVID-19. Furthermore, their data show that VDD is not likely to be the underlying reason for the significant risk observed in blacks and other ethnic minorities. Various publications suggest a mega-dose of vitamin supplements, especially for those infected with SARS-CoV-2. However, many researchers have questioned the use of the mega-doses to achieve adequate vitamin D status because this may not

Table 2. Registered trials/studies on vitamin D in COVID-19 in various trial registries.

Sl.No.	Trial registration number/Place of study	Study title	Study design/Phase	Intervention/Exposure	Timeline
1.	NCT04394390 Turkey	Do vitamin D levels really correlated with disease severity in COVID-19 patients? (COVIDVIT)	Prospective observational case-control study	Exposure: Blood vitamin D levels	May 2020 to June 2020
2.	NCT04385940 Canada	Vitamin D and COVID-19 management	Double blind, randomized controlled clinical trial (RCT) Phase 3	Group 1: Vitamin D_3 oral high dose (50,000 IU) (Week 1: Twice, Week 2,3: Once) Group 2: Vitamin D_3 oral low dose (1000 IU/day) for 3 wk	June 2020 to December 2020
3.	NCT04370808 Portugal	VITACOV: Vitamin D polymorphisms and severity of COVID-19 infection (VITACOV)	Prospective observational case-only study	Exposure: Vitamin D polymorphisms and blood vitamin D levels	June 2020 to March 2021
4.	NCT04334005 Spain	Vitamin D on prevention and treatment of COVID-19 (COVITD-19)	Double blind, RCT	Group 1: Usual care Group 2: Vitamin D 25,000 IU single dose + Usual care	April 2020 to June 2020
5.	NCT04386044 United Kingdom	Investigating the role of vitamin D in the morbidity of COVID-19 patients	Prospective observational study	Exposure: Blood vitamin D levels	June 2020 to June 2021
6.	NCT04363840 USA	The LEAD COVID-19 trial: low-risk, early aspirin and vitamin D to reduce COVID-19 hospitalizations (LEAD COVID-19)	Multicenter, open label, RCT Phase 2	Group1: No intervention Group 2: Aspirin 81 mg/day orally for 14 d Group 3: Aspirin 81 mg/day orally for 14 d + Vitamin D 50,000 IU orally once weekly for 2 wk	May 2020 to December 2020
7.	NCT04351490 France	Impact of Zinc and vitamin D_3 supplementation on the survival of aged patients infected with COVID-19 (ZnD_3-CoVici)	Open label, RCT	Group1: Vitamin D_3 drinkable solution 10 drops (2000 IU)/day during 2 mo + Zinc gluconate capsule 15 mg twice/day for 2 mo Group 2: Usual care	April 2020 to July 2020
8.	NCT04335084 USA	A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection (HELPCOVID-19)	Double blind RCT Phase 2	Group 1: Hydroxychloroquine + Vitamin D + Vitamin C + Zinc Group 2: Vitamin D + Vitamin C + Zinc	June 2020 to September 2021
9.	NCT04344041 France	COvid-19 and vitamin D supplementation: a multicenter randomized controlled trial of high dose versus standard dose vitamin D_3 in high-risk COVID-19 patients (CoVitTrial)	Multicenter, open label, RCT Phase 3	Group 1: Vitamin D_3 oral high dose (4,00,000 IU) once Group 2: Vitamin D_3 oral standard dose (50,000 IU) once	April 2020 to May 2021
10.	NCT04372017 USA	Hydroxychloroquine as post-exposure prophylaxis against COVID-19 infection	Double blind, RCT Phase 3	Group 1&3: Hydroxychloroquine 800 mg on day 1 followed by 400 mg on days 2–5. Group 2&4: Vitamin D 1600 IU on day 1 and 800 IU on days 2–5	May 2020 to June 2021
11.	NCT04386850 Iran	Oral 25-hydroxyvitamin D_3 and COVID-19	Multicenter double blind, RCT Phase 2 Phase 3	Group 1: Vitamin D_3 25 mcg/day for 2 mo Group 2: Placebo/day for 2 mo	April 2020 to March 2021
12.	NCT04366908 Spain	Prevention and treatment with calcifediol of COVID-19 induced acute respiratory syndrome (COVIDIOL)	Open label, RCT Phase 2	Group 1: Usual care Group 2: Usual care + Calcifediol capsule 266 mcg (Day 1: two capsules; Days 3, 7, 14, 21, 28: one capsule)	April 2020 to August 2020
13.	NCT04326725 Turkey	Proflaxis using hydroxychloroquine plus vitamins-zinc during COVID-19 pandemia	Prospective observational case-control study	Exposure: Hydroxychloroquine + Vitamin C, D and zinc	March 2020 to September 2020
14.	NCT04449718 Brazil	Vitamin D supplementation in patients with COVID-19	Double blind, RCT	Group 1: Vitamin D_3 2,00,000 IU + Usual care Group 2: Placebo + Usual care	June 2020 to November 2020
15.	NCT04483635 Canada	Preventing COVID-19 with high-dose vitamin D supplements (PROTECT)	Triple blind, RCT Phase 3	Group 1: Vitamin D_3 loading dose of 1,00,000 IU + 10,000 IU/week for 16 wk Group 2: Placebo/week for 16 wk	September 2020 to June 2021
16.	NCT04407286 USA	Vitamin D testing and treatment for COVID-19	Open label, RCT Phase 1	Intervention: Vitamin D 10,000 IU twice/day (age 18–69 years) or 15,000 IU thrice/day (age 70+)	May 2020 to May 2021
17.	NCT04482673 USA	Vitamin D supplementation in the prevention and mitigation of COVID-19 infection (VitD-COVID19)	Double blind, RCT Phase 4	Group 1: Vitamin D_3 6000 IU/day for 12 mo Group 2: Placebo/day for 12 mo Group 3: Vitamin D_3 bolus 20,000 IU/day for 3 d + Vitamin D_3 6000 IU/day for 12 mo Group 4: Placebo/day for 12 mo	July 2020 to December 2021

(*continued*)

Table 2. Continued.

Sl.No.	Trial registration number/Place of study	Study title	Study design/Phase	Intervention/Exposure	Timeline
18.	NCT04411446 Argentina	Cholecalciferol to improve the outcomes of COVID-19 patients (CARED)	Double blind, RCT Phase 4	Group 1: Vitamin D 5 capsules of 1,00,000 IU orally given all at once Group 2: Placebo	June 2020 to December 2020
19.	NCT04459247 India	Short term, high dose vitamin D supplementation for COVID-19 (SHADE)	Double blind, RCT	Group 1: Vitamin D_3 oral liquid 60,000 IU for 7 d Group 2: Vitamin D_3 60,000 IU single dose	June 2020 to July 2020
20.	NCT04435119 France	Covid-19 and vitamin D in nursing-home (COVIT-EHPAD)	Retrospective cohort study	Exposure: Blood vitamin D levels	March 2020 to May 2020
21.	NCT04407572 Turkey	Evaluation of the relationship between zinc, vitamin D and B_{12} levels in the Covid-19 positive pregnant women	Prospective observational case-control study	Exposure: Serum zinc, vitamin D and B_{12} levels	April 2020 to June 2020
22.	NCT04476745 Jordan	The effect of D_3 on selected cytokines involved in cytokine storm in the Covid-19 uninfected Jordanian people	Open label, RCT	Group 1: Vitamin D_3 50,000 IU/week for 8 wk Group 2: No intervention	August 2020 to December 2020
23.	NCT04476680 United Kingdom	Reducing asymptomatic infection with vitamin D in Coronavirus disease (RAID-CoV-2)	Double blind, RCT	Group I: Vitamin D3 1000 IU/day for 24 wk Group 2: Placebo	September 2020 to April 2021
24.	NCT04403932 Spain	Increased risk of severe Coronavirus disease 2019 in patients with vitamin D deficiency (COVIT-D)	Prospective cohort study	Exposure: Blood vitamin D levels	April 2020 to July 2020
25.	ChiCTR2000029732 China	Impact of vitamin D deficiency on prognosis of patients with novel coronavirus pneumonia (COVID-19)	Prospective observational study	Exposure: Blood vitamin D levels	February 2020 to April 2020
26.	CTRI/2020/06/026189 India	Randomized, double blind, parallel group study of vitamin D_3 & magnesium in COVID-19 infection	Double blind, RCT Phase 2	Group 1: Vitamin D_3 60,000 IU single dose + Magnesium glycinate 250 mg BD for 14 d Group 2: Vitamin D 4,00,000 IU single dose + Magnesium glycinate 250 mg BD for 14 d	August 2020 to January 2022
27.	CTRI/2020/06/026191 India	Randomized, double blind, comparative, parallel group study of vitamin D_3 (Cholecalciferol), Vitamin K2-7 & magnesium in prophylaxis of COVID-19 infection in health care professionals	Double blind, RCT Phase 2	Group 1: Vitamin D_3 60,000 IU/week for 5 wk Group 2: Vitamin K2-7 100 mcg/day for 5 wk Group 3: Magnesium glycinate 250 mg/day for 5 wk	August 2020 to January 2022

NCT stands: ClinicalTrials.gov; CTRI stands: Clinical Trial Registry- India; ChiCTR stands: Chinese clinical trial registry.

benefit everyone, especially those with GSH deficiency (50,83,84), because GSH is essential for endogenous vitamin D synthesis (46). A recent finding suggests that more than VDD, GSH deficiency is the primary culprit in secondary VDD and COVID-19 complications and mortality (50). Few researchers suggest that co-administration of L-cysteine with vitamin D, is more effective in improving serum vitamin D levels than mega-doses of vitamin D alone (26,46,47,49). Moreover, a short original report warns that without robust evidence, supplementation of more than 4000 IU per day of vitamin D might be harmful (85). Mega-doses could be toxic, particularly in the elderly (86).

Conclusion

Evidence supports vitamin D's role in regulating the immune system, suggesting a definitive role for vitamin D in viral infections. Vitamin D supplementation could reduce severe COVID-19 complications and mortality. Vitamin D can inhibit cytokine storm by simultaneously boosting the innate immunity and evading the exaggeration of the adaptive immunity, which is challenged to respond quickly to the viral onslaught. Vitamin D-induced suppression of the inflammatory cytokine response may prevent the severity and the occurrence of ARDS, making vitamin D an attractive adjunct. While we await the development of a vaccine and a drug, available evidence favors maintaining adequate levels of serum vitamin D. Therefore, supplementation of vitamin D in high-risk individuals, VDD patients, and front-line health workers, might limit the infection and flatten the COVID-19 curve. However, currently, there are no RCTs to demonstrate conclusive evidence. On the other hand, circumstantial evidence has reliably shown an association between vitamin D supplementation and decreased severity of COVID-19 responses, including death.

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Disclosure statement

There are no conflicts of interest to declare.

Author contributions

NV, SJK and SSM wrote the manuscript. DB, MKM, KS, MKU, CM and MR critically evaluated the manuscript. All the authors participated in literature collection and review. All the authors approved the final draft of the article.

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