REVIEW ARTICLE

Evaluation of Deficiency of Vitamin D and Advantages of Supplementation of Vitamin D in COVID-19 Infections: A Narrative Review

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Abstract

Continuously evolving literature has helped to understand the vitamin D contribution to the coronavirus disease 2019 (COVID-19) manifestations and the associated clinical outcomes in different patient populations. Evidence suggests a widespread occurrence of deficiency of vitamin D among patients presenting COVID-19 and a possible link between vitamin D insufficiency and disease progression or mortality. Furthermore, studies worldwide have reported that supplements of vitamin D have a beneficial effect on COVID-19 outcomes. Contradictory data, however, suggest that there is no association between levels of vitamin D and the likelihood of COVID-19 infections. Therefore, a comprehensive search of the published literature is conducted to better understand any harmful effects of vitamin D deficiency (VDD), advantages of vitamin D supplementation, and the relationship between status of vitamin D and risk, severity, and mortality in patients with COVID-19. The information was gathered from the PubMed database published between January 2020 and July 2022 regarding the function of vitamin D in the immune system, the link between deficiency of vitamin D and COVID-19 infection, severity, risk of mortality of COVID-19, and the impact of vitamin D treatment on outcomes of COVID-19. Vitamin D modulates the immune system by elevating the levels of cathelicidins and β-defensin in the body. Deficiency of vitamin D is markedly attributed to the risk of acute respiratory distress syndrome (ARDS), which determines the severity of disease in patients with COVID-19. Levels of vitamin D below 20 ng/mL in patients with COVID-19 are linked to an increased mortality and morbidity. Vitamin D concentration of >30 ng/mL can diminish the COVID-19 severity and risk of mortality. Supplementation with vitamin D to maintain a serum concentration of 30 ng/mL would mitigate the incidence of COVID-19 and poor prognostic outcomes.

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Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) pandemic commenced in early December 2019, the challenges posed have been daunting to the world and have severely put healthcare delivery into a major crisis. Generalized immunity cannot be guaranteed against every pathogenic organism; thus, specific immunity is possible only through a rigorously evaluated vaccination. The absence of a specific antiviral therapeutic approach for COVID-19 is a major hurdle in the management of patients. Hence, there has always been a search for ways and means to reduce susceptibility through appropriate nutritional interventions. Although numerous antiviral agents and immunotherapies are under research and development to discover potential therapy for COVID-19, current treatment strategies used for managing these patients are mainly supportive.

Continuously evolving literature has helped to understand the vitamin D effect in the COVID-19 manifestations and associated clinical outcomes within different patient populations, including pediatric, adult, and older individuals with or without comorbidities. However, debate continues concerning the presence or absence of a correlation between vitamin D concentration and occurrence of COVID-19 infection and associated morbidity and mortality. Against this backdrop, we conducted a comprehensive review of the literature of the published data on vitamin D along with COVID-19 to understand any harmful effects of vitamin D deficiency (VDD) or advantages of vitamin D supplementation in COVID-19 infections and to gather insights into the link between status of vitamin D and the risk, severity, and mortality associated with COVID-19. Additionally, this review could help determine the role of supplementation or physiological boost of vitamin D production to improve and manage patients with COVID-19.

Methodology

Through the PubMed database, a literature search was conducted comprehensively for articles published between January 2020 and August 2022 using different combinations of the following search terms: "COVID-19," "vitamin D," "severity," "pediatric," "children," "mortality," "supplementation of vitamin D," and "immune function." Aligning to the focus of the research to understand any harmful impact of vitamin D depletion or advantages of using its supplementation in infections of COVID-19, all the identified articles were screened for appropriateness of content about the mechanism of action, deficiency correlation, value of supplementation, concentration of vitamin D, as well as COVID-19 severity. The selection of publications was based on full-text availability and restricted to publications in English only.

Immune System Modulation: Role of Vitamin D

Vitamin D plays a unique role in immunomodulation, and its endocrine system affects several unrelated diseases, such as infectious diseases, in addition to musculoskeletal health.[1–3] Patients with deficiency of vitamin D pose a

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higher chance of developing serious consequences from lower respiratory tract infections, necessitating intensive care in terms of oxygen therapy (117%) and needing mechanical ventilation (217%) than those with adequate levels of vitamin D.[4] Additionally, vitamin D helps to diminish the frequency and severity of respiratory infections.[5] VDD (<30 ng/mL) is inversely correlated with infection frequency.[6]

Evidence shows vitamin D and its biologically active by-products regulate the immune system function, further accelerating allergic responses.[7] The active metabolite 1,25-dihydroxy vitamin D ($1,25[OH]_2D_3$) circulates within blood, binds to vitamin D receptor (VDR), and regulates several hormones through its activity. Several immune cells, like T-cells, dendritic cells, and macrophages, have significant levels of VDR expression. Hence, vitamin D has a higher number of target genes that control immune responses, inflammatory responses, and responses to microbial infections.[8] Antimicrobial peptides produced by the defensin and cathelicidin genes prevent replication of the virus and promote macrophage and immune cell movement to the area of inflammation, which are established targets of vitamin D–dependent transcriptional regulation.[9]

Vitamin D metabolites contribute to the process of autophagocytosis through the generation of innate antiviral responses by upregulation of two key antimicrobial peptides, human cathelicidin and defensins.[10–12] Vitamin D also aids in generating the adaptive immunological response, such as stimulation of Th2 and regulatory T-cells (Tregs) and suppression of Th1/Th17 CD4+ T-cells along with cytokines, including tumor necrosis factor (TNF)-α and interferon (IFN)-γ.[11–14]

Vitamin D may be involved in preventing, treating, or reducing the severity of symptoms linked to infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), such as severe pneumonia. In particular, cytokine storm activated by viral stimuli is a crucial clinical manifestation of the progression of COVID-19 disease. Suppression of the cytokine storm with the aid of vitamin D is possible because of its role in proinflammatory (Th1 and Th17) response transition into the anti-inflammatory (Th2 and Treg) response.[15] Therefore, vitamin D can ultimately decrease the risk of successive tissue damage due to uncontrolled inflammation.[11,12,14]

Deficiency of Vitamin D and COVID-19 Risk: Clinical Evidence

Several studies have documented that deficiency of vitamin D is linked with more severe symptoms of COVID-19. A steady elevation in inflammatory cytokines, a higher risk to develop pneumonia, as well as viral infection which affect the upper respiratory tract, are all linked to VDD.[16] Furthermore, a deficiency of vitamin D can contribute to the incidence of acute respiratory distress syndrome (ARDS), which is a key element affecting the acuteness of COVID-19 symptoms.[17,18] Deficiency of vitamin D is linked to the greater risk of thrombotic events in patients presented with COVID-19.[16] According to the report, VDD in patients with COVID-19 is linked with unfavorable clinical outcomes such as hospitalization to intensive care units, the need for invasive/noninvasive ventilation, prolonged hospitalizations, and death.[19] According to the study by Ali, a significant inverse relationship ($p = 0.033$) was observed between the vitamin D concentration and the cases of COVID-19 per million people.[20]

In a cross-sectional study by Faniyi et al., blood examinations in patients suspected of COVID-19 infections showed a deficiency of vitamin D (12 ng/mL; 30 nmol/L) in about 15% of the samples. Additionally, they observed that patients with insufficient levels of vitamin D had significantly greater concentrations of SARS-CoV-2 antibodies than patients showing adequate levels of vitamin D ($p = 0.003$). Therefore, VDD can be considered a significant risk factor for SARS-CoV-2, and nutritional enrichment with vitamin D supplements may aid in preventing or managing COVID-19.[21]

Different subgroups of patients, such as the elderly, obese, or those with chronic diseases (diabetes, hypertension), were severely affected by COVID-19 infection; poor prognostic outcomes and deficient vitamin D levels are common observations among these subgroups.[22,23] A significant proportion of the European population (around 40%) suffers from a deficiency of vitamin D, and a vast number of COVID-19 patients from several European countries, including Austria (19.3%), Portugal (21.2%), and France (27.3%), suffered from a serious VDD.[22–25] Similarly, the level of vitamin D reported in about 20 European countries to be inversely related to the incidence, mortality, and morbidity of COVID-19.[22] Evidence from European countries strongly shows the relation between VDD and a higher COVID-19 risk.

According to the study carried out by Baktash et al., patients presented with COVID-19 were reported to have lower vitamin D levels when compared with those without the virus.[26] Deficiency of vitamin D may significantly boost inflammation and may result in a grave COVID-19 phenotype. Similarly, the Jain et al. study reported significantly elevated serum levels of inflammatory biomarkers, including IL-6 ($p = 0.0300$) and ferritin ($p = 0.0003$), in patients whose vitamin D concentration is 20 ng/mL.[27] However, these observations were in discordance with the Baktash et al. study, which showed no link between VDD and clinical characteristics of patients with COVID-19. The authors attributed this finding to the elderly study population.[26]

Furthermore, evidence from the Pereira et al. study depicts a noteworthy observation: a link between VDD and systemic inflammation during COVID-19. This systemic inflammatory response primarily affects the concentration of vitamin D in the circulatory system, contributing to the increased prevalence of severe deficiency of vitamin D seen in COVID-19 patients with cytokine release syndrome.[28,29] Table 1 summarizes studies and meta-analysis examining COVID-19 risk and the status of vitamin D, while Table 2 outlines the link between vitamin D and inflammatory biomarkers.

Levels of Vitamin D and COVID-19 among the Pediatric Population

Several studies over the past 2 years have shown the link between vitamin D concentration and COVID-19 risk among the pediatric population. Alpcan et al. reported substantially lower vitamin D levels (21.5 vs 28.0 IU) and higher VDD prevalence (44 vs 17.5%) among children infected with SARS-CoV-2 compared to healthy controls ($p < 0.001$).[51] Observations from other studies worldwide also depict an association between lower vitamin D concentration and COVID-19 pathogenesis.[16,38,52,53] Observations resulting from a cross-sectional study (Iran) support the relation between vitamin D status and different factors (tachycardia, tachypnea, fever, gastrointestinal problems, and oxygen levels) determining the severity of the disease.[53] Similarly, deficiency of vitamin D is linked to improved disease severity and higher levels of inflammatory markers in children with COVID-19, highlighting the important role of vitamin D in the progression of the disease.[42] Heidari et al. reported similar findings, showing that children with more severe COVID-19 symptoms had significantly elevated levels of inflammatory biomarkers [C-reactive protein (CRP), fibrinogen, and D-dimer], indicating inflammation and

Table 1: Studies correlating with vitamin D and COVID-19 severity

References	*Study design*	*VDD levels*	*Results*
Baktash et al., 2021[26]	Prospective cohort study Patients aged ≥65 years presenting with COVID-19 symptoms *n* = 105	COVID-19 positive patients with median 27 nmol/L and non-COVID-19 patients with 52 nmol/L	Elderly population with VDD may show worsened COVID-19 consequences
Meltzer et al., 2020[30]	Retrospective cohort study Patients with a 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol level evaluated within 1 year before being tested for COVID-19 *n* = 489	VDD for 124 participants (25%), sufficient levels for 287 (59%), and ambiguous for 78 (16%)	COVID-19 was linked with aging up to the age of 50 (relative risk, 1.06; 95% CI: 1.01–1.09; $p = 0.02$); and having probably insufficient vitamin D status as opposed to having sufficient vitamin D status (relative risk, 1.77; 95% CI: 1.12–2.81; $p = 0.02$) VDD is linked with COVID-19
Bahat et al., 2020[31]	Case–control study High-risk population involving pregnant women *n* = 44	The serum 25(OH)D level were evaluated to be 9.70 ± 59.14	Vitamin D supplementation may be beneficial in prevention of COVID-19 in pregnancy
Subramanian et al., 2021[32]	Cohort study involving patients with PCOS and mild COVID-19 *n* = 78,310	NA	Infection with COVID-19 is more likely in women with PCOS. VDD was more prevalent in women with PCOS
Abdollahi et al., 2021[33]	Case–control study Patients with COVID-19 infection and VDD *n* = 201	NA	Patients who have lower serum vitamin D levels are more susceptible to COVID-19 infection
Ye et al., 2021[34]	Case–control study comparing the serum 25(OH)D levels and VDD Patients grouped into asymptomatic, mild/moderate, and severe/critical disease *n* = 142	Compared to healthy controls (11.1%), COVID-19 subjects had greater rates of VDD (41.9%). Additionally, compared to moderate cases (36%), VDD was highest in severe/critical cases (80%)	A severe COVID-19 infection was more likely to affect the elderly and those with concomitant conditions. For severe/critical instances of COVID-19, VDD was a risk variable
Gaudio et al., 2021[35]	Retrospective study Hospitalized patients with COVID-19 and VDD *n* = 150	Median serum levels of 25OHD were lower (12.5 vs 20.5 ng/mL) in patients than in control group	There are significant lower levels of vitamin D in COVID-19 patients
D'Avolio et al., 2020[36]	Retrospective study Patients with lower 25(OH)D levels and COVID-19 infection *n* = 107	By stratifying patients by age >70 years, who had lower median SARS-CoV-2 PCR positivity rates (median vitamin D value of 11.1 ng/mL) than patients who tested negative (vitamin D value of 24.6 ng/mL)	Supplementing with vitamin D may be a helpful strategy to lower the risk of infection
Sulli et al., 2021[37]	Retrospective study COVID-19 and non-COVID-19 patients *n* = 130	COVID-19 group with median 7.9 ng/mL and control group with 16.3 ng/mL vitamin D level	Vitamin D serum levels in COVID-19 patients were significantly lower than in controls, and lower levels were linked to a longer overall disease duration
Yilmaz and Sen, 2020[38]	Retrospective study Pediatric patients (1 month to 18 years) with COVID-19 and VDD *n* = 85	Vitamin deficiency (<20 nmol/L)	Significantly lower levels (mean: 13.14 nmol/L) of vitamin D in patients with COVID-19 than control group
Demir et al., 2021[39]	Retrospective cohort study COVID-19 and non-COVID-19 patients, *n* = 487	VDD (<30 nmol/L) and severe VDD (<10 ng/mL)	Patients with COVID 19 had a significantly higher prevalence of severe vitamin D insufficiency (10 ng/mL) than non-COVID patients
Mazziotti et al., 2021[40]	Retrospective single-center study COVID-19 hospitalized patients *n* = 348	VDD cutoff at <12 ng/mL	Acute hypoxemic respiratory failure at study admission and the necessity for ventilation during the hospital stay were both substantially correlated with secondary hyperparathyroidism and VDD

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References	*Study design*	*VDD levels*	*Results*
Ünsal et al., 2021[41]	Study involving patients with COVID-19 and VDD *n* = 56	VDD (<30 ng/mL)	The patients who needed oxygen therapy had lower vitamin D levels than patients who did not need oxygen therapy
Bayramoğlu et al., 2021[42]	Study involving patients with moderate to severe COVID-19 *n* = 103	VDD (12–20 ng/mL)	Along with increased inflammation indicators (such as CRP and fibrinogen), a lower lymphocyte count, and lower vitamin D levels, COVID-19's clinical severity has been linked to lower levels of vitamin D, particularly when there was a deficiency (i.e., 25 OH vitamin D 12 ng/mL)
Charoenngam et al., 2021[43]	Retrospective chart review study Adult hospitalized patients (≥18 years) *n* = 287	VDD (<20 ng/mL)	An independent relationship between a sufficient level of vitamin D, as measured by serum 25(OH)D at 30 ng/mL, and a lower risk of COVID-19 mortality in elder patients and individuals without obesity
Kaufman et al., 2020[44]	Retrospective, observational analysis Patients with mild to moderate COVID in VDD *n* = 1,91,779	VDD (<20 ng/mL)	Showed an inverse correlation between vitamin D levels and SARS-CoV-2 positivity
Abrishami et al., 2021[45]	Retrospective study Patients with confirmed diagnosis of mild COVID-19 *n* = 73	Optimal cutoff level of vitamin D <25 ng/mL	The clinical trajectory, degree of lung involvement, and prognosis of patients with COVID-19 may all be predicted by serum vitamin D level
De Smet et al., 2021[46]	A retrospective observational trial Patients with severe acute respiratory syndrome and moderate to severe COVID-19 *n* = 186	VDD defined <20 ng/mL	Low levels of vitamin D at baseline were related to COVID-19 disease stage and death
Faniyi et al., 2021[21]	Cross-sectional study Patients with COVID-19 infection and VDD *n* = 392	VDD defined as <30 nmol/L	VDD may be considered as a potent risk variable for seropositivity to SARS-CoV-2 and nutritional enrichment with vitamin D supplements may aid in avoiding or managing COVID-19
Shah et al., 2021[47]	Meta-analysis involving hospitalized patients; mild COVID-19 and vitamin D–deficient patients *n* = 532	NA	Vitamin D lowers the intensity of the disease, but the outcomes about enhancing survival statistics were inconclusive
Ersöz and Yılmaz, 2021[48]	COVID-19 patients >18 years of age (310 patients) with moderate to severe COVID-19 in vitamin D–deficient patients	NA	Poor prognostic variables such hospitalization to the ICU, intubation, and death were linked with inadequate levels of serum iron, folate, vitamin D, and high levels of vitamin B12

inadequate levels of vitamin D as compared to those with milder disease presentations. Further authors revealed an inverse association between vitamin D levels and the concentration of inflammatory markers.[50] Therefore, assessing vitamin D status in children with COVID-19 may help in better disease management, with moderate vitamin D levels potentially serving as an indicator of more severe disease in the pediatric population.

There is limited availability of literature on the effect of vitamin D supplementation on outcomes of COVID-19 in the pediatric population. An open-label single-blind RCT among children showing moderate COVID-19 infection who needed hospitalization and oxygen supplementation showed that vitamin D supplementation (1,000 IU/day in infants or 2,000 IU/day in children over 1 year) might improve clinical prognosis by decreasing the risk of progression of disease as well as mortality.[54] More studies are required to confirm these outcomes.

Vitamin D and All-cause Hospital Mortality in COVID-19

Available data from the past 2 years suggest that the higher hospital mortality rate is linked to VDD among COVID-19 patients. Evidence from European countries shows a significant positive association ($r = 0.79$, $p = 0.007$) with the severity of VDD (vitamin D: < 25 nmol/L) and COVID-19 deaths per million. Every 1% rise in the percentage of patients showing severe deficiency of vitamin D was linked to a 55 per million increase in deaths [95% confidence interval (CI): 8–102; $p = 0.03$].[55] Observations reported in the elderly population affected with COVID-19 by Ilie et al. study support the association among levels of vitamin D, COVID-19 prevalence, and deaths.[22] Although another European study found that levels of vitamin D and the COVID-19 prevalence inversely correlated, the authors did not establish a connection between vitamin D levels and COVID-19 mortality.[20] Lower levels of vitamin D were observed in patients with severe COVID-19 as compared to those patients presenting with nonsevere disease.[56]

According to a study from India, mortality rates were significantly greater among patients with the severe form of the disease along

with deficient vitamin D levels (mean level 6.2 ng/mL) compared to asymptomatic, mild to moderate COVID-19 infection and mean vitamin D concentration of 27.9 ng/mL. Furthermore, the vitamin D–deficient patients had increased inflammatory markers such as IL-6, serum ferritin, and TNF-α.[27] According to a study by Carpagnano et al., patients showing severely inadequate levels of vitamin D (<10 ng/mL) reported 45% greater risk of mortality than those with concentrations over 10 ng/mL ($p = 0.019$).[57] This data denotes that deficiency of vitamin D might be a potent determinant for mortality due to COVID-19. However, these results were contrary to the observations made by Ling et al. study that reported no correlation among vitamin D concentration and COVID-19 mortality. The multivariate analysis suggested that COVID-19 mortality risk can be combated with vitamin D3 booster treatment. These observations strongly support the global use of vitamin D as an effective clinical approach for the management of COVID-19.[58]

Vitamin D may be an essential add-on treatment modality for patients presenting severe COVID-19 who have insufficient levels of vitamin D. This is supported by another meta-analysis, which reported that COVID-19 patients with deficiency of vitamin D were more likely to require hospitalization and exhibited higher mortality rates.[28,59]

Studies That Show No Correlation among Vitamin D Deficiency and COVID-19 Infections

In order to lack of significant observation, mainly in terms of infection and mortality, few studies do not provide strong evidence for the intervention of supplementation of vitamin D in COVID-19 patients. Study by Hastie et al., using UK Biobank, found no strong evidence to support a probable link among serum concentration of vitamin D and the risk of severe COVID-19 infection with associated mortality.[60] A study by Hernández et al. concluded that compared to population-based controls, the vitamin D level was lower in patients hospitalized for COVID-19, and the deficiency prevalence was higher in these patients. No connection was reported among the concentration of vitamin D or its insufficiency and disease progression.[61] A different study by Butler-Laporte et al. reported the absence of association among the level of vitamin D and the prevalence, grade, or the need for hospitalization of COVID-19. Therefore, there is no genetic evidence to support the use of vitamin D supplementation to prevent adverse outcome in COVID-19. The randomized controlled trials of COVID-19 should prioritize other therapeutic or preventative approaches more strongly.[62]

A higher risk of SARS-CoV-2 infection has been linked with lower levels of vitamin D. Yet it is unknown if vitamin D shortage is related to the COVID-19 intensity. Despite the lack of current evidence to consider vitamin D supplementation as a recognized treatment option for managing COVID-19 patients, dietary dosage or lifestyle modifications require consideration in individuals with vitamin D insufficiency/deficiency as it is inexpensive as well as generally safe to practice.[63]

Observations from several other observational and retrospective studies evaluated the relationship between inadequate concentration of vitamin D and the incidence and mortality of COVID-19. There seems to be a dispute in their association, and few studies have failed to reveal any difference in mortality rates among patients with adequate and inadequate levels of vitamin D. All these studies strongly suggest the need for new trials to determine a substantial association among vitamin D supplementation and reduced mortality and infection rates in patients with COVID-19. Table 3 summarizes the studies that show no link between deficiency of vitamin D and COVID-19 outcomes.

Biomarkers of Inflammation and Vitamin D

Proinflammatory cytokines, like IL-1, IL-2, IL-6, IFN-γ, and TNF, are elevated in the blood, leading to multiorgan failure, disseminated intravascular coagulation, ARDS, and finally death. This dysregulated immune response, also known as cytokine storm, is a major factor in the etiology of the most advanced cases of COVID-19.[68,69] Inflammatory cytokines, including IL-2R, IL-6, macrophage inflammatory protein (MIP)1A, granulocyte colony-stimulating factor (GCSF), macrophage chemotactic protein-1 (MCP1), and TNF-α, as well as anti-inflammatory substances like CRP, are noticeably raised in serious COVID-19 patients.[49,70] Beyond its function in controlling bone homeostasis, vitamin D is known to possess anti-inflammatory and immune-regulating characteristics. Another option for managing the immunomodulatory response in SARS-CoV-2 patients is using a glucose-lowering drug class, dipeptidyl peptidase-4 inhibitors (DPP-4i), generally used to treat type 2 diabetes.[71] In addition to this, tocilizumab and vitamin D are speculated to be able to diminish the cytokine release syndrome that occurs in COVID-19 by altering the levels of IL-6.[72] Calcitriol, the active metabolite of vitamin D, demonstrated to regulate several immune functions [stimulation of phagocytosis and chemotaxis by macrophages, activation of antimicrobial peptide transcription (in various immune cells) and Treg cells, inhibition of proinflammatory cytokine production, reduction of antigen presentation, and activation of T-cells], ultimately preventing the activation of inflammatory response and immune system dysfunction.[73,74] Supplementation of vitamin D and their concurrent elevation (above 50 ng/mL) play a crucial role in alleviating the prevalence and the symptoms of COVID-19.[75] Studies attributed to vitamin D levels and biomarkers of inflammation are summarized in Table 2.

Vitamin-D Supplementation and COVID-19

Evidence from the above data states that deficiency of vitamin D can deteriorate morbidity due to SARS-CoV-2, which further worsens mortality outcomes, mainly due to its anti-inflammatory and immunomodulatory characteristics, which stimulate the state of hyperinflammation and the cytokine release syndrome in patients with COVID-19 morbidity. Hence, the usage of vitamin D as an anti-inflammatory and potent compound of immunoregulation has gained attention for COVID-19 management, mainly focusing on the prevention of infection and delaying the cytokine storm to avoid the progression of nonsevere disease into severe form.[71] Many studies have explored the use of supplementation of vitamin D in hospitalized patients presented with COVID-19 and have shown assuring results. Evidence supporting the supplementation of vitamin D in patients with COVID-19 has been categorized into two groups according to the maintenance dose administered.

Supplementation of Vitamin D with Maintenance Doses of ≤2,000 IU

Studies have demonstrated promising results of vitamin D supplementation with a maintenance dose of ≤2,000 IU in different age-groups. Zurita-Cruz et al. conducted a randomized controlled study to assess the effects of supplementation of vitamin D on the pediatric population, administering 1,000 IU/day to children <1 year old and 2,000 IU/day for children aged 1–17 years. The trial concluded that supplementation of vitamin D was linked with a lower risk of COVID-19 progression and mortality in pediatric patients.[54] Supplementation of vitamin D was effective in lowering the likelihood of catching infection of COVID-19. It was well tolerated among at-risk individuals who were highly exposed to the COVID-19-infected population,

regardless of their vitamin D levels.[76] Another study evaluated the impact of vitamin D supplementation across various age-groups: pediatric (<18 years), young adult (18–39 years), middle-aged (40–64 years), and elderly (≥65 years), with supplementation doses of <1,000 IU, 1,000–4,000 IU, and >4,000 IU. It was concluded that vitamin D supplementation is inversely linked with severity of COVID-19. Vitamin D supplementation is advised in both pre- and post-COVID-19 infection.[77]

Vitamin D Supplementation with Maintenance Dose of >2,000 IU

Research has investigated the benefits of vitamin D supplementation with >2,000 IU dose in hospitalized COVID-19 patients and has shown assuring results. Patients who are hospitalized, particularly middle-aged and elderly individuals with infection of COVID-19, vitamin D supplementation at consistent elevated doses and various concentrations has been demonstrated to be both safe and effective, as it aids in promoting viral clearance, reducing fibrinogen levels, and mitigating disease progression, while also reducing the need for intensive care unit interventions.[78–81] These results are similar to another study by Rastogi et al., wherein high-dose cholecalciferol supplementation (60,000 IU) resulted in more vitamin D–deficient patients with COVID-19 infection being turned into SARS-CoV-2 RNA negative along with a considerable drop in fibrinogen.[79] Such supplementation might be useful to decrease COVID-19 infection risk.[36] An additional pilot study compared the standard treatment (azithromycin and hydroxychloroquine) and calcifediol (0.532 mg, 0.266 mg) in COVID-19 hospitalized patients. It concluded that the calcifediol treatment (50%) might alleviate the need for ICU in these patients more than the standard treatment (2%).[78] A study by Annweiler et al. observed the effect of supplementation of vitamin D among elderly frail patients with COVID-19. They reported that the oral bolus of vitamin D supplementation (80,000 IU) before or

Table 2: Biomarkers of inflammation, vitamin D, and COVID-19

References	*Study design*	*Vitamin deficiency levels*	*Results*
Huang et al., 2020[49]	Prospective cohort study *n* = 41	NA	Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF-α
Jain et al., 2020[27]	Prospective observational study of 6-week duration Asymptomatic COVID-19 patients vs critically ill COVID-19 patients *n* = 154	VDD defined as <20 ng/mL	Mean IL-6 level (pg/mL) and serum ferritin (ng/mL) were 19.34 and 319.17 in patients with VDD vs 12.18 and 186.83 in patients with normal vitamin D level ($p = 0.03$ and 0.0003)
Heidari et al., 2022[50]	Retrospective study Hospitalized pediatric COVID-19 patients *n* = 144	Vitamin D <20 ng/mL vs vitamin D >20 ng/mL	An inverse association of serum vitamin D with CRP, fibrinogen, and D-dimer values Compared to mild disease, moderate, or severe COVID-19 cases had significantly increased inflammatory markers profile (CRP, D-dimer, and fibrinogen), as well as lower levels of vitamin D ($p < 0.001$)
Bayramoğlu et al., 2021[42]	Study involving patients with moderate to severe COVID-19 *n* = 103	VDD (12–20 ng/mL)	An inverse association of vitamin D level with markers of inflammation (CRP: $r = -0.309$, $p = 0.002$ and fibrinogen levels: $r = -0.381$, $p = <0.001$) was noted Insufficient levels of vitamin D, D-dimer, and fibrinogen levels at the time of hospitalization were independent predictors of advanced stage of the disease
Pereira et al., 2022[28]	Systematic review and meta-analysis *n* = 8176	NA	Vitamin D levels can reduce levels of the CRP—an increased inflammatory marker in infection—as well as the negative immunomodulation of the inflammatory cytokine storm caused by COVID-19

Table 3: Studies showing no correlation between VDD and COVID-19

References	*Study design*	*VDD*	*Results*
Lohia et al., 2021[64]	Retrospective cohort study Patients with COVID-19 and VDD *n* = 270	NA	COVID-19 patients' severe illness outcomes were examined, and it was discovered that there was no correlation between COVID-19 patients' vitamin D levels and mortality, the requirement for mechanical ventilation, ICU hospitalization, or thromboembolism
Raisi-Estabragh et al., 2020[65]	Retrospective study COVID-19 positive, *n* = 1326 COVID-19 negative, *n* = 3184	NA	There was no link between 25(OH)-vitamin D status and COVID-19 infection, indicating that the association was solely based on ethnicity and BMI
Hua et al., 2021[66]	Pregnant participants with mild COVID-19 *n* = 7148	NA	The vitamin D levels between the pregnant participants, pre- and post-COVID-19 pandemic were comparable
Osman et al., 2021[67]	Observational cohort study Adult patients admitted with COVID-19 *n* = 445	<30 nmol/L	Vitamin D levels does not represent a particular significance in the population to recommend correction or otherwise

through COVID-19 infection was linked to improved morbidity and mortality. Such an effect was not associated with any other treatment modalities.[80] Research conducted by Parant et al. evaluated the impact of vitamin D supplements (80,000 or 1,00,000 IU) in individuals of older age-group (>70 years). It concluded that vitamin D supplementation before COVID-19 infection helped to protect elderly patients against the gradual worsening of COVID-19 symptoms.[82] In addition, it was indicated to administer the oral bolus of vitamin D for a prolonged duration before COVID-19 infection as a preventative measure than after the diagnosis of COVID-19.[81] This concords with the observations from De Niet et al. study, which demonstrated that the patients who received cholecalciferol (25,000 IU) required short hospital stays and supplemental oxygen for a shorter period and significantly enhanced the clinical status as per the WHO scale. There were promising effects of vitamin D on different comorbidities as well.[83] A study by Mariani et al. showed that the vitamin D (5,00,000 IU) supplementation at a single dose was not useful in avoiding the deteriorating respiratory symptoms in hospitalized patients presented with mild to moderate COVID-19 infection compared to placebo.[84] A study by Grant et al. recommended 10,000 IU/day of vitamin D3 initially for several weeks and then rapidly elevate its concentration among patients who are susceptible to the flu and/or COVID-19, and then to 5,000 IU/day to decrease their potential risk for infection.[75]

Another study by Burahee et al. analyzed the impact of vitamin D supplementation (2,00,000 IU over 4 weeks and 1,00,000 IU over 4 days in the immediate postoperative period) in COVID-19 patients and patients with femoral neck fracture, and it was seen that supplementing with vitamin D may help COVID-19-infected patients to recover rapidly.[85] There is an ongoing trial by Beigmohammadi et al., where they have reported supplementation of vitamin D (6,00,000 IU) to determine the mortality rate, serum WBC, CRP, ESR, IL-6, SpO_2 level, and severity of pulmonary involvement.[86]

In contrast to all the studies cited above, a study by Tentolouris et al. reported that supplementation of vitamin D among COVID-19 patients considerably impacted admission to the ICU with no benefits in mortality risk.[87]

The results from various population-based studies focusing on vitamin D supplements and COVID-19 are consistent; lower plasma 25(OH)D levels are a distinct attributable factor for hospitalization and SARS-CoV-2 infection in African American and Israeli populations. Both studies propose that supplementation of vitamin D in COVID-19 patients provides the highest net therapeutic benefit.[88,89] However, other studies have reported contrasting opinions, indicating vitamin D inadequacy in assessing the risk of severe infection of SARS-CoV-2 in specific populations.[65]

All the studies mentioned above highlight that vitamin D supplementation serves a critical function in managing COVID-19

Table 4: Studies evaluating vitamin D supplementation and COVID-19

References	*Study design*	*Supplementation doses*	*Results*
Beigmohammadi et al., 2020[86]	Randomized, single-blinded, two-arm (1:1 ratio) parallel group clinical trial Patients with COVID-19 *n* = 60	Single dose of vitamin D 6,00,000 IU	Mortality rate, serum WBC, CRP, ESR, IL-6, IFN-G, and TNF-α, SpO_2 level, severity of pulmonary involvement assessed
Rastogi et al., 2022[79]	Randomized, placebo-controlled study Patients with COVID-19 *n* = 40	7 days of routine 60,000 IU cholecalciferol	On high-dose cholecalciferol treatment, a higher percentage of SARS-CoV-2 infected patients who were vitamin D–deficient reverted SARS-CoV-2 RNA negative and had a significant reduction in fibrinogen levels
Castillo et al., 2020[78]	Parallel randomized open label, double-masked clinical trial *n* = 76	Oral calcifediol (Faes-Farma, Lejona, Spain), in soft capsules (0.532 mg), oral calcifediol (0.266 mg), thereafter every week until discharge or ICU admission; 26 lacking calcifediol treatment, 50 following calcifediol treatment	Calcifediol administration may reduce the requirement of hospitalization for COVID-19 but it is unknown whether the same is applicable for early stage of COVID-19 and how baseline vitamin D can modify the result
Abdulateef et al., 2021[77]	Observational study Patients with different age-groups: pediatric (<18 years), adult (18–39 years), middle aged (40–64 years), and old age (≥65 years) *n* = 428	Daily dose: <1,000 IU 1,000–4,000 IU >4,000 IU	A low severity rating is significantly correlated with vitamin D. Vitamin D supplementation is advised in both pre- and post-COVID-19 infection
Nogues et al., 2021[90]	Observational cohort study Patients with COVID-19 infected individuals *n* = 930	532 µg followed by an increment by 266 µg on days 3, 7, 15 and 30	Calcifediol treatment significantly reduced ICU admissions and mortality rate
Burahee et al., 2021[85]	Retrospective cohort study Patients with femoral neck fracture *n* = 29	2,00,000 units over 4 weeks if blood vitamin D levels show an inadequacy (30 nmol/L) and 1,00,000 units over 4 days in the immediate postoperative period	Supplementing with vitamin D may help COVID-19-infected patients recover more quickly

patients of all age-groups, including the vulnerable geriatric and pediatric populations, in terms of hospital stays, duration of supplemental oxygen, and mortality. Some studies observed contrasting results; hence, more research is needed to evaluate the effectiveness of vitamin D supplements in reducing mortality and morbidity associated with COVID-19. Studies related to the COVID-19 risk and supplementation of vitamin D are summarized in Table 4.

Synergism between Vitamin D and DPP-4 Inhibitors in COVID-19

Vitamin D along with DPP-4 inhibitors have complementary anti-inflammatory and immune-modulating characteristics that can be used to reduce the pathogenicity of COVID-19 and halt or slow down the development of the cytokine storm spurred by COVID-19. Vitamin D supplements may be a feasible pharmacological option to stop the advancement of disease and/or control the cytokine release syndrome in COVID-19 due to its demonstrated complementary safety profile (even after heavy dose), low cost, as well as convenience of management.[71] The combined therapy of vitamin D plus DPP-4 inhibitors (VIDPP-4i) exerts better collaborative anti-inflammatory as well as immunomodulatory activities than vitamin D or DPP-4 inhibitor as monotherapy. In addition, endothelial dysfunction, a key component in COVID-19 pathophysiology,[91] is also protected by VIDPP-4i.[92,93] By indulging with the renin-angiotensin system, ACE/Ang II/AT1R axis, and inhibiting the downregulation of ACE2 induced by SARS-CoV-2 and the interplay among DPP-4 and SARS-CoV-2 spike glycoprotein, VIDPP-4i may also help in preventing infection of SARS-CoV-2. However, studies with randomized controlled design are essential to determine the safety and reliability of VIDPP-4i treatment for suppressing COVID-19 infections and to advance the development of cytokine release syndrome.[71]

Vitamin D and Critically Ill Patients with COVID-19 on Steroid Therapy

Multiple available evidence indicates that vitamin D and corticosteroids are used for advanced COVID-19. It was reported that the use of a combination of vitamin D and corticosteroids had promising results in lowering the mortality of COVID-19 hospitalized patients.[94] These results were similar to the RECOVERY study, which showed that dexamethasone alleviated the mortality in patients needing mechanical ventilation or oxygen.[95] The main rationale for using glucocorticoids is their ability to reduce cytokine production, thereby preventing damage to the pulmonary structures in the case of SARS-CoV-2.[96] Another study found that administering regular doses of corticosteroids (methylprednisolone) to individuals with COVID-19-induced pneumonia considerably decreased their risk of dying (62% of 201 patients).[97]

Conclusion

Overall observations from several studies demonstrated the crucial role of vitamin D in immune modulation and a strong link among low levels of vitamin D and COVID-19. Deficiency of vitamin D was reported in cases of severe COVID-19 infection that have caused morbidity and death. Therefore, optimal vitamin D concentrations of >30 ng/mL (in the desired range of 40–60 ng/mL) can be maintained by vitamin D supplements of 60,000 IU/week and 1,000 IU/day for VDD patients, thereby allowing them to respond better to immunoprotection against COVID-19 infection. However, it is necessary to conduct randomized clinical trials in a large cohort to determine the clinical role of vitamin D in such patients.

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