Vitamin D deficiency: concern for rheumatoid arthritis and COVID-19?

Sneha Verma[1] · Ved Chaturvedi[2] · N. K. Ganguly[1] · Shivani Arora Mittal[1]

Abstract

Vitamin D is an immunomodulatory hormone with an established role in calcium and phosphate metabolism and skeletal mineralization. Evidence showing its immunological benefits by regulating essential components of the innate and adaptive immune system is prevalent. Vitamin D deficiency is reported worldwide and is thereby found to be associated with various immune-related diseases. Rheumatoid Arthritis and COVID-19 are two such diseases, sharing a similar hyperinflammatory response. Various studies have found an association of lower Vitamin D levels to be associated with both these diseases. However, contrasting data is also reported. We review here the available scientific data on risk factor association and supplementation benefits of Vitamin D in Rheumatoid Arthritis and COVID-19, intending to critically evaluate the literature.

Keywords Vitamin D · Deficiency · Association · Rheumatoid arthritis · COVID-19 · Supplementation

Abbreviations

TNF-alpha	Tumor necrosis factor-alpha
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-17	Interleukin 17
GM-CSF	Granulocyte–macrophage-colony stimulating factor
CCL2	Monocyte chemoattractant protein 1
CXCL10	C-X-C motif chemokine ligand 10
CCL3	Chemokine (C–C motif) ligand 3
VDR	Vitamin D receptor
SLE	Systemic lupus erythematosus
NET	Neutrophil extracellular traps
NOD2	Nucleotide-binding oligomerization domain-containing protein 2
mTOR	Mammalian target of rapamycin
PI3KC3	Class III phosphatidylinositol 3-kinase
RCT	Randomized clinical trial
DAS28	Disease activity score 28
VAS	Patient global pain score
ESR	Erythrocyte sedimentation rate
SJC	Swollen joint count
CRP	C reactive protein
ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
MASP2	Mannose-binding lectin (MBL)-associated serine protease 2
C5	Complement component 5
CAD	Coronary artery disease
MKP1	Mitogen-activated protein kinase phosphatase-1

✉ Shivani Arora Mittal
shivanimittal@icloud.com

1 Department of Research, Sir Ganga Ram Hospital, New Delhi, India

2 Department of Rheumatology & Clinical Immunology, Sir Ganga Ram Hospital, New Delhi, India

Introduction

Vitamin D, a secosteroid, primarily exists in 2 forms, Ergocalciferol (vitamin D2) and Cholecalciferol (vitamin D3). Its deficiency is a common global health concern and contributing factors include diet, geographic location, and ethnicity [1]. Generally, vitamin D levels less than 20 ng/ml are defined as 'deficient and less than 30 ng/ml as 'insufficient. Its key roles include maintaining calcium homeostasis throughout circulation and skeletal mineralization. It is reported to have an anti-inflammatory role and established benefits in osteoporosis and osteomalacia [2]. Observational studies have reported a negative correlation between vitamin D levels and various diseases such as diabetes, cardiovascular, autoimmune diseases, and cancer [3]. However, contrasting reports suggesting no association also exist, for example in a study in CAD patients, no association with angiogenic

severity was found [4]. Hence, role of vitamin D in various diseases needs detailed analysis.

Vitamin D deficiency has been associated with incidence and severity of Rheumatoid Arthritis (RA), an autoimmune syndrome, and supplementation is also clinically prescribed. Recently, various reports implicating Vitamin D deficiency as a possible risk factor for COVID-19 incidence and severity are also emerging. Both RA and COVID-19 have shared pathological mechanisms. A common pro-inflammatory cytokine (TNF-alpha, IL-6, IL-8, IL-17, GM-CSF) and chemokine profile (CCL2, CXCL10, CCL3) is frequently reported [5, 6]. Similar radiological aspects of pneumonia (Ground-glass opacities and vascular enlargement) are also observed in the two diseases. Various anti-rheumatic strategies, like IL-6 inhibitor (Tocilizumab) and JAK inhibitor (Baricitinib) are being investigated for COVID treatment [7–10]. Observational, meta-analysis and multi-omics approach-based studies indicate that the autoimmune disease group patients are at significant risk for COVID-19 infection [11–13] which calls for the inclusion of adjuvant therapies. In lieu of the above, we have reviewed here the scientific literature on vitamin D deficiency as a risk factor and its supplementation benefits in RA and COVID diseases.

Methods

Information source and search keywords

Studies were extracted from the following electronic databases: PubMed, Google Scholar, and Connected Papers. The search criteria included English language original articles that were identified using the following keywords "vitamin D association", "rheumatoid arthritis", "vitamin D COVID-19 association", "vitamin D supplementation" from 2016 onwards.

Study selection

Titles and abstracts were evaluated for inclusion (English language original articles from 2016 onwards on vitamin D association and supplementation in Rheumatoid Arthritis and COVID-19 infection) or exclusion (studies reporting mixed reports on vitamin D association, related to other autoimmune diseases or respiratory infections). If eligible for inclusion, full-text articles were read and evaluated.

Data collection process

The following data were extracted from the articles: title, journal, authors, and year of publication, study design,

sample size, main findings, and limitations. This information was evaluated and classified accordingly in a tabular form.

Vitamin D: immunomodulatory function

Apart from Vitamin D's well-known functions in calcium and bone homeostasis, it exerts substantial immunomodulatory action through transcriptional and epigenetic mechanisms. This is evident from widespread expression of Vitamin D Receptor (VDR) in most immune cell types and their ability to express CYPB21 enzyme, which metabolizes vitamin D into its active form, $1,25(OH)_2D_3$ [14]. Alterations in the VDR gene have been indicated in several diseases including Diabetes Mellitus [15], Pulmonary Tuberculosis [16], Systemic Lupus Erythematosus (SLE) [17], and Rheumatoid Arthritis [18].

Vitamin D reduces microbial infection and death through various mechanisms, including regulating physical barrier and innate and adaptive immune cells. It also helps maintain tight junctions, gap junctions and adherent junctions [19]. It induces various pathways like autophagy in monocytes [20]; phagocytic ability, ROS production, chemotaxis, and induction of VDR responsive genes (e.g.: antimicrobial peptides) in activated macrophages; increased microbicidal activity and reduced NET formation in neutrophils. Vitamin D also prevents dendritic cells from maturing, by reducing their expression of MHC-classII and costimulatory molecules, resulting in a more tolerogenic and anti-inflammatory phenotype. Additionally, it is shown to inhibit plasma cell and post-switch memory B cell formation. It represses Th1 cell formation and stimulates Th2 cells along with the formation of regulatory T cells [21]. The vitamin D mediated cytokine regulation through various effectors is shown in Fig. 1. It regulates the epigenetic programming of immune cells (mainly monocytes, macrophages, and dendritic cells) during immune challenges and thereby affects their immunological memory and subtype differentiation [22]. It also stimulates endothelial NOS production and has pleiotropic effects on the vascular endothelium that are protective against injury due to inflammation [23].

Various anti-inflammatory mechanisms attributed to vitamin D are, inhibition of Prostaglandin (PG) synthesis, nuclear translocation of NF-kB [24], stress-activated kinase signaling, and production of inflammatory cytokines [25]. Prostaglandins are pro-inflammatory molecules and play important role in mediating cell proliferation, differentiation, and apoptosis. They are reported to increase TNF-alpha, IL-6, CXCL1, and COX-2 levels, mediating the inflammatory cascade [26]. Vitamin D inhibits PG mediated inflammation through three mechanisms: reduced PG receptor, reduced COX-2 expression

Fig. 1 Immunomodulatory Effects of Vitamin D. The figure describes some of the gene targets of vitamin D and its effect on innate as well as adaptive immune system. Cathelicidin antimicrobial peptide (CAMP), Integrin alpha M (ITGAM), CD93, Nuclear Factor NF-Kappa-B (NFKB1A), Receptor Activator of Kappa-B Ligand (RANKL), Cyclooxygenase-2 (Cox-2)
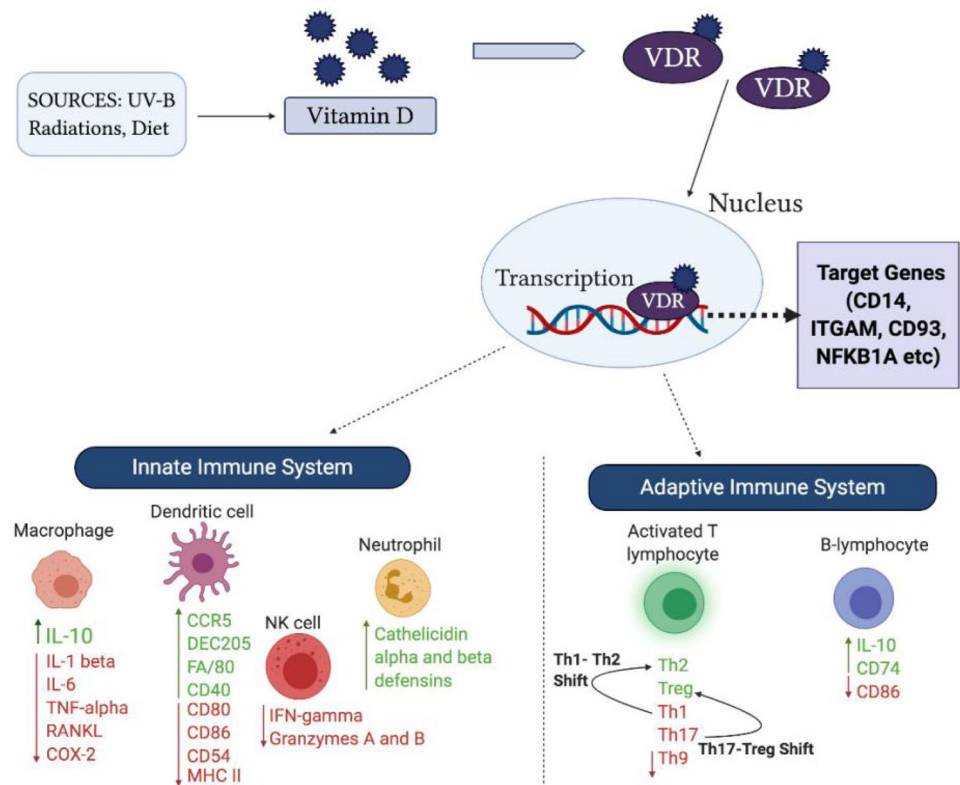
and increased 15-PGDH (PG Dehydrogenase) expression [27]. Studies also reveal inhibitory action of vitamin D on Lipopolysaccharide (LPS)-induced p38 phosphorylation along with TNF-alpha and IL-6 expression [28, 29]. Significant anti-inflammatory effects of vitamin D were also observed by inhibiting expression of TNF-alpha, COX-2, and iNOS (inducible nitric oxide synthase), using the classical model of inflammation in mice [30].

Antimicrobial and antiviral actions of vitamin D are mediated through induced expression of peptides such as Cathelicidin, Beta-defensin 2, Nucleotide-binding Oligomerization Domain-containing protein 2 (NOD2). Cathelicidin induces activation of pro-inflammatory cytokines, neutrophil chemotaxis, monocytes, and T cells at the site of infection. Additionally, it blocks viral entry and suppresses viral replication. Vitamin D also suppresses bacterial growth through suppression of Hepcidin, which restricts the export of iron, thereby increasing intracellular iron. Decreased Hepcidin activity also promotes activation of Ferroportin, followed by increased transcellular export of iron. Since iron is one of the crucial factors for bacterial survival, decreased levels lead to reduce bacterial growth. Vitamin D also induces autophagy, by downregulating mTOR pathway and inducing Beclin 1 and PI3KC3, the key enzymes driving autophagy. Vitamin D-mediated autophagy is found to reduce many viral infections like HIV-1, influenza A, rotavirus and hepatitis C [31].

Vitamin D: role in rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune condition, resulting in synovial inflammation around joints, progressively leading to cartilage and bone destruction. Although the main cause is unknown, various factors are involved in its pathogenesis, including genetic, environmental, and dietary components.

A large body of epidemiological data demonstrates that vitamin D insufficiency/deficiency is associated with various disease conditions, especially of the musculoskeletal and autoimmune types. An inverse association between serum vitamin D levels and RA incidence and disease activity is widely reported [32–36]. Some reports with larger sample sizes also have shown similar associations. Lee used a meta-analysis approach from data of more than 1,100 patients to conclude an inverse association with RA prevalence and activity [37]. In another cross-sectional observational analysis of 1413 patients from different countries across latitudes, similar results were obtained

[38]. In addition, in treatment-naïve RA patients, a significant negative association was observed between vitamin D levels and disease activity parameters [34]. Recently, in a study with 645 early RA patients, vitamin D deficiency correlated with more active and severe disease and was suggested as a useful biomarker to predict disability progression over one year [39]. However, contrasting data showing no association is also reported [40, 41]. Reports demonstrating vitamin D insufficiency to be associated with RA prevalence along with its immunosuppressive role have led to further studies evaluating its preventive/therapeutic supplemental benefit. In a prospective cohort study of 152 elderly RA women through 11 years of follow-up, total dietary and supplemental vitamin D intake was found associated with reduced RA risk. However, here patients were not clinically assessed and sunlight exposure was not taken into account [42]. In a randomized interventional study on 73 RA patients with low DAS28 scores and vitamin D levels, a significant improvement in mean scores was seen with vitamin D supplementation over 3 months [43]. A randomized trial conducted in 150 patients from India concluded that weekly supplementation of 60,000 IU in early treatment-naïve RA patients resulted in greater pain relief [44]. In a meta-analysis of six RCTs with 438 participants, vitamin D complementary therapy resulted in more beneficial effects on DAS28, ESR. However, no improvement was observed in other parameters such as VAS (Patient Global Pain Score), SJC (Swollen Joint Count), CRP. Notably, in a subgroup analysis, a significantly improved VAS score was observed with vitamin D supplementation of more than 50,000 IU/week, for more than 12 weeks [45]. In another small cohort (61) study, supplementation with 1,00,000 IU/month, resulted in a significant decline in DAS and VAS scores in only vitamin D sufficient patients [46]. Another randomized, interventional study evaluating the relationship between vitamin D deficiency and RA concluded significant improvement in disease activity after administrating vitamin D in specific concentrations along with other therapeutic drugs [43]. This suggests that the dose and duration of supplementation could be a critical determinant of the overall response. However, few studies found no additional clinical benefit after vitamin D supplementation [47–49]. Also, in a meta-analysis of 5 studies, no significant association was observed between vitamin D supplementation and RA recurrence [50]. Significant studies on the association of vitamin D with RA incidence/severity and its supplemental benefit are described in Table 1. Thus, although the association of vitamin D with incidence and severity of RA patients is conclusive, there is a lack of robust evidence supporting its supplementation in improving clinical outcome, due to heterogeneity in dosages and durations of supplementation. Hence, well-conducted large RCTs with rigorous research designs and appropriate clinical endpoints are required to determine the efficacy of vitamin D supplementation.

Vitamin D: role in COVID-19

Coronavirus disease 2019 (COVID-19), is an ongoing pandemic, caused by a novel beta coronavirus, SARS CoV-2 [57]. It is found to majorly cause a severe respiratory type illness along with direct and indirect effects on other organs, including neurological and musculoskeletal systems. Autopsy reports from severe cases revealed venous thromboembolism, fibrin deposition, widespread penetration by immune cells, and excessive alveolar damage. Involved pathologies includes exacerbated systemic inflammation with infiltration of immune cells, necrosis and hyperplasia of lung tissue, endothelial dysfunction and a pro-coagulatory state [58]. Unregulated Complement activation is considered a key pathological mechanism [59, 60]. Terminal complement components like C5-9, MASP2, and CD4 were found to colocalize with the spike glycoproteins in lung and also found in the microvasculature in COVID patients [61]. Growing evidence suggests deposition of complement activation products, C5b-9 in lung, skin and kidney vasculature in COVID patients and supports targeting of C5 as a possible therapeutic intervention [62, 63].

Vitamin D has long been known for its antiviral effects. Its deficiency is associated with higher risk of developing Influenza/respiratory illness, Dengue, Hepatitis, HIV and other viral diseases. It is known to inhibit production and secretion of cytokines from bronchial smooth muscle cells like RANTES, PDGF, MMPs, leading to reduced smooth muscle proliferation and lung inflammation. As for COVID-19, vitamin D may regulate the pathophysiology of the disease by various mechanisms. Most of the mortalities in COVID-19 patients are due to Acute-Respiratory-Distress-Syndrome (ARDS). ARDS is characterized as a heightened inflammatory response of lung macrophages. Certain reports suggest an involvement of vitamin D in the modulation of macrophage response in COVID-19 [64]. The SARS-CoV-2 virus enters the lung cells through the ACE2 receptor, and subsequently downregulates these, leading to an increased risk of pulmonary edema [31]. Vitamin D, on the contrary, upregulates the ACE2 receptors, potentially reversing this effect. Vitamin D deficiency promotes the Renin-Angiotensin system which may lead to cardiovascular disease and reduced lung function [65]. Interestingly, DPP-4/CD26 receptor binding is one of the pathological mechanisms of closely related COVID-MERS and similar binding of this receptor has been predicted with the SARS-Cov-2 spike glycoprotein [66]. Vitamin D

Table 1 Vitamin D related clinical trial studies for Rheumatoid Arthritis

Study AIM	Country	Sample Size (N)	Main Findings	Limitations	References
Vitamin D-RA association studies					
Association between Vit. D levels and disease activity, disability and radiographic progression in early RA patients	France	645 (treatment-naïve, early RA patients)	• Vit. D deficiency (<10 ng/ml) correlated with more active and severe disease • Deficiency may predict radiographic progression over 1 year	• Heterogenous population • Small percentage of patients had vit. D supplementation at baseline	[51]
Correlation of Vit. D levels and inflammatory cytokines and ROS in RA	India	100 RA patients 50 controls	• Reduced Vit. D levels in RA patients • Negative correlation between inflammatory cytokines and vit. D levels and positive association with ROS levels	• Correlation between vitamin D and ROS or many pro-and anti-inflammatory cytokines not observed	[52]
Assessment of Vit. D status in RA patients & development of a new Patient Reported Outcome (D-PRO) questionnaire	European countries	625 patients	• 64% of the sample (not supplemented) showed reduced Vit. D level • Negative correlation between vitamin D levels and DAS28-CRP • A first D-PRO questionnaire was validated • Negative association between Vit. D levels and D-PRO global risk score was found	• Cross-sectional Study Design and lack of interventional data • No prior statistical testing of single items in the questionnaire • Heterogeneous food intake among a diverse population	[53]
Association of Vit. D status with disease activity in RA patients: "COMORA study"	Across 15 countries	1413 RA patients	• Low Vit. D levels are prevalent in different countries & under different latitudes • Low levels associated with RA (disease activity & corticosteroid dosage) & co-morbidities	• High variability in Vit. D levels in different countries • High variability in precision and accuracy of Vit. D assays in different countries	[38]

Table 1 (continued)

Study AIM	Country	Sample Size (N)	Main Findings	Limitations	References
Cross-sectional study to investigate relationship between severity of pain and Vit. D levels in RA patients	Finland	77 RA patients	• Negative correlation found between Vit.D levels and Visual Analog Score (VAS) • Vit.D déficient patients are more prone to muskulosketal pain	• Small sample size	[54]
Vitamin D supplementation studies					
Parallel, double-blind randomized trial on effect of Vit.D on clinical features and experimental parameters in early RA patients	Italy	18 (VitD3) 18 (Placebo)	• Vit. D supplementation (300,000 IU single dose; evaluated after 3 months) along with standard treatment improved global health in eRA patients • No significant effect on RA symptoms measured as DAS28, CRP and VAS scores	• Only females included • Limited sample size • Inclusion of patients regardless of their baseline Vit. D levels	[55]
Effect of Vit D supplementation for pain relief in early RA, treatment-naïve (duration < 2 years) RA patients	India	75 patients Two arms (along with DMARD therapy) Group A: Combination VitD3 (60,000 IU/week) + Calcium (1000 mg/day) Group B: Calcium (1000 mg/day)	• After 8 weeks, Vit. D supplementation resulted in 50% higher pain relief and DAS-28 scores but not on the time required for the onset of pain relief (Tm) • Vit. D deficiency is a risk factor for developing active RA	• Limited sample size • Lack of placebo control • No Double Blinding	[44]
Retrospective study to evaluate the clinical efficacy of Vit.D supplementation in RA patients	China	1180 patients: VitD & Control Group	• No significant change in primary efficacy & secondary efficacy outcomes was observed	• Retrospective study • Heterogeneity in the study population in terms of disease duration, activity & oral glucocorticoid	[56]
A randomized, controlled trial to evaluate short term efficacy of Vit D supplementation on functional disability	France	59 patients: 2 arms 29: VitD (100,000 IU) 30: Placebo/week for 6 months	• Significant improvement in Health Assessment Questionnaire (HAQ) score • No difference in disease activity scores (DAS28ESR/DAS28CRP)	• Small sample size • No Vit.D assessment done after the end of the study	[51]

The table summarizes the published clinical trial studies (Phases III & IV) on vitamin D. Details of associative and supplementation studies of vitamin D in Rheumatoid Arthritis are stated under different subheadings

is shown to significantly reduce the expression of DPP-4/CD26, suggesting its potential for attenuating COVID-19 infection [67]. Studies indicate that vitamin D ameliorates the key immunomodulators with prognostic value in COVID-19, like IL-6 and CRP [68]. Additionally, the cardiac features and vasculopathies observed in COVID-19 could also be related to vitamin D deficiency.

Circumstantial evidence also points to the association of vitamin D levels with COVID outcomes. The spread of the virus began in the northern hemisphere during the end of winter (2019) when the vitamin D levels are already low. The burden of mortality has been similarly higher in the northern hemisphere. Various retrospective studies have also found a positive correlation of vitamin D levels with severity and mortality in COVID patients [69–71]. However, there are contradictory reports as well. In a UK Biobank analysis of 449 COVID-positive patients, no association was found between vitamin D levels and COVID incidence after adjusting for potential cofounders [72]. However, their samples were not representative of the general population. A prospective observational study provided primary evidence for disturbed parathyroid hormone (PTH)—vitamin D levels in severe cases of COVID-19, however, a definitive association of low vitamin D levels with disease severity and symptoms such as impaired pulmonary function testing could not be obtained [73].

Various ongoing trials are evaluating Vitamin D supplementation for its prophylactic and therapeutic benefit for COVID. An ongoing phase IV trial is investigating the efficacy of its supplementation in reducing disease severity and elucidating anti-inflammatory response in older COVID patients (> 50 years) (NCT04482673). Comparison of Standard (50,000 IU) and High Dose (4,00,000 IU) one time vitamin D supplementation is also ongoing in a multicentric superiority high-risk COVID Phase III trial (CoVitTrial, NCT04344041) [74]. Additionally, Vitamin D supplementation as a prophylactic intervention is also being explored in healthcare workers (NCT04535791). A clinical case series of 4 COVID patients is reported wherein vitamin D deficient patients showed clinical improvements upon supplementation. Increased levels of vitamin D in blood serum after administration resulted in a significant decrease in IL-6 levels, providing insights into the mechanism of action in COVID patients [75]. Results obtained are limited to an extremely small number of patients and to validate the efficacy of vitamin D supplementation, randomized clinical trials are again required. A planned pragmatic, randomized, double-blind trial (VIVID) to assess the effect of vitamin D supplementation for early treatment and post-exposure prophylaxis of COVID-19 patients is ongoing. The study population consists of 1500 newly diagnosed individuals receiving a daily dose of 3200 IU vitamin D3 (9600 IU vitamin D3 on the first 2 days) or placebo (for the control group) for four weeks [76]. Key studies exploring association of Vitamin D deficiency and its supplementation benefit in COVID patients are summarized in Table 2. Hence, although there is not enough evidence to conclude a strong association of vitamin D deficiency with COVID incidence or severity, randomized controlled trials and cohort studies with larger sample sizes are required to prove this.

Discussion

A significant proportion of the population worldwide is vitamin D deficient. However, there is no formal universal consensus on circulating serum levels of 25(OH)D, which define deficiency and various definitions exist. Data from animal studies suggest that vitamin D suppresses arthritis [85]. Various prospective studies also indicate vitamin D deficiency to be associated with RA incidence. However, its dietary supplemental benefit is not yet clearly established. Hence larger randomized trials with clearly defined clinical outcomes, which take into account sunlight exposure and include measurement of serum 25(OH)D levels, are required. In addition, potential limitations of accounting for confounding factors and reverse casualty need to be addressed in study designs. For instance, old-age RA patients with restricted mobility and requiring repeated hospitalization would be spending lesser time in the sunlight, leading to vitamin D deficiency, rather than the reverse. Moreover, vitamin D deficiency is also found to correlate with various chronic conditions of the kidney and heart, and hence it is unclear if the deficiency is the cause or effect of the disease.

Vitamin D metabolites have been shown to have antiviral effects ranging from the release of antimicrobial peptides and autophagy. However, there is limited preclinical data available exploring vitamin D's role in SARS-CoV-2 infection. Few epidemiological studies have revealed a link between circulating levels of vitamin D and the severity of COVID-19 infection. However, contrasting reports showing no such association are also available. These studies have limitations because of the use of previously measured vitamin D levels, which may not reflect the status at the time of infection. Also, other confounding effects may be present. There are several ongoing trials for assessing the supplementary benefit of vitamin D in COVID patients. Such supplementation studies are also challenging because patients present to hospitals in the hyperinflammatory stage, which may be too late for any benefit, and also because it would be difficult to assess the advantage of a micronutrient in presence of a strong anti-inflammatory agent such as Dexamethasone. Hence, a population-based trial on prophylactic benefits of vitamin D in mitigating COVID-19 infections may be more befitting.

Table 2 Vitamin D related clinical trial studies for COVID-19

Study AIM	Country	Sample Size	Main findings	Limitations	References
Vitamin D-COVID-19 association studies					
Assessing the potential association between mean levels of Vit.D in various countries with cases and mortality caused by COVID-19	20 European Countries		• Inverse correlation between mean levels of vitamin D and number of COVID-19 cases	• Variability in number of cases/ country and number of tests performed • Difference in number of infected patients/country	[77]
Association of Vit. D levels with COVID-19 infection and hospitalization	Israel	Study Arms: COVID-positive: 782 COVID-negative: 7025	• Suboptimal VitD levels were an independent risk factor for COVID infection and hospitalization	• Retrospective database study • Assessment of clinical outcomes was not performed	[69]
Association between Vit. D deficiency and outcome of COVID-19 infection	Germany	185 COVID Positive	• Median Vit. D level was significantly lower in the inpatient versus the outpatient subgroup • Vit. D deficiency (<12 ng/ml/30 nM) was associated with a sixfold higher course of disease and 15-fold higher risk of health	• Confirmation required in larger patient cohorts • Randomised controlled trials required	[78]
Comparison of Vit. D levels in between COVID-positive and negative patients	Switzerland	27 COVID Positive; 80 COVID negative	• Significantly lower Vit. D levels in COVID-positive patients	• Small sample size • Lack of clinical information on severity of COVID-19 infection • No information on symptoms of COVID-negative patients	[79]
Analyzing Vit.D levels in patients with acute respiratory failure due to COVID-19 and evaluating correlation with disease severity and prognosis	Italy	42 COVID-positive patients with acute respiratory failure	• High prevalence of Vit. D deficiency in patients with severe infection posing higher mortality risk • Hypovitaminosis D as a marker for poor prognosis	• Small sample size • Relatively short follow-up of patients enrolled	[80]
Assessing association of Vit. D deficiency with COVID-19 incidence and severity in Chinese population	China	335 COVID-19 patients & 560 controls	• Significantly lower Vit. D levels in COVID-19 group after adjustment of age, sex and co-morbidities • Vit. D deficiency (<30 nmol/L) was significantly associated with COVID-19 severity	• Cross-sectional study design • Lacks sufficient number of Vit. D measurements during the study period	[81]
Vitamin D supplementation studies in COVID-19 patients					
Randomized, placebo controlled study to assess the effect of high dose Vit. D supplementation for COVID-19 viral clearance (SHADE study)	India	40 patients, 2 arms: Intervention (n=16) 60,000 IU Vit.D dosage daily for 7 days and control (n=24) received 5 ml distilled water for 7 days	• 62.5% patients in the intervention arm turned COVID-19 negative as compared to 20.8% patients in the control arm at the end of 7 days	• Only asymptomatic and mildly-symptomatic individuals were included • Higher than usual dosage of vitamin D provided that requires close follow-up for toxicity	[82]

Table 2 (continued)

Study AIM	Country	Sample Size	Main findings	Limitations	References
Quasi-experimental study to explore whether Vit.D supplementation received in the previous year and after COVID-19 infection improves survival in elderly patients	France	77 patients	• Significant negative correlation observed between regular Vit. D supplementation (single oral dose of 80,000 IU vitamin D3 every 2–3 months) • Vit. D supplementation (80,000 IU) after diagnosis was not associated with reduced mortality	• Study cohort restricted to nursing-home patients; unrepresentative of all older adults • Quasi-experimental design less robust than RCT • Participants in the comparing group did not receive placebo and no randomization present	[83]
Multicenter, double-blind, randomized controlled trial to test safety and efficacy of Vit. D supplementation in severe COVID-19 patients	Brazil	240 patients received a single dose of 200,000 IU vitamin D3	• Vitamin D3 does not confer therapeutic benefits	• Sample heterogeneity • Vit. D deficient patients included less compared to other cohorts	[84]

The table summarizes the published clinical trial studies (Phases III & IV) on vitamin D in COVID-19. Details of associative and supplementation studies of vitamin D in COVID-19 are stated under different subheadings

Recently, evidence suggesting association of severe COVID-19 infection with reduced Vitamin D levels is growing. In a meta-analysis, Bassatne et al. found no significant association between low Vitamin D levels and COVID-19-related outcomes. However, they noticed a positive trend between low serum 25(OH)D levels (< 20 ng/ml) and mortality, ICU admission, ventilation, and SARS-CoV-2 positivity. They observed significantly reduced serum vitamin D levels in COVID-positive patients [86]. In a first retrospective study on children and adolescents, vitamin D deficiency (< 12 ng/ml) was found associated with clinical severity and inflammatory markers [87]. They also propose the need for vitamin D supplementation as a prophylactic measure in adolescents. Hence, vitamin D supplementation is now being widely suggested as a rational approach to reduce risk of COVID-19 infections and deaths [75]. For deficient population and those in high-risk category, it is suggested to take 10,000 IU/day of vitamin D supplementation (loading dose) for a few weeks with an aim to quickly achieve target serum levels of 40–60 ng/ml (100–150 nmol/L), followed by dose of 5000 IU/day for few weeks [88]. Thus, practical and safe dosing guidelines for supplementation should be drafted and implemented in deficient populations, enabling slowing down of pandemic and improved quality of life.

Declarations

Conflict of interest The authors have no financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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