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AN INSIGHT INTO THE ROLE OF VITAMIN D IN COVID-19: A REVIEW

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is declared as global pandemic by the World Health Organization, and a very few information is known about its treatment and prevention. The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2) a causative agent of COVID-19 is spreading rapidly, and it's an issue of public health of emergency worldwide. Epidemiological data have been reported that lower status of vitamin D level may enhance COVID-19 mortality. Literature reviews showed the various pathophysiological mechanism links between Vitamin D and COVID-19. Past reports suggest that vitamin D supplementation may significantly decrease COVID-19 mortality effects and boosts immunity to tackle this deadly virus. Aim: To reveal the role of vitamin D in COVID-19 and suggestion of vitamin D supplementation as a potential therapy in COVID-19. Methods: We had performed a systematic review based on available literature of vitamin D in COVID-19 using PubMed, Google Scholar, and Willey online library databases up to August 2020. Conclusion: Based on available data we propose that vitamin D supplementation may play a significant role in preventing COVID-19 mortality rate and/or also act as a prophylactic agent for COVID-19. However, there is a need to generate clinical evidences or future trials to prove the association between vitamin D and COVID-19.

Keywords: COVID-19, Vitamin D supplementation, Mortality rate, Prophylactic agent, SARS-CoV-2, clinical evidences

INTRODUCTION

The novel coronavirus (n-CoV) 2019 that has emerged from Wuhan, Hubei province, China, and now became pandemic worldwide **[1]**. World Health Organization named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a causative agent for Coronavirus Disease 2019 (COVID-19) **[2]**. This novel coronavirus is spreading rapidly, and it's an issue of public health of emergency worldwide. On 30 August 2020, 24,854,140 confirmed cases and 8,38,924 deaths are being reported of COVID-19 at WHO **[3]**. The demographics of COVID-19 revealed that elderly populations with or without comorbidities are at higher risk of being affected by this novel virus **[4]**. It also revealed that children are least affected by COVID-19 across all the ages, but they can transfer this virus to the most vulnerable group of COVID-19 **[4]**. The previously reported studies identified vitamin D deficiency as a potential risk factor and reported in COVID -19 infection **[5]**. Studies showed an inverse correlation between vitamin D and COVID-19 severity **[6]**.

Risk factors that can worsen COVID-19 infection include aging, male gender, diabetes mellitus, coronary artery disease, chronic renal disease, COPD, hypertension, and obesity **[5]**. Surprisingly, many risk factors are prevalent between COVID -19 and vitamin D deficiency, including obesity, older age, black or Asian ethnic origin, which directed the scientists to hypothesis vitamin D as a therapeutic or prophylactic agent for COVID-19 **[6]**.

METHODS

We had searched the PubMed, Google scholar, and Willey online library databases for all research and review papers based on vitamin D and COVID-19 up to August 2020. Search terms which included vitamin D, COVID-19, SARS-CoV-2, trials on vitamin D supplementation on COVID-19.

VITAMIN D AND ITS EFFECTS

Vitamin D is a lipophilic secosteroid pro-hormone that is mainly synthesized endogenously from human skin and obtained from fortified foods **[7]**. Its primary function is in calcium homeostasis and bone metabolism. An extra skeletal benefit of Vitamin D is on research worldwide. Aponte *et al*. reported that vitamin D can be used for prevention of respiratory tract infection **[7]**. There is increased susceptibility to several viruses under vitamin D deficiency **[8]**. The function of vitamin D is mediated through vitamin D receptor (VDR) through genomic/non-genomic pathways present in most cell types, including adipocytes,

pancreatic β-cells, endothelial cells, cardiomyocytes, innate and adaptive immune cells **[9]**. In the genomic pathway, VDR, which is bound by calcitriol and then VDR, interacts with a retinoid-X receptor and forms a heterodimer complex that binds to response elements in the gene regions directly controlled by the active form of vitamin D {1,25 (OH)D} **[9]**. Activated complex modulates gene expression in several tissues and regulates gene transcription of proteins related to classical genomic functions of vitamin D **[9]**. In the non-genomic pathway, an active form of vitamin D binds to VDR associated with the caveolae of the plasma membrane to stimulate signal transduction pathways that generate rapid responses **[9]**.

VITAMIN D DEFICIENCY AND COVID-19

Vitamin D status is measured based on the circulating 25(OH)D concentration **[10]**. Lower serum 25(OH)D is also associated with increased susceptibility of this novel infection and also COVID-19 severity **[6]**. Biesalski *et al*. reported the relationship between comorbidities like cardiovascular diseases, hypertension, diabetes, and old age with Renin-Angiotensin-Aldosterone-System (RAAS), vitamin D status, and COVID-19 infection **[11]** which suggests that there is a link between vitamin D status and COVID-19. Studies reported that manifestations like the increased generation of pro-inflammatory cytokines, C-reactive proteins, Acute Respiratory Distress Syndrome (ARDS), pneumonia, and heart failure, which are associated with COVID-19 are inversely associated with 25(OH)D serum concentration **[12]**.

PATHOPHYSIOLOGY OF COVID-19

Dysregulation of RAAS and Acute Respiratory Distress Syndrome (ARDS)

RAAS system, which plays a vital role in several biologic functions such as water balance and blood pressure regulation, includes angiotensin-converting enzymes like ACE-1 and ACE-2 [2]. Zhou *et al*. demonstrated that ACE-2 as fusion receptor attachment of SAR-CoV-2 **[13]**. ACE-2 receptor is expressed in the lung, heart, kidney, intestine, and endothelium, showing the spectrum of tissues where viruses can attach **[14]**. ACE converts angiotensin I (Ang I) to angiotensin II (Ang II) via Ang II type 1 receptor (AT1R), causes lung injury, vasoconstriction, proliferation, inflammation, and apoptosis, whereas ACE2 causes hydrolysis of Ang II into Ang –(1-7) via Mas oncogene receptor (Mas R) to block the signaling pathways of STAT3 and extracellular signal-regulated kinases (ERK)

which causes the protective activity of lung and also acts an anti-inflammatory response which is contrary effect to ACE **[14, 15]**. SARS-CoV-2 uses the same ACE 2 receptor to enter into human cells through S –protein spike and enter human cells **[2]**. ACE2 acts as a fusion receptor of this novel virus and the protective activity of the lungs. Studies revealed that SARS-CoV-2 causes downregulation of the ACE 2 receptor **[2]**.

Acute respiratory distress syndrome (ARDS) is a pivotal mortality factor of seriously ill COVID-19 patients **[15]**. Clinical manifestations of COVID-19 patients associated with pneumonitis or ARDS have thick mucus secretions in the airways, increased levels of proinflammatory cytokines, widespread lung damage, and micro-thrombosis **[16]**. Uncontrolled release of proinflammatory cytokines (IFN-γ, IFN-α, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TNF-β, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) via immune effector cells during COVID-19 infection **[15]** results in "cytokine storm". Further, the excessive activation and recruitment of neutrophils into the inflammation site causes damage in alveolar space, which aggregates ARDS's pathogenesis **[17]**. Both mechanisms are responsible for ARDS with exaggerated neutrophil accumulation and edema increased pulmonary vascular permeability **[15]** which ultimately makes SARS-CoV-2 infection more lethal and fatal. Due to this phenomenon, activated neutrophils and macrophages' recruitment causes alveolar damage **[15]**. Ultimately, the alveolus is filled with activated neutrophils, cytokine/chemokine, and protein-rich exudate with activation of RAAS. It causes involvement in altering the coagulation cascade that happens with endothelial cell infection and endothelitis, which results in a prothrombotic state in ARDS **[15]**. ARDS causes damage in lung functions, which ultimately leads to loss of supply of oxygen to vital organs of the body leads to mortality in patients **[18]**.

Lymphopenia is a prominent feature of seriously ill COVID-19 **[19]**. Causes of Lymphopenia are

1) Cytokine storm causes significant decreases in T cell counts.
2) Exhaustion of T cells in SARS-CoV-2 infection. A study reported that both CD4+ and CD8+ T cells had increased cell surface expression of programmed cell death protein 1 and Tcellimmunoglobin and mucin domain 3 found in patients of

COVID-19, which are clinical features of T cell exhaustion.

3) Reports suggested that SARS-CoV-2 may infect T cells & 4) SARS-CoV-2 infection can interfere with T cell expansion **[19]**.

POTENTIAL MECHANISM OF VITAMIN D IN COVID-19

Vitamin D is the influential down regulator of RAAS, protecting the lung from injury **[2]**. The molecular effects of vitamin D on RAAS revealed that liganded VDR overturns renin expression by binding to the transcription factor called cAMP-response-element binding protein (CREB) **[20]**. In this way, vitamin D activated VDR causes renin expression, which causes downregulation of RAAS. Vitamin D causes up-regulation of ACE 2/Ang(1-7) activity, and inhibition of ACE/AngII/AT1R cascade in Lipopolysaccharide induces Acute lung injury (LPS-ALI) **[21]**. VDR activation by vitamin D causes blockade of viral replication of SARS-CoV-2 by inhibiting Skp 2 protein **[15]**. The dipeptidyl peptidase receptor (DPP-4/CD26) expression has been connected to the attachment with S1 domain of SARS-CoV-2 spike glycoprotein, which is responsible for the virulence of this infection; this expression is inhibited by the presence of sufficient vitamin D level **[12]**. VDR is present in immune cells, including CD4+ and CD8+ T cells, B cells, and antigen-presenting cells like macrophages and dendritic cells responsible for innate and adaptive immunomodulation immunity **[4, 22]**. Vitamin D promotes the expression of antimicrobial peptides, such as cathelicidin and β defensing **[4]**. Expression of this antimicrobial peptide can be due to the presence of CYP27B1 gene expression present in immune cells is responsible for encoding 1 α hydroxylase enzyme, which is used for conversion of the inactive form of vitamin D to the active form vitamin D; this process is accountable for the expression and regulation of antimicrobial peptide **[14]**. Microbicidal effects of human cathelicidin LL37 show a wide range of effects by interacting with formyl peptide receptor-like 1 (FPRL1) and stimulates the apoptosis of infected cells **[4]**. VDR is associated with the LL37 gene expression, which is the only identified member of the human cathelicidin family **[14]**. Cathelicidin also modulates the recognition of viral dsRNA by Toll-like receptor 3 (TLR 3) **[4]**. Toll-like receptors (TLRs) are responsible for the antimicrobicidal activity of intracellular pathogens, which are upregulated by VDR and vitamin D-1-hydroxylase genes **[4]**. This causes depletion of Th1 and Th17 cells,

which are linked to tissue damage and inflammation and upregulation of Treg (regulatory T cells) type 2 cells **[4, 23]**. 25(OH)D and 1,25(OH)2D also modulate T cell immunity by decreasing proinflammatory cytokines-1 and by increasing anti-inflammatory cytokines-2 (IL4, IL5, and IL10) **[24]**. 1,25(OH)2D exhibits B cell apoptosis by inhibiting plasma cells' proliferation and immunoglobulin secretion **[25]**. Defensins, which is promoted by vitamin D is responsible for respiratory mucosal defense **[14]**. Moreover, FokI T allele is thought to be related to viral infection susceptibility to enveloped viruses like SARS-CoV-2, which is the main polymorphism in VDR **[14]**. IκBα is responsible for inhibiting the expression of nuclear factor-κβ (NF-κβ), which is accountable for cytokine storm in SARS-CoV-2 infection may induce by vitamin D in airway epithelial cells **[14]**. Vitamin D receptors are actively present in high number in the cuboidal alveolar type 2 cells (ACII) of the lung, causing an inhibitory effect on proinflammatory cytokines/chemokines effect supported by in-vitro models **[15]**. The mechanism of action of the anti-inflammatory effect of vitamin D is by stimulating the suppressor of cytokine signaling factor 1 (SOCS1), which is known to modulate TLR receptors, which can cause suppression of proinflammatory cytokines **[26]**. Vitamin D up-regulates mitogen-activated protein kinase phosphatase 1 (MAPK) and inhibits p38 activation in innate immune response for suppressing cytokine storm by promoting anti-inflammatory factors **[1]**. The structure and function of epithelial barriers are mediated by alveolar epithelial junction and regulation of occluding and zonula occludens-1(ZO-1) gene expression **[15]**. Simonson reported that Treg lymphocytes are responsible for defense against uncontrolled inflammation, which is postulated that vitamin D may elevate these lymphocytes, which will help control cytokine storm in COVID-19 **[27]**.

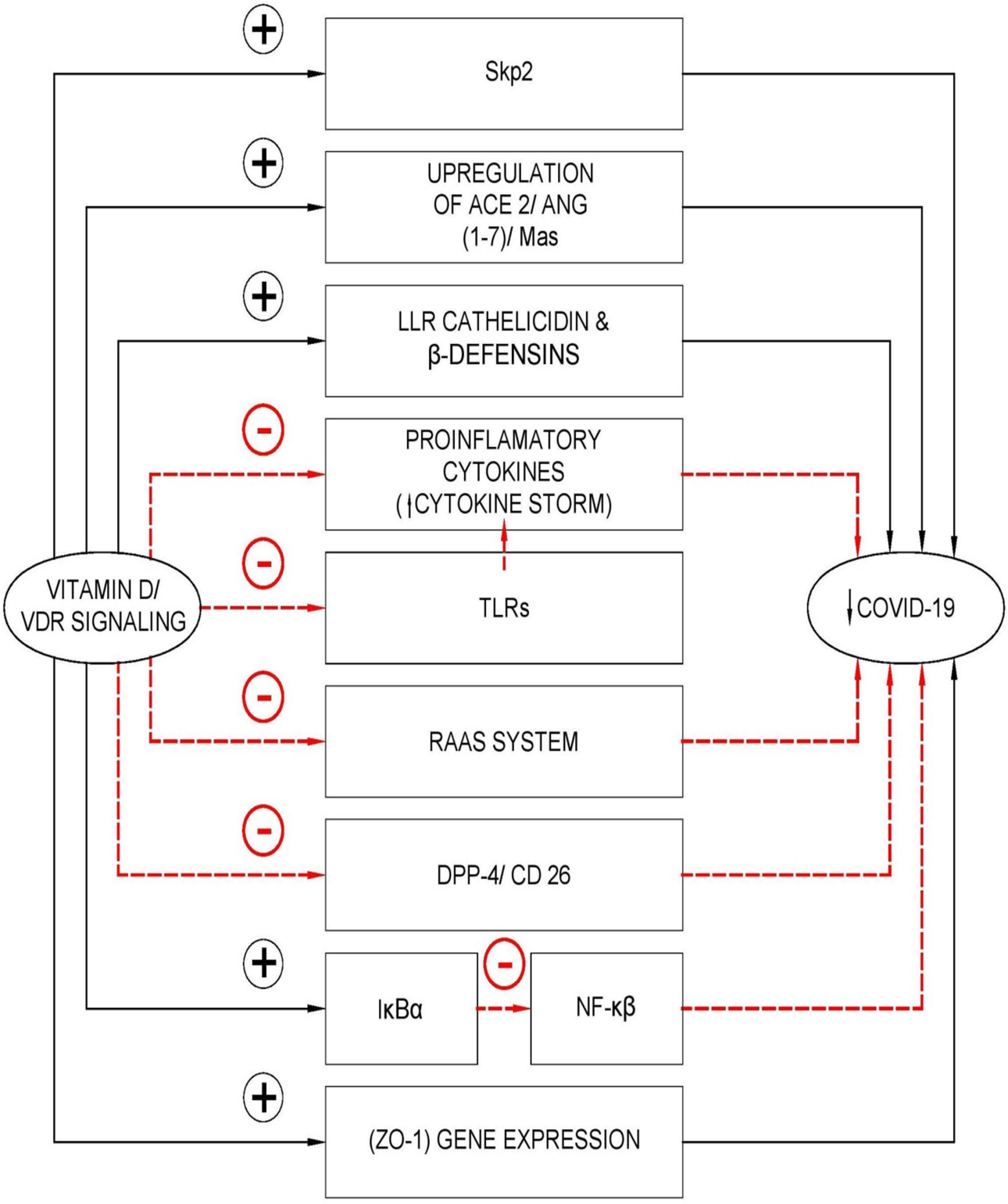

Figure 1: Proposed pathophysiological mechanism of Vitamin D in COVID-19

CLINICAL EVIDENCES OF VITAMIN D SUPPLEMENTATION AS POTENTIAL THERAPY IN COVID-19

Vitamin D status proved to be a vital element in combating enveloped viruses and respiratory tract infections. Studies, including observational and interventional studies, reported that vitamin D supplementation improves the risk from dengue, hepatitis virus (including B and C viruses), HIV viruses (Human Immunodeficiency Virus), pneumonia, herpesvirus, influenza, respiratory syncytial virus infection, rotavirus **[1, 28]**. The relationship between low levels of vitamin D and respiratory tract and enteric infections is recognized, including pneumonia, otitis media, vaginosis, UTI (urinary tract infections), sepsis and *Clostridium* infections **[1]**. Quraishi *et al*. reported that maintaining a vitamin D status of above 50 ng/ml (125 nmol/L) reduces 27% risk of Influenza-like Illness (ILI) **[28]**. One study reported that a higher dosage of vitamin D rapidly risescathelicidin levels, which will help in combating cytokine storm **[2]**. Metaanalysis reported that vitamin D supplementation might help prevent acute respiratory infections (ARI), and many observational trials reported that vitamin D deficiency is directly related to ARDS **[1, 2, 29]**. The study showed that the Vitamin D group has significantly lower RTIs than the control group (OR=0.582 [0.417-0.812], *P*=0.0001) **[29]**. A retrospective study conducted by Alipio reported an inverse association between vitamin D and COVID-19 confirmed patients **[30]**. Zhao *et al*. reported in a meta-analysis study that Vitamin D deficiency causes an increase in the risk of community-acquired pneumonia (CAP) **[31]**. One study found that there is a negative correlation between C-reactive proteins (CRP), an inflammatory marker, and vitamin D concentration (Coefficient correlation is ranged from -0.84 to -1) **[2]**. The factors mentioned here are responsible for cytokine storm in severely ill COVID-19 patients. Grant *et al*. investigated that the patients with sufficient 25(OH)D level have a lower risk of ILI i.e., 43% when compared to insufficient 25(OH)D level ($p<0.0001$) **[1]**. Grant *et al*. also revealed that mortality in COVID-19 patients might be due to the lower levels of 25(OH)D level in countries like Korea and China **[1]**. Ilie *et al* reported the negative correlation between mean vitamin D level [56.79±10.61 nmol/L] and number of COVID-19 cases per 1 million population in European countries [1393.4±1129.984, r(20)=-0.4435, pvalue=0.05] and between the vitamin D status and number of mortality rates caused by COVID-19 per 1 million of population

[80.42±94.61, r(20)= -0.4435;p value=0.05] **[32]**. In case-control studies, Bangladeshi children with low vitamin D status are very much susceptible to acute lower respiratory tract infections (ALRTIs), mean 25(OH)D was <11.7 ng/mL. In this study, every 4 ng/mL increase in vitamin D reduces the odds of ALRI development by half **[33]**. One meta-analysis study confirmed the association of vitamin D deficiency and RTIs. Moreover, in this analysis, vitamin D supplementation reduces the risk of ARTIs among all wide ranges of the population, including 10,933 individuals of all ages between 0-95 years (OR, 0.88;95%CI,0.81-0.960. In the subgroup analysis, Martineau *et al*. suggested that the protective effect of vitamin D supplementation happens in the daily or weekly dose of vitamin D supplementation among severely vitamin D deficient only (25(OH)D is <10.02 ng/mL) **[34]**. The death rate of critically ill patients is higher in vitamin D deficient patients in the intensive care unit (ICU) when compared with vitamin D insufficient and sufficient level (mean±SD) of 25(OH)D of survivors vs. non-survivors, 27.9±9.7 vs. 9.7±4.7 ng/mL).

RECOMMENDATION FOR THE USE OF VITAMIN D SUPPLEMENTATION IN COVID-19

Pathophysiological studies and clinical studies suggest that vitamin D may act as a potent therapy in COVID-19. Gomez *et al*. recommended that the benefits of vitamin D supplementation in COVID-19 can be achieved in the severely deficient vitamin D deficiency only with calcifediol use **[15]**. A proper randomized trial must be established to prove this hypothesis. There are various clinical studies ongoing for the effect of vitamin D supplementation in COVID-19 mortality patients. Studies also recommended the use of vitamin D supplementation with the proper dosage in COVID-19 patients. To decrease the risk of SARS-CoV-2 infection, the people at risk must take 10,000IU/day of cholecalciferol (vitamin D3) for a few weeks for rapidly increasing in 25(OH)D concentration, which is followed by 5000 IU/day. The aim is to take 25(OH)D concentration is up to 40-60 ng/mL. For the treatment purpose against COVID-19, a higher dosage of cholecalciferol might be helpful. For these recommendations, randomization controlled trials must be established to prove the strong association between vitamin D and COVID-19 **[27]**.

CONCLUSION

COVID-19, an acute respiratory tract infection caused by an enveloped virus known as SARS-CoV-2, is a deadly

pandemic infection may be reduced by vitamin D supplements through various mechanisms like reduction of proinflammatory cytokines/chemokines storm, regulation of RAS, regulating innate/adaptive immunity, maintaining the integrity of pulmonary epithelial health. Data supports that vitamin D can be proved to be a vital therapy in acute respiratory tract infections and enveloped viruses. However, vitamin D's role in coronaviruses is still unclear. Systematic clinical studies must be established to get insight about this association. Vitamin D deficiency may be considered as highly predominant risk factor for COVID-19, and vitamin D supplements may be helpful as potent therapy or prophylactic therapy for COVID-19. However, there is a need for more clinical studies that show the potential beneficial effect of vitamin D in COVID-19.

ETHICAL CLEARANCE: Not Required

CONFLICT OF INTEREST: None

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