

REVIEW ARTICLE

Vitamin D: A cheap yet effective bullet against coronavirus disease-19 – Are we convinced yet?

Suresh K Sharma¹, Shiv Kumar Mudgal¹, Venkatesh S Pai², Jitender Chaturvedi³, Rakhi Gaur¹

¹College of Nursing, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India, ²Department of General Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India, ³Department of Neurosurgery, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Correspondence to: Suresh K Sharma, E-mail: suresh.nur@aiimsrishikesh.edu.in

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ABSTRACT

Novel corona virus disease (COVID-19) pandemic has seriously affected the entire world; moreover, infection and case fatality rate is quite high in countries located in North Hemisphere, where a large proportion of the population is living with Vitamin D (Vit D) deficiency. Vit D is a secosteroid hormone, which plays an important role in calcium and phosphorous homeostasis, and hence bone strength and also has a significant role in the immune health of an individual. It induces the expression of antimicrobial peptides that can decrease viral replication and also reduces the level of pro-inflammatory cytokines while enhancing the level of anti-inflammatory cytokines. Vit D supplementation in daily single doses (300–2000 IU/day) for 8–12 weeks had more protective effect for viral infections than large doses given at fixed intervals (100,000 or 200,000 IU per month or every 3 months). This evidence based review emphasizes the role of Vit D in the immune response to viral infections and proposes the immense value of Vit D supplementation, for the prevention and treatment of COVID-19.

KEY WORDS: Coronavirus Disease-19; Cytokine Storm; Immune Response; Influenza; Severe Acute Respiratory Syndrome-Coronavirus-2; Vitamin D

INTRODUCTION

As the world is in the grip of the Coronavirus (CoV) disease (COVID-19) pandemic, we are in the quest for measures to reduce the morbidity and mortality associated with this highly contagious viral infection, which emerged in Wuhan city of China. Winter season, with the least sun exposure, was the time of origin of this infection in China. Lesser sun exposure during winter is associated with lesser Vitamin D (Vit D) levels, evident in several studies.^[1,2] Further, COVID-19

pandemic has a high mortality in countries such as United States of America (USA), Italy, Spain, United Kingdom(UK), Switzerland, Germany, Iran, France, and Turkey, where a significant portion of their populations live with lower level of Vit D level.^[3] USA is the most severely affected country with COVID-19, where, according to the US National Center for Health Statistics, an estimated 70% of individuals may be considered Vit D deficient.^[4] This signifies that Vit D deficiency may be one of the predisposing factors in the severe acute respiratory syndrome (SARS)-(CoV)-2 infection and case fatality rate (CFR). CFRs rise with age and with disease comorbidities, which are both associated with lower Vit D levels. Air pollution is also one of the factors that affect the ultraviolet light B (UVB) level on ground and thereby results in Vit D deficiency,^[5] which could be one of the factors that people living in metros are more affected by COVID-19 as compared to rural areas and poor people.

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Vit D is a steroid hormone, which plays an important role in calcium and phosphorous homeostasis, and hence bone strength,^[6,7] and also has a significant role in the immune health of an individual.^[4] Human skin can produce Vit D naturally, when exposed to UVB rays of sunlight. This evidence based review emphasizes the role of Vit D in immune response to viral infections and proposes the immense value of Vit D supplementation, for the prevention and treatment of COVID-19.

VIT D AND IMMUNITY

Vit D is a hormone that has critical functions for regulating calcium-phosphate homeostasis. Apart from its conventional role, recent evidences support its crucial role in cell proliferation and immunomodulation.^[8] Vit D is critical for immune function. A deficiency of this nutrient may compromise immune response and increase the risk of infection and disease. Although there is a dearth of evidence about the role of Vit D supplements in decreasing the risk SARS-CoV-2 infection, having adequate serum level of Vit D can promote immunity.^[9] In addition, Vit D supplements show protective mechanism against respiratory infections. Studies suggested various mechanisms by which Vit D decreases the risk of viral infection and death. It is reported that the incidence and CFR of COVID-19 infection increased in patients with comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and areas with higher levels of air pollution and Vit D levels are inversely correlated with many of these factors.^[7,9] A review discussed the action of Vit D in decreasing the viral infection (common cold) summarized the action of Vit D into three main groups: Physical barriers, innate immunity, and adaptive immunity.^[10]

Physical Barriers

Physical barriers through tight junctions, gap junctions, and adherens junctions are the first line defense against microbes. The proteins encoding these structures occur through gene regulation, where Vit D has a crucial role through

1α -hydroxyls.^[11-13] Vit D also promotes the production and expression of cathelicidin and defensins which enhance immune response.^[14]

Innate Immunity

Vit D modulates innate immune response by enhancing expression of antimicrobial peptides, cathelicidin (LL-37), and defensins. Figure 1 explains the role of Vit D on immune response. Cathelicidins show its antimicrobial actions against different microorganisms, including bacteria (Gram-positive and Gram-negative), viruses (enveloped and non-enveloped) and fungi.^[15] These peptides destroy the invading infectious agents by damaging the cell membranes and also neutralize the effects of endotoxins released by them.^[16]

Vit D stimulates monocyte maturation to macrophage and thus promotes immunoglobulin and complement-mediated phagocytosis. Furthermore, it supports to maintain self-tolerance by diminishing an overactive adaptive immune system.^[17] Studies have shown that Vit D decreases the replication of viruses including that of influenza A,^[18] rotavirus,^[19] and dengue.^[20] Vit D is also effective in decreasing the cytokine storm that is caused by innate immune response, against viral and other microbial infection, as seen in SARS-CoV-2 patients.^[21]

Adaptive Immunity

It is evident from human studies that Vit D modulates adaptive immune responses. Vit D plays a key role in decreasing production of pro-inflammatory T-helper cells type 1 (Th1) cytokines, including tumor necrotic factor, interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor, and interferon, thus diminishing Th1 mediated autoimmunity. Furthermore, $1,25(\text{OH})_2\text{D}_3$ enhance the synthesis of Th2 cells, and their anti-inflammatory Th2 cytokines, IL-4, IL-5, and IL-10.^[22] In addition, Vit D increases the production of regulatory T cells, decreases production of IgG, and inhibits dendritic cell differentiation.^[10,23,24]

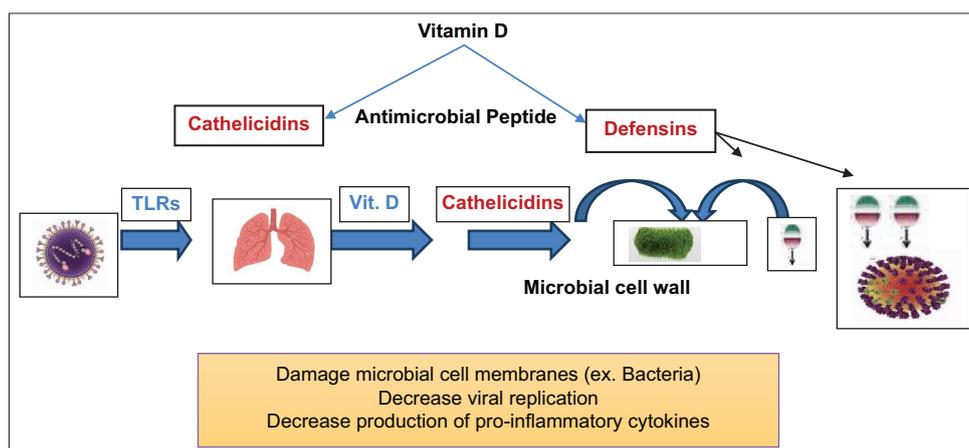


Figure 1: Association of Vitamin D with viral infections

Mortality of the COVID-19 patient is attributed to an overzealous immune response causing an inflammatory maelstrom, a cytokine storm, which seriously damages the lungs resulting in an acute respiratory distress syndrome (ARDS). Vit D has shown a crucial role not only in enhancing innate immune response but also applies brakes to a racing immune response. This suggests that having adequate serum levels of Vit D could protect patients against the most sinister complications and death from SARS-CoV-2.^[25]

Vit D also increases expression of genes associated with anti-oxidation (glutathione reeducates and glutamate–cysteine ligase modifier subunit).^[26] The enhanced production of glutathione allows the utilization of ascorbic acid that has antimicrobial actions and has been suggested to protect the patients with COVID-19.^[27-29] Moreover, Dr. Tom Frieden, a former director of CDC, suggested the use of Vit D supplementation to fight against the SARS-CoV-2 pandemic on March 23, 2020.^[9]

Apart from its role in modulating immune responses, evidence exists to uncover the crucial role of Vit D in mediating the immune response to viral infections. Several experimental and observational studies report that populations with decreased serum levels of Vit D have a significantly increased risk of respiratory tract infection and influenza. Insufficiency of Vit D is seen commonly in patients with HIV infection. Recent evidences from cell culture studies have demonstrated the effect of Vit D against viruses, especially the enveloped ones. These anti-viral effects are also mediated by upregulation of cathelicidin and defensins.^[15,22,30]

Macrophages, monocytes, epithelial, and polymorphonuclear cells play a central role in the innate immune response. These cells have Toll-like receptors (TLRs), which have the ability to identify specific molecular patterns which are conserved in infectious agents (e.g., TLR2 identifies bacterial lipopolysaccharides) including viral proteins and nucleic acids.^[31-33] On detection of pathogens, stimulated TLRs induce release of cytokines which in turn triggers the release of cathelicidin, antimicrobial peptide (LL-37), defensins, and possibly supports expression of reactive oxygen species. Some human antimicrobial peptides related to TLRs have shown anti-viral properties and their production and release are directly correlated with serum level of Vit D.^[34]

Human antimicrobial peptide, LL-37, has shown antibacterial, antifungal properties, and abilities to destroy bacteria/fungi by disrupting the integrity of cell membrane and proton gradient.^[35] A mouse-model study shows that LL-37 has ability to kill viruses with lipid envelopes, by compromising the viral membrane integrity and defensins block the viral binding by generating a protecting barrier of immobilized surface proteins.^[36,37] Cathelicidin has anti-viral properties and ability to inhibit the replication of herpes simplex virus type one, vaccinia virus, retrovirus, and of some serotypes of adenovirus at specific LL-37 concentrations.^[36,38,39]

These evidences explain a positive effect of Vit D on immune system and support the belief that anti-viral properties of cathelicidin and defensins may disrupt the cell membrane integrity of enveloped viruses, hence protecting against viral infections.

Mounting evidence suggests that Vit D has an important role against viral respiratory infections. Epithelial cells of lung tissues release more CYP27B1 and less CYP24A1, supporting the transformation of Vit D to 1,25-dihydroxy Vit D₃ (active form).^[40] In airway epithelium, this active form of Vit D triggers IκBα, a NF-κB inhibitor which reduces respiratory syncytial virus (RSV) initiation of NF-κB stimulated genes like interferon-β. When a patient is treated with Vit D supplementation, immune cells enhance the level of cathelicidin and TLR coreceptor CD-14 and this leads to reduction of viral stimulation of inflammatory genes.^[41]

A recent study reported that SARS-CoV-2 enter into alveolar and intestinal cells using angiotensin converting enzyme-2 as viral receptor.^[42] Subsequent alteration in the rennin-angiotensin mechanism may cause production and release of inflammatory cytokines which may lead to the development of ARDS.^[43] As Vit D has a central role in immune response modulation that include reduction of pro-inflammatory cytokines, a mice-model study, demonstrated its ability to reduce lung injury by inhibiting the angiotensin-2-Tie-2 signaling and the renin-angiotensin mechanism.^[44] Another experiment in mice and humans showed that Vit D is locally activated in epithelial cells of lung tissues and has an ability to prevent intestinal pneumonitis.^[45] The results of these studies support the notion that Vit D has protective effect against SARS-CoV-2 because of its properties to reduce cytokine response and decreased risk and severity of ARDS.^[43]

Table 1 presents findings from meta-analyses that Vit D is protective against acute respiratory tract infection, particularly in patients with Vit D deficiency. These findings could be utilized during the prevention and treatment of SARS-CoV-2 infection.

Several articles report that SARS-CoV-2 is more prevalent and fatal among the elderly and the possible reasons for this could be more comorbidities such as diabetes mellitus, hypertension, COPD, and Vit D deficiency associated with aging. Participants with chronic illnesses have low serum level of Vit D than healthy controls.^[9] Male and female participants with COPD had mean Vit D level of 16 ng/mL and 13 ng/mL, respectively, in an Italian study.^[49] A South Korean study reported mean serum level of Vit D of 14 ± 8 ng/mL at the time of admission, among patients with community acquired pneumonia.^[50] Many viral infections like influenza, SARS-CoV2 are prevalent in winter, as poor exposure to sunlight is associated with low Vit D levels. A study found correlation between lower levels of Vit D across 20 European countries and more morbidity and mortality of SARS-CoV-2.^[51] Substantial indirect evidences suggest

the protective effect of Vit D against SARS-CoV-2. Table 2 displays the results of individual studies regarding the effect of Vit D on enveloped viruses.

With these strong evidences, it makes us in believe that Vit D supplementation may result in decreased incidence of cases, reduced severity of disease and mortality caused by SARS-CoV-2.

PROPOSED THERAPEUTIC VIT D SUPPLEMENTATION IN COVID-19

The reviewed studies provide evidence to support the hypothesis that higher serum level of Vit D is associated with a low risk of microbial infections and deaths from acute RTIs caused by pneumonia, CoV, and influenza. Further, the normal serum Vit D levels may be effective

against the SARS-CoV-2 infection and decrease the severity and mortality associated.^[9] Unfortunately, there is a lack of standard guidelines about the dose and desirable concentration of Vit D required to protect the people from RTIs during winter season.

A recent article reports that Vit D level >20 ng/mL is desired and many countries follow this recommendation.^[59] Another study recommends a similar level for RTIs and suggests levels >30 ng/mL as beneficial in decreasing risk of cancer, unfavorable pregnancy and birth outcomes, and type 2 diabetes mellitus.^[60] It is recommended from another study that desirable level of Vit D should be 40–60 ng/mL for prevention of breast and colorectal cancer.^[61]

Initial data from the Philippines on 212 confirmed COVID-19 patients showed that Vit D levels strongly correlated with

Table 1: Meta-analyses on efficacy of vitamin D on respiratory tract infections

Study characteristics	Participants	Results
Bergman <i>et al.</i> ^[46] Eleven randomized placebo-controlled trials	5660 participants (age ranging from 6 months to 75 years)	Supplementation with Vitamin D significantly decreased the risk of RTI (OR: 0.64; 95% CI: 0.49, 0.84; <i>P</i> =0.0014)
Charan <i>et al.</i> ^[47] Five clinical trials	1868 participants (aged 1–83 years)	The reduction of episodes of RTI was significantly lower in Vitamin D supplementation group compared to the control group (OR=0.58; 95% CI: 0.42, 0.81; <i>P</i> =0.001)
Martineau <i>et al.</i> ^[48] Twenty five randomized controlled trials	10,933 participants (aged 0–95 years) from 14 different countries	Overall results showed that Vitamin D supplementation has protective effective in decreasing the risk of suffering at least one acute RTI (OR 0.88; 95% CI: 0.81, 0.96; <i>P</i> =0.003)

OR: Odds ratio, RTI: Respiratory tract infection, CI: Confidence interval

Table 2: Empirical evidences on association of Vitamin D and virus infections

Study characteristics	Virus	Results
Martinez-Moreno <i>et al.</i> ^[20] Randomized controlled trial. 20 participants	Dengue virus (DENV) infection	Study reported that participants who were treated with 4000 IU/day of Vitamin D showed low susceptibility to DENV-2 infection than those participants who were treated with 1000 IU/day of Vitamin D. Study support the evidence that Vitamin D has possible role in modulating the innate immune response and protective effect against DENV
Villamor <i>et al.</i> ^[52] Case-control study. 345 participants	Dengue	Study reported negative correlation between Vitamin D concentration and progression of dengue fever to dengue hemorrhagic fever/dengue shock syndrome
Brice <i>et al.</i> ^[53] Laboratory study	Kaposi's sarcoma-associated herpes virus (KSHV)	Study proposed that LL-37 inhibits KSHV infection in oral epithelial cells by disrupting KSHV envelope
Currie <i>et al.</i> ^[54] Laboratory study	Respiratory syncytial virus (RSV)	Study reported that LL-37 inhibited cell death due to viral infection, significantly reduced the expression of new infectious particles and reduced the spread of infection
Zhao <i>et al.</i> ^[19] Laboratory study	Respiratory syncytial virus (RSV)	Study demonstrated the mechanism how Vitamin D decreased the risk of RSV
Gui <i>et al.</i> ^[55] Mice-model study	H9N2 influenza virus	The results suggest that calcitriol treatment reduced the production of the influenza M gene, IL-6, and IFN- β in A549 cells in mice with H9N2 influenza
Bucak <i>et al.</i> ^[56] 137 participants	Rotavirus	Study reported that 25(OH)D(3) was significantly different 14.6 \pm 8.7ng/mL versus 29.06 \pm 6.51ng/mL in patient with rota viral diarrhea versus in the health controls respectively and concluded that Vitamin D is inversely associated with rotavirus diarrhea
Hu <i>et al.</i> ^[57] Systematic review and meta-analysis (7 studies included)	Hepatitis B virus	Study revealed that decreased level of Vitamin D in chronic hepatitis B patients than that of healthy participants [pooled <i>r</i> -2.03ng/mL (-2.60, -1.46)] and inversely associated with HBV viral loads [pooled <i>r</i> -0.41(-0.54, -0.27)]
Alvarez <i>et al.</i> ^[58] extensive review of 29 clinical studies	HIV	Results showed that Vitamin D supplementation led to normal Vitamin D level and its effect on decrease inflammation, increase in CD4+ T cell count and antibacterial response

Table 3: Evidences regarding the effect of different Vitamin D doses

Study characteristics	Doses of Vitamin D	Results
van Groningen <i>et al.</i> ^[67] 208 participants	Group A (<i>n</i> =30): treated with 25,000 IU every fortnight (a total dose of 100,000 IU) in 2 months. Group B (<i>n</i> =68): treated with 25,000 IU/week (a total of 150,000 IU) in 2 months Group C (<i>n</i> =110): treated with 25,000 IU/week (a total dose of 200,000 IU) in 2 months	Vitamin D level (nmol/L) Before/after 19.0±7.4/48.3±13.0 20.4±9.7/63.6±27.5 20.7±8.4/89.7±26.9 Study concluded that to achieve adequate level of Vitamin D a loading dose of 100,000–200,000 IU over 2 months (1800 or 3600 IU/d) may be administered
Amir <i>et al.</i> ^[68] 40 participants	Participants treated with 10,000 IU/d of vitamin D and 1000 mg/d of calcium supplementation for 4 months	Vitamin D 10,000 IU/d supplementations for 4 months appear safe in participants without comorbidities
Charoenngam <i>et al.</i> ^[69] Twenty participants	Participants were treated with 600, 4000, or 10,000 IU/day of oral Vitamin D for 2 months.	Results demonstrated that Vitamin D level increased from 20±6 to 39±9 and 19±4 to 67±3 for 4000 IU/d and 10,000 IU/d, respectively. Increased Vitamin D concentration was related with enhance beneficial bacteria and reduction of pathogens without adverse effects
McCullough <i>et al.</i> ^[70] 112 participants	36 participants treated with 5000 IU/d for 1 year or more while 78 participants were treated with 10,000 IU/d for 1 year or more	Results summarized that long-term Vitamin D supplementation in doses ranging from 5000 to 10,000 IUs/day seems to be safe. Participants who were treated with 5000 IU/d and 10,000 IU/d the mean level of Vitamin D increased from 24 to 68 ng/mL, and 25 to 96 ng/mL, respectively
Bergman <i>et al.</i> ^[46] Eleven randomized placebo-controlled trials	5660 participants (age ranging from 6 months to 75 years)	Meta-analysis reported that the studies using daily single doses (300–2000 IU/day) had more protective effect of Vitamin D than those studies used large doses given at fix intervals (100,000 or 200,000 IU per month or every 3 months)

severity of COVID-19 reporting 85.5% of patients with sufficient (>30 ng/mL) level of Vit D having mild disease while 72.8% of patients with Vit D deficiency (<20 ng/mL) having severe or critical disease.^[62] A larger study in Indonesia investigated Vit D level in 780 confirmed COVID-19 cases. According to their report, compared to COVID-19 patients with sufficient levels of Vit D, the patients with Vit D levels in the categories, 20-30 ng/mL and <20 ng/mL, were 12.55 times and 19.12 times more likely to die from COVID-19, respectively. The key finding is that, even after controlling for age, gender, and having comorbidities, deaths were 10.12 times more likely in Vit D deficient patients than patients with normal Vit D level.^[63]

Moreover, it is observed that the degree of protection usually increases as Vit D concentration reaches to its optimum range of 40–60 ng/mL. To achieve this level, an individual should take 2000–5000 IU/day of Vit-D3.^[64] In 2011, the U.S. Institute of Medicine suggested Vit D supplementation of 600 IU/d and 800 IU/d for people younger than 70 years and older than 70 years, respectively, and a serum Vit-D level of 20 ng/mL or more, for skeletal health.^[65] Moreover, the Endocrine Society issued guidelines recommending Vit-D supplementation of 1000–4000 IU/d and Vit D level of 30 ng/mL or more for patients, including anyone with chronic disease.^[66] Table 3 summarizes the findings of some studies which suggest various doses of Vit D to achieve normal concentration of this vitamin.

Therefore, from reviewed literature, it seems fairly appropriate to suggest taking Vit-D at 10,000 IU/day as an adequate dose to enhance circulatory concentration of Vit-D into the optimal range of 40–60 ng/mL; after 1 month the dose can be reduced to 5000 IU/day to maintain serum levels.^[71,72] A recent article proposed the loading doses of 200,000–300,000 IU to achieve the optimal serum range to decrease the risk and severity of COVID-19.^[29]

A multicenter randomized control study, CoVit trial, which is in its recruitment phase at Angers, France, to compare high dose versus standard dose Vit-D3 in high risk COVID-19 patients, may give us further answers to this question.^[73]

CONCLUSION

Evidences for the protective effects of Vit-D against bacterial, viral and fungal infections are immense. It has properties to enhance innate immunity, modulate adaptive immunity, and also increases the expression of anti-oxidation-related genes. Therefore, we suggest daily low dose (1000–2000 IU) Vit-D supplementation to maintain optimum serum levels for prevention and treatment of COVID-19.

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