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Review Article

Interdictory contribution of Vitamin D to prevent corona virus infections

Neelam Lahari[1]*, Vinoy K Shrivastava[1], Arathi Sreenikethanam[2], Subhisha Raj[2] and Amit K Bajhaiya[2]*

[1]Laboratory of Endocrinology, Department of Bioscience, Barkatullah University, Bhopal, Madhya Pradesh, India

[2]Algal Biotechnology Lab, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Thirvarur, India

Abstract

The impact of vitamin D on the musculoskeletal system is well known. The diverse role of vitamin D is well supported by the functionality of vitamin D receptors and vitamin D activating enzymes (hydroxylase) present in tissues and cells. Hypovitaminosis D causes rickets, osteomalacia, hyperparathyroidism, and an increased risk of bone fracture. Vitamin D has immune-stimulatory effects on both the innate and adaptive immune systems. Vitamin D induces antimicrobial peptide cathelicidin and defensin that can inhibit viral replication of pro-inflammatory cytokines that regulate inflammatory encasement. Moreover, several studies on vitamin D have shown its interdictory role in the immune and respiratory systems. This global crisis, the COVID-19 pandemic condition has increased the risk of acute respiratory tract infection by immune dysregulation along with cytokine storm, which further progress into acute respiratory distress syndrome. Vitamin D has immunomodulatory and anti-inflammatory properties which are effective against respiratory viral infections. Vitamin D supplementation has shown a compatible effect on viral infection. This review article discusses the role of vitamin D in reducing the risk of respiratory infections including the severity of COVID-19 infections. This review focuses on the therapeutic role of vitamin D to improve clinical outcome during COVID-19 infection and suggest its possible role in the prevention and treatment of respiratory infections.

More Information

***Address for correspondence:** Amit K Bajhaiya, Algal Biotechnology Lab, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Thirvarur, India, Email: amitkumar@cutn.ac.in

Neelam Lahari, Laboratory of Endocrinology, Department of Bioscience, Barkatullah University, Bhopal, Madhya Pradesh, India, Email: barsana.neelam@gmail.com

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ORCiD: https://orcid.org/0000-0002-9912-4278

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Introduction

Vitamin D is a secosteroid that can either be produced in the skin from a cholesterol-like precursor 7-dehydrocholesterol when exposed to sunlight (ultraviolet B radiation 290 nm - 315 nm) or by providing the precursors in the diet. The version made in the skin is referred to as vitamin D3 (cholecalciferol), whereas the dietary form can be vitamin D3 or a closely related molecule of plant origin known as vitamin D2 (ergocalciferol) [1,2]. As vitamin D can be made in the skin, some nutritional texts refer to it as a pro-hormone. It's carried in the bloodstream by vitamin D binding protein (VDBP) and is hydroxylated at C-25 by cytochrome P450. Further the 25-hydroxylase (CYP2R1) enzyme present in the liver results in the formation of the main circulating inactive form 25-hydroxyvitamin D [25(OH)D] (Calcidiol). The 1,25-hydroxylase (CYP27B1) enzyme converts this metabolite to the biologically active form 1,25-dihydroxy vitamin D [1,25(OH)2D] (Calcitriol) in the kidney [3,4] (Figure 1). Several factors affect the vitamin D levels such as age, being indoors, dark skin, pollution, sunscreen uses, and

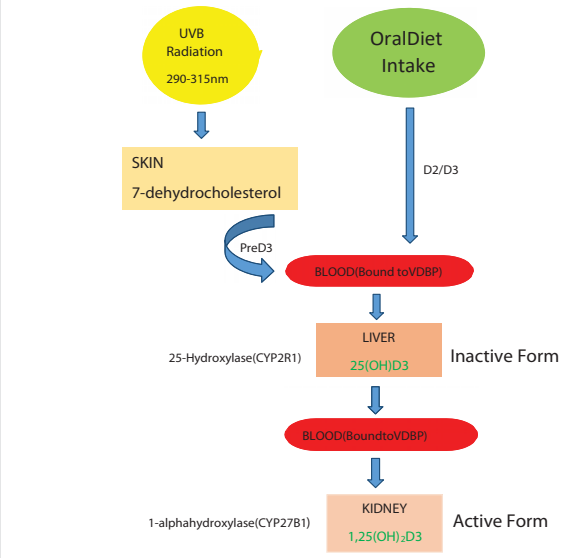

Figure 1: Diagrammatic representation of Vitamin D synthesis: Exposure to sunlight relay photolysis of the 7-dehydrocholesterol in the skin, which is converted to previtamin D3 by a heat-dependent process. Vitamin D made in the skin or ingested in the diet is converted to 25(OH)D3 (inactive form) by CYP2R1 in the liver, then 25(OH)D3 converted 1,25(OH)2D3 (active form) by CYP27B1 in the kidney [1,4].

low cholesterol levels. All these factors negatively regulate vitamin D biosynthesis in the skin [5]. The 25(OH)D is used as an indicator to determine the vitamin D levels in the body as it depends on the availability and circulating vitamin D in the blood. According to the classification given by the US Endocrine Society, < 20 ng/ml of serum 25(OH)D with a consequent and consistent elevation of parathyroid hormone and decrease in intestinal calcium absorption is considered to be vitamin D deficiency, > 30 ng/ml is sufficient and 21 ng/ml - 29 ng/ml is considered as an insufficient condition. The World Health Organization (WHO) also defined vitamin D insufficiency as a serum level of 25(OH)D below 20 ng/ml [6-8] (Tables 1,2).

At the biochemical level, 1,25(OH)2D binds to the nuclear receptor superfamily member called the vitamin D receptor (VDR). VDR mediates the biological actions of vitamin D to maintain mineral homeostasis in the intestine, kidney, bone, and parathyroid gland. But its deficiency can lead to certain disorders like rickets in children, osteoporosis in adults, muscle weakness, certain cancers, multiple sclerosis, diabetes, blood pressure, and another physiological process [9,10]. Further vitamin D is also known to play role in the immune system as VDR is expressed in immune cells (monocytes/macrophages, dendritic cells, T cells, B cells, NK cells, etc.) as well [11]. The expression of the VDR receptor in immune cells has highlighted an interesting role of vitamin D in the immune response. Recent data demonstrate a link between vitamin D and various infectious diseases caused by different pathogens. Further, many studies have suggested that vitamin D can reduce the risk of viral diseases [12-14].

The current Corona Virus Disease- 19 (COVID-19) was an epidemic and was detected first in Wuhan city, China in December 2019. The 2019-CoV was later named SARS-CoV2 (Severe Acute Respiratory Syndrome Corona Virus 2). On 11th of February 2020, WHO named it COVID-19.

As the number of COVID cases increased rapidly worldwide [15-19]. So, WHO declared it a global pandemic on the 11th of March 2020 [http//www.who.int]. The main symptoms of COVID-19 were fever, dyspnea (shortness of breath), cough, sore throat, nasal congestion, bone & muscle aches, headache, and fatigue [20-25]. The corona symptoms were very much similar to that of viral pneumonia and common influenza

Table 1: Blood serum status of vitamin D [25(OH)D] (Adapted from [70]).

Vitamin D Status	25(OH)D–ng/ml	25(OH)D-nmol/L
Sufficiency	> 30	75
Insufficiency	21 - 29	51 - 74
Deficiency	< 20	< 50

Table 2: Classification of Vitamin D deficiency (Adapted from [7]).

Stage	Vitamin D status(ng/ml)	Vitamin D status(nmol/L)
Severe Deficiency	<5	< 12.5
Moderate Deficiency	5-10	12.5 - 25
Mild Deficiency	10-20	25 - 50

infections. Human to Human transmission is implicated with droplets as the main mode of transmission. In some cases like asymptomatic or with mild symptoms, the infection is referred to as Acute Respiratory Distress Syndrome (ARDS). In severe cases like a respiratory failure along with multi-organ dysfunction, COVID infected person shows a preferment of cytokines such as interleukin (IL) -6, 10 and tumor necrosis factor (TNF)-α [26,27]. So, the viral infection provokes tissue injury through increased production of pro-inflammatory cytokines, mobilization of pro-inflammatory macrophages, granulocytes, and activation of T cells. This phenomenon was commonly known as cytokine storm and is also referred to as macrophage activation syndrome. This cytokine storm was considered the main reason for some of the serious manifestations of COVID-19. Some of the recent studies on COVID-19 showed that the infection was mainly associated with increased production of pro-inflammatory cytokines, C-reactive protein, causing an increased risk of pneumonia, sepsis, ARDS, and heart failure [28-30]. Vitamin D also plays an immuno-modulatory role via suppression of immune responses in respiratory epithelial cells during viral infections. Vitamin D reduces the levels of pro-inflammatory cytokines including IL-1, IL-6, IL-12, TNF-α and IL-17, while increasing the anti-inflammatory IL-10 and TNF-β. Several studies showed that vitamin D deficiency can detract from the zone of acquired immunity. In this review, we discuss the innovative source and defensive role of vitamin D against coronavirus infections [30-33].

Immuno-regulatory action of cholecalciferol

The contribution of vitamin D as an immune-modulator or immune-regulator has been the subject of interest among immunologists. The importance of vitamin D in the regulation of the immune system (innate and adaptive) was demonstrated by the discovery of the presence of metabolizing hormones and VDR expression in almost all immune cells [34,35]. The effect of vitamin D on immune cells is complex as illustrated by the fact that VDR expression in immune cells is differently controlled according to their activation status. Inside the cell, vitamin D binds to the nuclear D receptor and subsequently activates VDRs to dimerize with themselves or with retinoid X receptor (RXR) and translocate to the nucleus to engage the vitamin D receptor element (VDRE) [36-40]. VDRE regulates the expression of numerous host genes like β defensin and cathelicidin. These can directly cleave the membrane of a virus and are involved in the activation of different immune cells. Vitamin D suppresses responses of adaptive immunity in respiratory epithelial cells during viral infections [41-43]. It reduces the Th 1 proliferation that results in lower levels of pro-inflammatory cytokines and diminished acquired immune responses and these may be counter-protective in mounting a successful immune response against a virus [44,45] (Figure 2).

Vitamin D influences T-cell maturation and can divert the

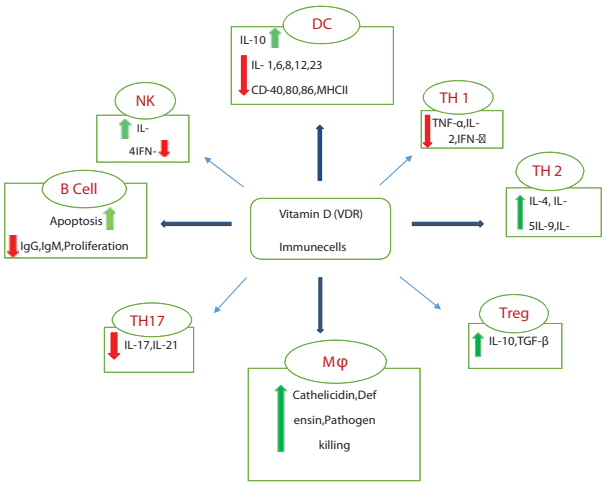

Figure 2: Schematic representation of the defense mechanism of Vitamin D in Immune Cells. DC: Dendritic Cells; TH: T Helper Cells; Mϕ: Macrophage; Treg: T regulator cell; NK: Natural Killer Cells; red arrow indicate-downregulation, green arrow indicate-upregulation.

development of inflammatory T-helper cells. 1,25(OH)2D and suppresses the responses mediated by Th 1 by repressing the production of inflammatory cytokines IL-2, IFN-γ, and TNF-α. Additionally, vitamin D promotes cytokine production by Th-2 cells (IL-4, IL-5). Vitamin D also promotes the induction of the T regulatory cells, which help to inhibit inflammatory processes and these cells promote the production of IL-10 and TGF-β [46-50]. Vitamin D affects dendritic cells by down-regulating MHC-II, costimulatory molecules (CD-40, 80,86), IL-12, IL-6, IL-8, IL-1, and upregulating IL-10, CD-74. Another target cell of vitamin D is the macrophage/monocyte, which is responsible for antibacterial and antiviral defense by promoting the secretion of antimicrobial products such as cathelicidin (hCAP18 and LL37) and β defensin. Cathelicidin neutralizes endotoxins and helps to reduce viral infections [51-59]. Furthermore 1,25(OH)2D, VDR complex acts on cathelicidin gene promotor vitamin D response elements to enhance transcription of cathelicidin [60-63]. The antiviral responses produced by host immunity try to limit viral spreading, and inflammation and remove infected cells. Vitamin D involves in immune system functions in response to viral infection generating both pro-inflammatory and anti-inflammatory cytokines. Further, these cytokine productions are down-regulated and upregulated against any foreign pathogen [64-68].

Clinch between hypovitaminosis-D and COVID-19

The recently evaluated mean levels of vitamin D in the population across ~40 countries, show more than 50% vitamin D deficiency [69]. The pandemic COVID-19 affected countries including India, which has a substantial population (~ > 75%) of vitamin D deficient. This deficit can be attributed due to major factors like sunlight avoidance, poor diet, and improper lifestyle [70,71]. In Europe, ~ 45% of the population is deficient in Vitamin D, and prevalence is higher in dark-skinned people compared to white sinned. Similarly, ~ 24% of US citizens and ~ 37% of Canadians are deficient in vitamin D [72-74]. Studies have recognized the association between vitamin D deficiency and viral respiratory infections. Meantime, systematic review and meta-analysis have concluded that vitamin D has potential in respiratory tract infections, especially in those who have a high level of Hypovitaminosis-D [75,76]. There could also be other correlations between vitamin D deficiency and health issues such as diabetes, hypertension, reproduction, and viral infections because vitamin D receptor is distributed in different tissues in the body [77-85]. In some clinical studies, low levels of serum vitamin D were associated with acute respiratory tract infections like influenza and the risk of community-acquired pneumonia. Some retrospective studies determined the correlation of vitamin D status with the severity and mortality of COVID-19 [86-88].

The SARS-CoV2 infects pulmonary epithelial cells using angiotensin-converting enzyme2 (ACE) receptors. Further, the macrophages, neutrophils, and T cells get activated through sustained elevation of cytokines including IL-1, IL-6, and TNF-α resulting in acute respiratory distress syndrome [89-91]. Vitamin D enhances the production of antimicrobial peptides like cathelicidin and β-defensin, which are key factors in immune responses in many respiratory diseases. The cytokines and antimicrobial peptides are responsible for some serious manifestations of COVID-19. But some recent studies have shown vitamin D enhances the expression of ACE2 and increase vascular endothelial growth factor production. A possible role of vitamin D in coronavirus infection based on its impact on innate immunity, adaptive immunity, and rearrangement of the immune response [92-95]. The multicentric study has suggested that whilst COVID-19 patients (vitamin D deficient) generally had poor outcomes, those with high levels of vitamin D fared better outcomes [96,97]. A review has concluded that there was substantial ecological evidence to correlate hypovitaminosis D with the severity of COVID-19 infections [98-100]. A study has observed that African Americans with vitamin D deficiencies as well as those with poorer COVID-19 outcomes may stand to benefit from supplementation. All the above studies suggested that vitamin D supplementation may help patients with COVID-19 [101-105].

The relationship of vitamin D with oxidative stress and cell apoptosis in COVID

$1,25(OH)_2D$ is involved in a variety of intracellular genomic activities as well as biochemical and enzymatic reactions, 25(OH)D concentrations are crucial for preventing inflammation, eliminating parasites and microbes that have invaded the body, reducing oxidative stress after routine exposure to toxins, and managing the aging process. For instance, a healthy level of 25(OH)D increases the expression of the nuclear factor erythroid-2(Nf-E2)-related factor 2(Nrf2) as well as Klotho, a hormone that regulates phosphate levels and an antiaging protein. Additionally, it aids in protein

stability [106]. The production of antioxidants is one of the cellular signaling systems that Klotho also controls. Therefore, the Klotho gene knockout method or functional defects of the Klotho gene in mice cause premature aging syndrome. Ineffective Klotho and/or FGF23 expression has been demonstrated to accelerate aging in animal experiments. One of the things that make this cycle of oxidative stress stronger and speed up premature cell death is a vitamin D deficit. Numerous intracellular oxidative stress-related activities are downregulated, and vitamin D level is acceptable. Serum 25(OH)D levels that are below ideal levels fail to control oxidative stress, increase intracellular oxidative damage, or slow down the pace of apoptosis. The level of intracellular Nrf2 is inversely linked with the buildup of mitochondrial ROS and the subsequent increase in oxidative stress. Thus, Nrf2 is essential for protecting cells from oxidative stress, which vitamin D regulates. The general positive effects of calcitriol include the upregulation of the expression of several antioxidant and anti-inflammatory cytokines, which shields the tissues from toxins, abnormalities caused by micronutrient deficiencies, and parasite- and intracellular microbe-induced damage. Through its anti-inflammatory properties and the mitochondrial-based expression of antioxidants via the cell signaling pathway, it controls ROS levels. Calcitriol controls the numerous roles of several of the genes in the Klotho-Nrf2 regulatory system. These include boosting the number of intracellular antioxidants, preserving redox equilibrium, and restoring the normal intracellular environment by eliminating excess ROS and so reducing oxidative stress. In addition, the expression of the important redox agent glutathione reductase, glutamate cysteine ligase, and -glutamyl transpeptidase is dependent on vitamin D. Additionally, vitamin D stimulates the production of glutathione peroxidase, which breaks down the ROS molecule H_2O_2 into water. Through the activation of the enzyme glucose-6-phosphate dehydrogenase, vitamin D also influences the production of glutathione by upregulating superoxide dismutase and downregulating nitrogen oxide, a potent precursor for the production of reactive oxygen species (ROS) that convert oxygen into H_2O_2 (SOD). Together, these vitamin D-related effects lessen the load of intracellular ROSs [107,108].

Microalgae as a potential source of vitamin D

Vitamin D plays a major role in the human body and is involved in maintaining calcium homeostasis. Moreover, its deficiency is associated with several disorders like osteoporosis, diabetes, cancer, hypertension, and autoimmune diseases [109]. So, it is very important to maintain Vitamin D levels in the body. Vitamin D is naturally synthesized in the skin when exposed to UVB radiations by chemical conversion of the precursors [110]. Limited exposure to sunlight, application of sunscreens, protective clothing, aging, and dark skin are some of the factors which affect the synthesis of Vitamin D in adequate amounts. So, the dietary supplementation of Vitamin D is essential to protect the body from the adverse effects of vitamin D deficiency [111]. Vitamin D is naturally present in the foods like milk, fish, eggs, meat, *etc.* Most of them are of animal origin and cannot be consumed by vegetarians and vegans. The nowadays vegan population is increasing and because they completely avoid animal products, their diet is usually protein and vitamin-deficient [112]. Therefore, there is a need for an alternate source of supplements that can be adopted by people including the vegan population. Microalgae are photosynthetic organisms with higher growth rates and minimal nutritional requirements. Microalgae remain a prominent source of vitamin D which can be used as a supplement to maintain a balanced diet as well as to resist viral diseases such as COVID-19. Moreover, the well-known source of vitamin D is fish, which acquire it through the food chain from algae due to its inability to de-novo synthesis [113]. Even though microalgae are found to be a prominent producer of vitamin D, their role in microalgal cellular functions is still not clear.

Microalgae are mostly found on stagnant water surfaces and it is assumed that exposure to sunlight, mainly UV-B causes Vitamin D production. Although microalgae are well known as a source of several bioactive compounds, vitamins, and proteins, using microalgae, particularly for vitamin D has been reported very recently [114]. Moreover, studies suggest that exposure of microalgae to UV-B enhances vitamin D production [115].

A recent study conducted in 2020 in which the vitamin D3/ cholecalciferol accumulation was assessed under different UVB intensities showed that *N. oceanica* exhibited the highest vitamin D3 buildup compared to other species studied. They also observed that the safe UVB dose range could vary according to species and going beyond the restricted UVB limit caused further damage to the respective microalgal cells [114,115]. Even though various experiments were conducted to detect Vitamin D production in microalgal species, some of the studies showed the vitamin D3 accumulation to be below the detection limits. A similar work conducted in 1996, examining vitamin D3 production in a mixture of microalgae such as *Scenedesmus, Chlorella, Cosmarium, Crucegenia, Oscillatoria, Gomphosphania, Gomphonema, Synedra, Navicula*, and *Cyclotella* indicated somewhat fair amount (~8µg/dry weight) of vitamin D3 accumulation [114,116] According to several other related studies, microalgal species like *Tetraselmis suecica (*14 µg/g dry weight), *Skeletonema costatum* (11 µg/g dry weight), *Isochrysis galbana* (5 µg/g dry weight), and *Pavlova lutheri* (39 µg/g dry weight*)* were found to be very prominent Vitamin D producing microalgae, even though some species like *Arthrospira maxima, Chlorella minutissima, Rhodomonas salina* showed very less vitamin D3 accumulation (less than 0.004 µg/g dry weight) in their cells [114,117,118]. So, microalgae can be cultivated on a large scale to commercialize them as a potent vitamin D supplement. However, increased intake of these vitamin D supplements higher than the recommended dose can result

in Vitamin D toxicity which is associated with asymptomatic hypercalcemia leading to the deposition of calcium in kidneys and arterial walls [119,120-127]. Hence, it is advised by health care professionals to intake these supplements not higher than the dosages suggested for respective age groups and physiques.

Conclusion

Most of the clinical data and experimental data demonstrate that vitamin D has a role in lung function and immune response against the foreign pathogen. Some other studies and randomized trials have shown that vitamin D has a protective effect on respiratory tract infections. Vitamin D deficiency may increase the risk of acute respiratory infections and also increase the risk of microbial infections and coronavirus disease. Immune dysregulation is a main feature of coronavirus disease. Their immune balance is important to prevent the hyper-inflammatory cytokine storm in COVID-19 severity and suppress acute respiratory distress syndrome. The role of vitamin D in reducing and modifying the inflammatory cytokine response of respiratory epithelial cells, macrophages, and other immune cells to various pathogens. The antiviral effect of vitamin D which can directly reduce viral replication is dependent on immune modulation and anti-inflammation. Evidently, vitamin D has shown a broad impact on immune cells in both the innate and adaptive immune systems. This is harmonious with the observation that the low status of vitamin D may contrarily impact the outcome of COVID-19 patients. A considerable drop in inflammatory markers and a higher percentage of asymptomatic vitamin D-deficient persons with SARS-CoV-2 infection were both made possible by high dosage, oral vitamin D supplementation to increase 25(OH)D > 50 ng/ml. Cholecalciferol supplementation may aid in lowering transmission rates of the extremely contagious SARS-CoV-2 illness by producing SARS-CoV-2 RNA negativity. It will be encouraging to reassure public health professionals about the higher risk of SARS CoV-2 RNA negative in people taking therapeutic cholecalciferol supplements. So, Vitamin D supplementation in corona-risk patients can maintain circulating 25(OH)D levels in the body and microalgae can be one of the potential sources. Moreover, it is relatively inexpensive, safe, and widely available and has also shown propitious effects against viral infections.

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Author contributions

NL and VKS conceptualized the manuscript. NL, AS, and SR collected the literature and prepared the draft of the manuscript. AKB edited and refined the draft critically. VKS and AKB supervised the writing process. All authors have read and agreed to the published version of the manuscript.

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