

Review Article**Does Vitamin D has Preventive or Treatment Potential to Covid-19 Illness?: A Brief Review**

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Abstract


The world's health in 2020 was in the grip of the COVID-19 pandemic and its adverse consequences and is still continuing in 2021. Most countries have been locked down or going through different forms of lockdown to prevent the transmission of the infectious virus SARS-CoV-2. To date, there is no specific treatment or vaccination preventive measures. World Health Organization has approved few vaccines for emergency use. Still, the emergence of mutations within SARS-CoV has put forward challenges for vaccine developers. Whether infectious or non-infectious, all diseases have an inflammatory aspect to alarm the body system along with an anti-inflammatory counterbalance mechanism to minimize harmful effects whether through immune modulation or antioxidant reserves. An approach to counteract the novel disease, COVID19, was also sought in enhancing the anti-inflammatory aspect, at the level of prevention and at the level of treatment. One of the methodologies was the recommendation of micronutrient Vitamin D whose immune-modulatory role has been well appreciated in many disease conditions. This short review aims to explore the relationship between vitamin D status through susceptibility and clinical outcomes of COVID-19.

Keywords: COVID-19 Pandemic, Immunity, Vitamin D deficiency

Introduction

The world is currently struggling to come out of the tight grip of the rapidly spreading coronavirus (CoV) infection. This is the third epidemic caused by the coronavirus, which has taken the face of pandemic within a very short period of time. Previous two pandemics include the severe acute respiratory syndrome (SARS)-CoV outbreak that occurred in Guangdong Province of China in 2002/03 [1] and the outbreak of the Middle East respiratory syndrome (MERS)-CoV

in 2012, Middle East [2]. SARS-CoV outbreak in Wuhan, Hubei Province, China, near end of the year 2019, was a novel corona virus and it was coined 2019-nCoV [3]. The name was later changed to SARS-CoV2 by the World Health Organization (WHO) on February 11, 2020. The disease as the result of SARS-CoV2 was called COVID-19. The current pandemic is believed to be a consequence of jump over of species barrier, which has proved too costly for human lives. The

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leading reason behind death after the COVID-19 infection is severe atypical pneumonia and respiratory failure[4].

The virus has spread cross borders, within community and again re-entry through mutation (as variants of concern). People suffering from chronic respiratory diseases, diabetes, cardiovascular diseases and the elderly above 60 years were at the highest risk in the first wave of COVID-19. The second wave scooped the adults above 30 years into the highest risk. Currently, there is neither specific treatment available nor any specific vaccine as preventive measure against the COVID-19 like other viral diseases (Hepatitis-B, polio, etc). Thus, researchers were searching for alternate ways to reduce the mortality rate. Several drugs such as hydroxychloroquine, dexamethasone, azithromycin, remdesivir, quercetin are being used for the treatment of the COVID-19 patients and adapted into treatment guidelines too in many countries. These drugs showed some clinical benefits. Recently, there has been a growing interest in the scientific community about the potential preventive and therapeutic benefits of vitamin D. Animal and clinical studies supported that vitamin D has anti-inflammatory and immunoregulatory effect and vitamin D appeared to be an attractive proposal for COVID-19 study [5,6]. In this review, we aim to explore vitamin D deficiency as a risk factor for COVID-19 as well as the potential role of vitamin D in the management and treatment of COVID-19 illness.

Vitamin D Metabolism

Vitamin D is a fat-soluble vitamin. It is synthesized by the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃) in the skin on exposure to the ultraviolet-B radiation [7]. The vitamin D₃ gets enzymatically converted to 25-hydroxy vitamin D (dihydroxycholecalciferol) in the liver, a storage form. Dihydroxycholecalciferol finally converts into 1,25-dihydroxy vitamin D (calcitriol), the active form in the kidney [7]. This active form of vitamin D, Calcitriol exerts its actions on the target tissues via specific nuclear vitamin D receptor (VDR) analogous to the steroid hormone receptors. The classic function of vitamin D is to maintain homeostasis of calcium and phosphate metabolism in conjunction with the parathyroid hormone (PTH) [7]. In addition to this classic function of calcium homeostasis, there is now increasing evidence suggesting the potential role of vitamin D in the regulation of the human immune system[7-9].

Vitamin D and the Immune System

Over the last decade, studies have highlighted the role of vitamin D in both innate and adaptive immunity. When a pathogen enters the human body, it comes across physical, chemical and immunological barriers that try to eliminate it [8]. When a respiratory pathogen enters human body, it comes in contact with the mucosal surface of the respiratory tract lined with ciliated epithelium. The ciliary movements are responsible for removal of the inhaled pathogens. The mucosal barrier is the physical barrier and also the first line of defense against SARS-CoV-2 [8]. Then second line of defense consists of antimicrobials like cathelicidins, defensins, lysozyme, lactoferrins and secretory leukocyte protease inhibitors [8]. Vitamin D has shown to upregulate the physical barrier functions as well as production of antimicrobial compounds [10]. Finally, the third line of defense is the initiation of inflammatory response [8]. Vitamin D is said to play a critical role in reducing the pro-inflammatory cytokines production [6] and probably suppressing the cytokine storm. Cytokine storm is an event associated with COVID-19 infection, in which a large amount of pro-inflammatory cytokines are released [11]. Thus, vitamin D is the upregulator of the innate and adaptive immune defenses.

Vitamin D and Innate Immunity

Innate immune defense players are natural killer cells, macrophages, neutrophils, dendritic cells, mast cells, basophils and eosinophils. This innate immune system cells consist of receptors, known as pattern recognition receptors (PRRs) that detect invading pathogens. Two main classes of PRRs are the toll-like receptors (TLRs) and nucleotide binding oligomerization domain (NOD)-like receptors [12,13]. Animal studies show that vitamin D signaling is active in innate as well as adaptive immune system [14]. Vitamin D activates Toll-like receptors (TLRs) on monocytes which upregulates the production of cathelicidins, peptides with antimicrobial function [15]. The only known human cathelicidin is hCAP18 (the C terminal domain of human cationic antimicrobial protein 18 or LL-37) which is encoded by cathelicidin antimicrobial peptide (CAMP) gene [16]. These peptides are found in the cells of macrophages and even in epithelial cells of skin, lungs and gastrointestinal tract. They are stored in lysosomes and disrupts microbial surface through ionic interactions with the pathogen surface bringing about antimicro-



bial effect [16]. Although vitamin D induces the expression of LL-37 along with TLRs in monocytes, LL-37 expression in the cells of respiratory epithelium and placenta is said to be TLR independent [16]. The transcription of LL-37 in the respiratory epithelium is probably enhanced by transcription factor C/EBP α [a CCAAT-enhancer-binding protein] and that C/EBP α functionally cooperate with VDR in the regulation of CAMP transcription [17]. Another antimicrobial peptide defensins, are cysteine rich cationic proteins. The production of antimicrobial defensin beta-4 (DEFB4) in monocytes is brought about by Interaction of 1,25-(OH) $_2$ D and VDR along with TLR and interleukin-1 β signaling pathway [18]. We see that both these major antimicrobials expressions require VDR activation [18]. Additionally, vitamin D may strengthened the innate immunity through the induction of reactive oxygen species and autophagy of the pathogens [19]. Thus, the strong evidence implicating vitamin D in the regulation of the innate immunity came from the study that identified vitamin D response elements located adjacent to the transcription sites of genes encoding CAMP and beta 2 defensin [20].

Vitamin D and Adaptive Immunity

Evidence supports that vitamin D boosts the innate immunity, but in the context of adaptive immunity, it shows the suppressive actions. Adaptive immune responses occur via either type-1 helper T-cells (Th1) or type-2 helper T-cells (Th2). Studies suggest that VDR-retinoid X receptor heterodimer blocks the NFATp/AP-1 complex formation and then stably associates with the NF-AT-1 element, thus suppressing the IL-2 production [21]. On the other hand, interferon- γ (INF- γ) suppression is also the direct effect of active vitamin D through the VDR/RXR binding of negative vitamin D response element on INF- γ promoter [22]. Thus, by suppressive actions on the Th1 cytokine production, the active metabolite of vitamin D helps to reduce cytokine storm.

In addition to the direct effect of vitamin D on Th1 suppression, it also helps in the activation of Th2 cells through various interleukins which may aid in indirect suppression of Th1 pathway through interaction between many cells, the outcome of which depends on physiological state [23]. A transcription factor Foxp3 which is responsible for the development and function of the regulatory T cells (Treg Cells) is upregulated by the active vitamin D [24]. Vitamin D suppresses

production of pro-inflammatory cytokines such as IL-17 by Th17 cells. The mechanism behind this inhibition may involve the blocking of nuclear factor for activated T cells (NFAT) and Runt-related transcription factor 1 (Runx1) binding to the IL-17 promoter and induction of Foxp3 [25] or the inhibition of the transcription factor ROR γ t which is essential for Th17 proliferation and differentiation [26].

The pro-inflammatory cytokine IL-12 repression and induction of anti-inflammatory cytokines IL-10 and IL-4 of Th2 cells are major effect of active vitamin D. VDR/RXR complex binds to the NF- κ B site in IL-12 promoter, inhibiting the activation by NF- κ B, thus, reducing the production of IL-12 [27].

Vitamin D and Antiviral Immunity

Once viral pathogens enter human body, they are first detected by pattern recognition receptors such as TLR3. This is followed by signaling cascades that lead to production of type 1 interferon, cytokines and other antiviral effectors [28]. Some epidemiological studies conclude that vitamin D reduces the rate of acute respiratory tract infections [29]. Available data suggest that vitamin D signaling enhances antiviral innate immunity, along with suppression of pro-inflammatory cytokine production. Hansdottir et al. showed that 1,25-OHD supplementation induced the expression of CAMP and CD14 and suppressed the pro-inflammatory NF- κ B signaling [30]. These antiviral mechanisms regulated by vitamin D may be of value in preventing or treating COVID-19 infection.

Vitamin D Status and COVID19: Biological Links

Given the roles of vitamin D in regulating immunity and wide spread vitamin D deficiency in old people, there is speculation that vitamin D supplementation might be a promising candidate in the management or prevention of COVID19 infection. However, clinical evidence demonstrating efficacy of vitamin D supplementation in the prevention or management of COVID-19 is lacking. We need large population based studies and RCTs to confirm the role of vitamin D in COVID-19 patients. A recent study in H5N1-infected mice showed decreased lung injury score, reduced lung edema and increased survival rate in vitamin D supplemented mice [31]. Above all, people with comorbid chronic conditions such as chronic obstructive pulmonary disease (COPD) and asthma are highly



susceptible to COVID-19 infection [32]. Epidemiological studies demonstrate people with these comorbidities have high vitamin D deficiency [32,33]. Whether vitamin D deficiency is a cause or consequence in these conditions is not clear.

Recent studies have demonstrated that people of any age with comorbid conditions of hypertension, obesity, diabetes, chronic lung and kidney disease, etc are at increased risk of SARS-CoV2 infection [42]. The S1 domain of the spike-glycoprotein of the COVID-19 interacts with the CD 26 cells of the humans for its virulence [34]. Earlier, MERS-CoV was found to use dipeptidyl peptidase-4 (DDP4) receptor, whose interactions with CD26 contributed to its virulence [35]. The adequate level of vitamin D was found to reduce the expression of receptors contributing to lowering the virulence [36].

Vitamin D is found to be a negative regulator of renin synthesis which reflects that high renin activity will occur in individuals with low serum vitamin D levels [37]. Renin converts the angiotensinogen synthesized by liver to angiotensin I (Ang I). Further, Ang I is converted to angiotensin II (Ang II) in the lungs and other tissues expressing the angiotensin converting enzyme (ACE). The Ang II is a potent vasoconstrictor responsible for increasing blood pressure. ACE2 is a homologue of ACE, which cleaves Ang I and Ang II, preferably Ang II, weakening the effect of Ang II. SARS-CoV2 virus interacts with ACE2 for initial binding in the respiratory epithelium [38]. ACE2 levels are found to be downregulated in SARS-CoV-2 patients as the virus spike proteins interact with ACE2 and internalize it. This leads to the upregulated expression of metalloproteinase (ADAM17) which sheds off ACE2 from cell membranes, thus reducing the counter regulatory action to renin-angiotensin system [39]. As a result, pro-inflammatory cytokines are released into the circulation via attenuation of ACE2, damaging the lungs (acute respiratory distress syndrome), blood vessels and heart, as observed in the COVID-19 patients. Studies have supported this supposed fact. According to the study done by Giacomo Grasselli et al. in Italy, out of 1043 SARS-CoV patients admitted to the ICU, hypertension was the most common comorbidity affecting 49% [95% CI (46%-52%)] of the total [40]. Another study from Wuhan, China also showed high prevalence of hypertension (55.6%), diabetes (30.6%), coronary artery disease and cerebrovascular disease (31.5%) in COVID-19 patients [41].

Is Vitamin D Deficiency a Risk Factor For COVID-19: Epidemiological and Clinical Evidence

The vitamin D has been found to be relatively deficient in all age groups [43,44]. With the start of winter, especially in northern but also in southern latitudes there are low ultraviolet-B radiation reaching the earth surface [44,45]. Thus, the synthesis of vitamin D in the skin is reduced. Another reason affecting the synthesis is the skin pigmentation and skin ageing [46]. Consequently, people who stay in door or quarantined for longer duration are at highest risk of developing vitamin D deficiency. Thus, adequate supplementation of vitamin D is essential for those who are severely deficient. In 2019, Mark Alipio et al. used logistic regression analysis to explore the link between serum vitamin D levels and clinical outcomes of patients infected with COVID-19 and it was found that serum 25(OH)D concentration was lower in critical cases compared with mild cases. Also, serum 25(OH)D concentration was found to be statistically significant among clinical outcomes of patients infected with COVID-19 [47]. Another strong support is provided by the study from Indonesia which reported that most of the COVID-19 patients who died had insufficient or deficient serum vitamin D levels [48]. More clinical studies in COVID-19 patients from Italy, Spain and France, also showed increase in case-fatality rate (CFR) with the increase in age and deficiency of vitamin D [49].

In contrast, a study from UK utilizing the UK Biobank that included samples from almost 350,000 people showed that serum vitamin D concentration was associated with COVID-19 infection univariably (OR=0.99, 95% CI, 0.99-.0999; p=0.013), but significance was lost after adjusting for confounders. The authors concluded that their findings didn't support the link between low serum vitamin D concentration and risk of COVID-19 infection. However, the UK Biobank samples were collected about a decade before the COVID-19 pandemic started, and therefore it may not recapitulate the actual serum vitamin D status just before the people were infected with COVID-19 [50]. Another study from US revealed an association between serum vitamin D concentration and SARS-CoV-2 positivity rates. The retrospective study utilized laboratory data from 191,779 patients tested for SARS-CoV-2. The serum vitamin D concentration data from these patients were from preceding 12 months. They found that SARS-CoV-2 positivity rate was higher in patients with



deficient serum vitamin D concentration (<20 ng/ml). Also, they found inverse association of SARS-CoV-2 positivity rates and serum vitamin D levels that persisted across latitudes, sexes, age ranges and races [51]. The findings from this study suggests that vitamin D deficiency may be linked to COVID-19 infection.

Is Vitamin D Supplementation Recommended to COVID-19 Patients?

As discussed in preceding section, there are studies that support and don't support vitamin D deficiency as a risk factor of COVID-19. There is plausible biological reasons to emphasize the benefits of vitamin D supplementation in COVID-19 patients because vitamin D has shown to promote mucosal immune as well as promote expression of ACE2, which is downregulated by SARS-CoV-2 [52]. According to the Institute of Medicine, the recommended daily allowance of vitamin D is 600 IU/day and 800 IU/day for young and adults respectively who do not belong to risk group [53]. According to a study done by Martineau AR et al, 4000 IU (100µg) of vitamin D supplementation for one year has found to significantly reduce the respiratory tract infection (RTI) [54]. Another analysis of vitamin D and RTI showed the reduction in infection with daily or weekly supplementation of vitamin D between dosage 20µg to 50µg [55]. Incidence of acute viral RTI was also found to be reduced in winter in temperate zones when the serum 25(OH)D level was maintained around 38ng/ml [56]. On the contrast, there is no recommendation of using the vitamin D for COVID-19 patients. Although, vitamin D concentration of 30 ng/ml (75nmol/L) is considered optimal, this is mostly relevant to its skeletal function [57], not in anti-inflammatory role. It is noteworthy that vitamin D toxicity is also not uncommon when more than usual daily supplement is taken without medical supervision [58].

Rigorous clinical trials showing efficacy of vitamin D supplementation in preventing or reducing the severity of COVID-19 illness are lacking. A published case study of 4 patients who were vitamin D deficient at the time of COVID-19 diagnosis, were supplemented with cholecalciferol 1000 IU daily or ergocalciferol 50,000 IU daily for five days. The supplemented patients had shorter hospital stay, improved clinical recovery and reduction in the inflammatory markers [59].

However, a hospital based study which recorded COVID-19 patients admitted taking vitamin D supplements and without taking supplements, showed no association of vitamin D supplement-

ation towards severity of COVID-19. In fact, they found more trend of mortality in the supplemented groups [60]. The limitation with this study are its small sample size, only severe cases of COVID-19 were admitted to the hospital and that could be the reason behind contrasting findings to the literature. Based on the available literature and clinical evidence, it is too early to clearly define the link between vitamin D and COVID-19. More well designed vitamin D supplementation trials in COVID-19 patients are required to validate this plausible link. In the meantime, in order to prevent further transmission and protect the vulnerable population, many countries have started the newly approved COVID-19 vaccines in their priority population.

By late 2020, WHO has already approved Pfizer/BioNTech, Sputnik Light, Covaxin and Astrazeneca vaccines while other vaccines remain in the pipelines for approval process [61,62]. As of today, the major vaccines currently being rolled out in the world are Pfizer/BioNTech, Oxford/Astrazeneca, Moderna and Sinovac [61]. There have been reports of side effects such as blood clots and reduced platelet counts after vaccination with Astrazeneca. However, WHO has recommended to continue roll out vaccination in the light of its tremendous protective benefits compared with very low side effects [62]. Whether the vaccines provide long term immunity and whether they will be able to provide immunity from the emerging new variants of concern [VOC], is a subject of wait and observation.

Conclusion

In the current COVID-19 pandemic, countries are bound to rely on preventive measures and newly developed vaccines. Several countries have already started national vaccination programs, and the number of people being vaccinated is increasing significantly. Vitamin D has shown some potential in strengthening the innate immunity and reducing severity in respiratory diseases. Thus, maintenance of adequate serum vitamin D level may be one way to prevent or fight with COVID-19 infection. However, currently available clinical and epidemiological data do not show significant benefits of vitamin D supplementation in COVID-19 patients. Randomised controlled trials with broad clinical outcomes must be conducted prior to recommending vitamin D supplement in the prevention, management or treatment of COVID-19 patients.

Conflict of interest: None



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