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## Short Communication

## Vitamin D Levels and COVID-19 Susceptibility: Is there any Correlation?

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## ABSTRACT

Coronavirus disease (COVID-19) is a major pandemic and now a leading cause of death worldwide. Currently, no drugs/vaccine is available for the treatment of this disease. Future preventions and social distancing are the only ways to prevent this disease from community transmission. Vitamin D is an important micronutrient and has been reported to improve immunity and protect against respiratory illness. This short review highlights the important scientific link between Vitamin D levels and susceptibility to COVID-19 in patients. This review also discusses recommendations for Vitamin D dose required for healthy as well as COVID-19 susceptible patients for protection and prevention.

## 1. Introduction

A third wave of coronavirus (CoV) infections has swept the world and brought it to its knees. This new CoV infection called as COVID-19 originated in Wuhan, Hubei Province, China in December 2019 [1]. The causative agent for this respiratory illness is severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) [2]. Previous epidemics of coronavirus include severe acute respiratory syndrome (SARS), which originated in China in 2002 [3] and the ongoing Middle East respiratory syndrome (MERS), first recorded in 2012 in the Middle East [4]. These epidemics have a high infection transmission rate and in general, the direct cause of death is severe atypical pneumonia [5]. The disease spread rapidly from the initial epicenter, Wuhan to rest of the world and has become a pandemic. A total number of 53,07,298 COVID-19 cases have been confirmed as of 25 May 2020 and more than 342,000 cases of deaths have been reported worldwide [6]. The main risk factors include pneumonia, acute kidney failure, acute heart failure. The global COVID-19 outbreak has placed devastating impact on every community. People with underlying health conditions such as cardiovascular disease, diabetes, chronic respiratory disease and the elderly above 60 years are most susceptible to COVID-19. There is currently no treatment available although vaccine development is under progress. This has led many researchers and clinicians to look for alternate or drug repurposing strategies that can lower the number of active COVID-19 cases and lead to subsequent reduction in the mortality rate.

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Vitamin D (Vit D) is a fat-soluble vitamin that plays major role in calcium homeostasis. It is synthesized endogenously in the skin when exposed to Ultraviolet-B (UV-B) radiations in sunlight. 1,25-dihydroxy vitamin D [1,25-(OH)<sub>2</sub>D] is the active form of Vit D [7]. Our body's innate and adaptive immune system provides protection against viral infections and aids in regulating cytokine levels in young and elderly populations, respectively. Vit D has been widely implicated in enhancing the immune response and suppressing the cytokine storm [8]. It's deficiency has been linked to increased susceptibility to viral infections [9]. In this short review, we hypothesize that correlation exists between vitamin D levels and susceptibility to COVID-19, and Vit D supplementation could decrease the risk and severity of COVID-19.

## 2. Mechanism for regulation of immunity in viral infections by Vitamin D

Immune cells have been known to express vitamin D receptors (VDR) and various immune cells (monocytes, dendritic cells, macrophages, B cells and T cells) are capable of converting 25-hydroxy Vit D (25OHD) into active form 1,25-(OH)<sub>2</sub>D. This permits local regulation of the 1,25-(OH)<sub>2</sub>D at the site of inflammation [10]. Binding of 1,25-(OH)<sub>2</sub>D to the VDR leads to translocation of the complex into the cell nucleus where it modifies the expression of hundreds of genes, including those for cytokine production [11]. The complex also induces the production of antimicrobial peptides including cathelicidin and defensins [12]. A study by Zhao et al [13] showed reduction in the replication of rotavirus both *in vitro* and *in vivo* by administration of Vit D at dose of 5000 IU/kg. Induction of cytokine storm is reduced by Vit D. The innate immune system generates both pro-

inflammatory and anti-inflammatory cytokines in patients suffering from COVID-19 [14]. Vit D can decrease the production of T helper cell type 1 (Th1) cytokines such as interferon- $\gamma$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [15]. Also, expression of pro-inflammatory cytokines by macrophages is reduced and anti-inflammatory cytokines is increased by Vit D administration [16].

Binding to dipeptidyl peptidase-4 receptor (DPP-4/CD26) is one of the molecular virulence mechanisms employed by CoV [17]. It has been demonstrated recently that human DPP-4/CD26 interacts with the S1 domain of SARS-CoV-2 spike glycoprotein [18]. In this context, fulfilment of Vit D deficiency has been shown to remarkably reduce expression of DPP4/CD26 receptor *in vivo* [19]. Vit D has been demonstrated to be a strong inducer of autophagy [20] and study by Campbell et al [21] reported inhibition of HIV replication in macrophages via VitD-mediated induction of cathelicidin, perhaps by enhancing autophagy and phagosomal maturation.

### 3. Role of Vitamin D deficiency in COVID-19 and dose recommendations

Vit D deficiency is a global health problem common among all age groups [22]. Negligible UV-B radiations reach the earth surface during winters at latitudes  $> 40^\circ$ . This increases the risk of Vit D deficiency during wintertime [22]. Epidemiological evidence suggests that during first month of winter, influenza infection is most common worldwide when Vit D levels are at their minimum [23]. Sufficient Vit D levels have shown to safeguard against influenza and respiratory syncytial virus (RSV) infections [24]. Also, serum 25-hydroxy Vit D levels tend to drop with age [25]. This is important with regard to COVID-19 as case-fatality rates (CFRs) surge with age [26]. Bergman et al [27] conducted a meta analysis of randomized controlled trials (RCT) of Vit D for prevention of respiratory tract infection (RTI). They demonstrated that risk of developing RTIs is reduced by prophylactic administration of Vit D (odds ratio: 0.64; 95% CI: 0.49 to 0.84). Rhodes et al [28] highlighted relationship between mortality from COVID-19 per million of population and countries based on their latitudes. It was observed that countries lying below  $35^\circ$  North latitude have low mortality rates. This could be attributed to the fact that people living in countries lying above  $35^\circ$  North do not encounter adequate sunlight during winter and suffer from Vit D deficiency. Likewise, Daneshkhan et al [29] showed that the age-specific case fatality rate (CFR) of COVID-19 was highest in Italy, Spain, and France where severe Vit D deficiency (mean 25OHD concentration  $< 0.25$  ng/L) is reported in comparison to other countries. In elderly population, overactivation of adaptive immune system results from a shortage of memory B cells and aberrant innate immune response, which leads to cytokine storm as observed in COVID-19 patients [30]. In another study, Lau et al [31] assessed 25OHD levels in twenty COVID-19 patients admitted in intensive care unit (ICU). 11 subjects had Vit D insufficiency (VID) and all patients below 75 years of age had VDI. Among these, 7 patients had  $< 20$  ng/mL and three had  $< 10$  ng/mL of 25OHD levels. This study demonstrated that VDI intensifies COVID-19 severity. A retrospective multinomial logistic regression study by Alipio [32] on data of 212 COVID-19 patients in south-Asian countries, suggests that increase in serum 25OHD levels could improve clinical outcomes. Statistical analysis was carried out using Mann-Whitney U and  $\chi^2$  tests. As the severity of disease increased from mild to critical, serum 25OHD levels decreased from 31.2 ng/ml to 17.1 ng/ml and were statistically significant with clinical outcomes ( $p < 0.001$ ). Out of 212 patients, 80 exhibited Vit D insufficiency (25 OHD  $< 21$ -29 ng/ml) and 77 exhibited Vit D deficiency (25 OHD  $< 20$  ng/ml). The odds of having mild clinical outcome increases and critical outcome decreases (OR = 0.051,  $p < 0.001$ ), with increase in serum 25 OHD level.

Above mentioned studies clearly indicate that having Vit D deficiency predisposes sensitive population (elderly and individuals with underlying health conditions) to an attack by its own immune system and exacerbate the RTI by damaging the lung tissue. Therefore, in order to maintain an appropriate Vit D status and reduce the mortality, supplementation is needed to restore the Vit D levels reduced due to inadequate exposure to sunlight.

There is currently no scientific consensus about the optimal dose of Vit D supplementation for COVID-19. Currently, The Institute of Medicine has placed the recommended dietary allowance, or RDA, for vitamin D at 600 international units (IU) per day for young adults and 800 IU per day for adults older than 70 years [33]. But this recommendation was issued in context with bone health. Based on observational studies, concentrations of at least 40-50 ng/mL are desired [34]. Another study reported that 38 ng/mL was suitable for reducing the risk of community acquired pneumonia [35]. In order to achieve the above concentration range, dose of 2000-5000 IU/day of Vit D<sub>3</sub> could be taken [36]. A study reported increase in 25OHD concentrations from  $20 \pm 6$  to  $39 \pm 9$  ng/mL for 4000 IU/day and from  $19 \pm 4$  to  $67 \pm 3$  ng/mL for 10,000 IU/day for 8 weeks administration of Vit D [37]. The U.S. Institute of Medicine noted that for daily doses of  $< 10,000$  IU/day no adverse effects have been reported for Vit D supplementation. However, the value for upper limit (UL) was corrected to 4000 IU/day based on all-cause mortality and chronic disease outcomes [33]. So, we recommend that keeping daily dose of Vit D below 4000 IU/day could be beneficial in improving the immunity to combat COVID-19 infection more effectively.

### 4. Conclusion

Dearth of treatment for COVID-19 leaves us with no choice but to take precautionary and prophylactic measures to stand a better chance to fight this pandemic. Hence, maintaining adequate Vit D levels is vital to prevent getting infected or to ward off the infection without mortality, in case it occurs. Clinical trials should be conducted in regard to COVID-19 for assessing the effect of Vit D supplementation and determining the appropriate dose. We conclude that correlation exists between Vit D levels and COVID-19 susceptibility and Vit D could prove to be an essential element in our fight against COVID-19.

### Credit author statement

DS and KS conceived the idea for the paper. DS, KS and KR wrote the whole draft. KR edited the draft and approved for the final submission.

### Declaration of interest statement

The authors hereby declare that they have no conflict of interest

### Ethics Information

No animals or human experiments were performed for this study

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