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**Review Article**

# Vitamin D and COVID-19

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## ABSTRACT

The ongoing COVID -19 pandemic is caused by severe acute respiratory syndrome corona virus -2 (SARS-CoV-2). Since its emergence in Wuhan in Hubei province of China in December 2019, the virus has spread to every continent except Antartica. Currently, there is no registered treatment or vaccine for the disease. In the current scenario of the deadly virus spreading across continents and the absence of a specific treatment of novel corona virus, there is an urgent need to search for alternative strategies to prevent and control the rapid replication of virus. Vitamin D supplementation may reduce the incidence, severity and risk of death from pneumonia (consequent to the cytokine storm) in the current COVID pandemic. Through its effect on innate and adaptive immunity, vitamin D can reduce the risk of viral respiratory tract infections. 1, 25(OH) vitamin D directly stimulates the production of anti-microbial peptides like defensin and Cathelicidin that can reduce the rate of viral replication. In addition, it can also reduce the concentration of pro-inflammatory cytokines that are responsible for causing cytokine storm and resultant fatal pneumonia. In order to reduce the risk of infection especially in developing country like India, it is recommended that people at risk of COVDI19 may be considered for vitamin D supplementation.

**Keywords:** Cathelicidin, Defensin, Novel corona virus, Vitamin D

## INTRODUCTION

After the first recognition of COVID-19 case in China in December 2019, it continues to spread around the world and the World Health Organization declared it a pandemic on 11th March 2020.

Vitamin deficiency is also now recognized as a pandemic that afflicts more than 1 billion people worldwide. There has been association of vitamin D deficiency with a myriad of acute and chronic disorders including type 2 diabetes mellitus, heart disease, stroke, autoimmune diseases, asthma and respiratory tract infections.[1,2] Reduced vitamin D status in calves had been reported to cause infection with bovine diarrhea virus.[3]

### *Historical perspective of vitamin D*

The discovery of vitamin D had a very long journey spanning several centuries and involving several research teams, all of which cannot be elaborated upon here due to constraints of space and time and the same has been briefly summed up in Table 1.[4-6]

In the mean-time a new cure for rickets had appeared and that was the UV light. Hess and Unger in 1921 explained that the seasonal incidence of rickets was due to seasonal variation in sunlight.[7]

Huldschinsky argued that if sunlight can prevent rickets then artificial light should also do so. He exposed rachitic

children to irradiation with quartz mercury lamp emitting UV light.[5]

In 1925, Hess along with his team isolated sitosterol (then called phytosterol) from cotton seed oil. What they discovered was that sitosterol was inactive against rickets in rats but upon irradiation by UV Light it becomes active. With their amazing foresight, Hess and his group proposed the hypothesis that it would seem quite possible that cholesterol (what we now call 7 dehydro cholesterol) in the skin is activated by UV light.[8]

Hess then collaborated with the famous German steroid chemist Adolf Windaus to understand the chemical structure of anti-rachitic factor formed by irradiation of UV light.[5]

**Table 1: Historical perspective of vitamin D.**

| Year | Discovery |
|---|---|
| 1650 | Francis Glisson recognized rickets as a childhood disease[4] |
| 1822 | Sniaderki reported the association between rickets and lack of sunlight exposure [5] |
| 1849 | Williams reported improvement in pulmonary Koch patients with cod liver oil (vitamin D)[6] |
| 1914-1922 | Elmer McCollum demonstrated anti-rachitic properties of fat-soluble factor now known as vitamin D[5] |

**Tale 2: Effect of vitamin D on immunity.**

| Effect on innate immunity | Effect on adaptive immunity |
|---|---|
| 1. Increased serum levels of AMP | |
| a) Defensins | Increase in regulatory cells |
| b) Cathelicidins | |
| 2. Increase in autophagy | Increase in t-helper cell type 2 |
| 3. Increase in cytokines | |
| a) Interleukin-6 | Increase in anti-inflammatory cytokines |
| b) Interleukin-8 | |
| | Decrease in proinflammatory cytokines |

AMP-Anti-Microbial Peptide

Adolf Otto Reinhold Windaus was awarded the Nobel award in 1928 for his work on vitamin D and elucidation of structure of cholesterol.

Another point worth mentioning here is that Windaus was a man of profound consciousness as he refused to carry out research on poison gas. It is also significant to mention that he stopped all scientific research in 1938 at the age of 62 even though he did not retire till 1944.[9]

***Vitamin D deficiency and tuberculosis***

Patients with tuberculosis have lower serum vitamin D levels than the general population. The use of vitamin D for tuberculosis started in 1849, with the observation that oil from fish liver improved appetite and strength.

In southeast countries including India, TB is a major public health problem. A study among the Vietnamese population in the city of Ho Chi Minh reflected that low vitamin D status is an antecedent risk factor of tuberculosis.[10]

A study by Gibney confirms strong association between vitamin D deficiency and latent tuberculosis infection in African migrants in Melbourne.[11] Vitamin D supplementation can safely and effectively increase proportion of sputum smear and culture conversion.

***Role of vitamin D in immune system in tuberculosis***

Vitamin D and its active metabolite 1,25 hydroxy vitamin D affect the activity of immune system in a number of different ways. Adams and his colleagues suggested that Cathelicidin and defensin are two anti-microbial peptides, which are strongly up regulated by 1,25 hydroxy vitamin D.[12] Cathelicidin have direct anti-microbial function against mycobacterium. In addition to antibacterial effect including membrane disruption, they have antiviral effects and they are known to inhibit herpes simplex virus, adenovirus and retrovirus.

***Vitamin D deficiency and respiratory tract infections including COVID-19***

COVID-19 is a respiratory infection caused by severe acute respiratory syndrome-associated corona virus SARS-COV-2. It causes flu like symptoms, which includes fever, dry cough, shortness of breath, body aches, loss of smell and fatigue.[13] The severity of COVID-19 illnesses can range from very mild to severe.

Some people may not develop any symptoms and serve as asymptomatic carriers of infection while the older people or those with pre-existing co-morbid conditions like heart disease, lung disease, diabetes or those who are immune compromised may develop a fatal illness. Acute respiratory tract infections are a major cause of global morbidity and mortality especially in those who are deficient in vitamin D.[14]

Vitamin D sufficiency decreases the risk of developing respiratory tract infections by the two main mechanisms:

- Vitamin D enhances the production of anti-microbial peptides (AMP) such as Cathelicidin and defensin.
- The second mechanism by which vitamin D reduces the risk of microbial infection and death is that vitamin D enhances natural cellular immunity.

The world right now is struggling to control morbidity and mortality due to COVID-19 Pandemic which began in the City of Wuhan, in Hubei Province of China. This is the 3rd Coronavirus, which has infected the world after SARS-CoV, which started in China in 2003, and MERS-CoV, which started in the Middle East in 2012. The cause of deaths in all these corona virus infections was pneumonia and ARDS. Scientists and researchers across the world are looking for ways and methods to reduce the risk of pneumonia in those at risk of COVID-19. Vitamin D known historically for its action on bone mineral metabolism also has immunomodulatory and anti-infective actions, and can be used as a possible adjuvant for both treatment and prevention of viral respiratory tract infections including COVID-19.

### *Vitamin D as an anti-infective agent*

Activation of pathogen recognition receptors on the respiratory epithelial cells is the most important step to limit viral spread. Pathogen recognition receptors are expressed on dendritic cells, macrophages, neutrophils and epithelial cells. Stimulation of pathogen recognition receptors leads to production of cytokines and anti-microbial peptides (AMP) such as Cathelicidin and beta defensin. These anti-microbial peptides serve as the first line of defense. Vitamin D enhances the production of these anti-microbial peptides (AMP) such as Cathelicidin and beta defensin. Vitamin D also enhances the chemotaxis and phagocytic capabilities of innate immune cells.[15,16] Lang and Samaras also showed the production of Cathelicidin is dependent on 1, 25 (OH) vitamin D. They showed that a serum concentration of Vitamin D in range of 30 ng/ml was necessary for optimal induction of Cathelicidin.[17]

### *Vitamin D and enhancement of cellular immunity*

COVID-19 is associated with release of proinflammatory cytokines (IL-2, IL-7, tumour necrosis factor-α) what is called as the cytokine storm. The release of pro-inflammatory cytokine by the virus also correlates with the severity of disease. Huang has reported that ICU patients in Wuhan showed higher plasma level of IL-2, IL-7, IL-10, TNF- α than non ICU patients suggesting that immunopathology may be playing a significant role in disease severity.[13] Vitamin D enhances the cellular immunity and reduces the cytokine storm induced by the innate immune system. Vitamin D can reduce the production of Pro-Inflammatory cytokines such as TNF-α and interferon γ.[14-16] Literature is full of reviews that conclude that vitamin D reduces the risk of viral infections through its action on immune cells.[16-20]

Actually, vitamin D can modulate the innate and adaptive immune response and I have tried to summarize this in Table 2

A recent review by Grant et al states that, during the COVID-19 epidemic, all people in the hospital, including patients and staff, should take vitamin D supplements to raise 25(OH)D concentrations as an important step in preventing infection and spread. Trials on this hypothesis would be worth conducting.[21]

## DISCUSSION

Vitamin D has important functions beyond those of calcium and bone metabolism that include modulation of the innate and adaptive immune responses. At least 1 billion people globally have vitamin D deficiency. Vitamin D deficiency and insufficiency makes our population more vulnerable and more susceptible to develop infectious diseases especially respiratory infections. Until a COVID-19 vaccine or a therapeutic agent is discovered, we can use vitamin D as an adjuvant for both treatment and prevention of respiratory tract infections like COVID-19. The beneficial effect of vitamin D supplementation as an adjuvant in COVID-19 can be due to a combination of anti-infective, immunomodulatory and anti-inflammatory effects.

Based on the current evidence of high prevalence of vitamin D deficiency in Indian population and also considering its benefit risk ratio, vitamin D supplementation can be and must be considered for infection prophylaxis. In 2011, the endocrine society recommended supplementation 1000-4000 IU of vitamin D per day and a serum concentration of 30 ng/ml or higher.[22] Grant, in the latest review recommends that testing for vitamin D status should be done only in a select group of patients that includes pregnant women, obese and elderly individuals and those suffering from other medical co morbid conditions.[23] The increase in vitamin D concentrations with respect to oral vitamin D supplementation depend on certain factors like the ability of assimilation by the gastrointestinal tract, body weight, genetic factors and the baseline 25(OH) vitamin D concentration. Given the extent of vitamin D deficiency taking 5000 IU of vitamin per day may be needed to raise 25 (OH) vitamin D levels to 40 ng/ml.[24]

## CONCLUSION

In summary, while the research has yet not proved that vitamin D is effective against the novel Corona virus, it does show that vitamin D helps to protect against respiratory tract infections. Vitamin D may have a role to play in suppressing the cytokine storm and thereby reducing the morbidity and mortality due to COVID-19.

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