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Relation of vitamin D to COVID-19

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ABSTRACT

The coronavirus pandemic has lasted for more than a year now and still remains the leading cause of concern, worldwide. The causal agent; SARS- CoV-2, leads to the development of respiratory distress in the lower respiratory tract, sometimes leading to fatalities. Keeping in mind the discovery of mutant strains across the world, as well as the delay in vaccinations across vast populations, most people speculate boosting their immune systems as a preventive and precautionary measure. One of the most commonly observed conditions that hamper immunity; Vitamin D deficiency has been linked to the onset and the alteration of course of the disease in patients and is also being explored as a potential drug supplement. These surmises make it essential to study deep into the speculations. This review aims to overview the possible correlations between Vitamin D and COVID-19.

1. Introduction

Vitamin D or calciferol is an immunomodulatory substance that is obtained generally from exposure to sunlight and some foods. When obtained from sun exposure, it is inactive and must undergo conversions; first to calcidiol [25(OH)D] and then into calcitriol [125(OH)2D]. Due to different geographical locations, occupations, and socio-economic backgrounds, different population groups have different levels of sun-absorbed vitamin D. Food products like fish and meat also harbor two main forms of this component namely, D2 (ergocalciferol) and D3 (cholecalciferol). Levels of vitamin D are generally measured by the serum concentration of 25(OH)D. People who qualify as deficient show less than 12 nG/mL of vitamin D. Apart from maintaining bone health; vitamin D has been reported to influence many other health conditions including respiratory health. Deficiency in vitamin D has been associated with decreased lung function. Besides, deficiency in vitamin D is also reported to increase the risk of respiratory infection with Influenza A and *Mycobacterium tuberculosis* (Finklea et al., 2011).

Covid-19 is caused by SARS-CoV-2, an RNA virus transmitted through respiratory droplets. The spike protein present on the surface of SARS-CoV-2 binds to the ACE2 (angiotensin converting enzyme) receptor on the host cells of the nose and respiratory tract. Immune response against the virus includes uncontrolled non-specific inflammation and cytokine release which cause injury to lung and other vital organs. Vitamin D has been noted to inhibit the pro-inflammatory cytokine secretion and manipulate the ACE2 receptors through which the virus manifestation spreads apart from being an immunomodulator that affects both innate and adaptive immune responses. A study conducted by Radujkovic on 185 hospitalized and home quarantined subjects showed a clear inverse relationship between the magnitude of the disease and the levels of vitamin D on admission. Out of these, 50 % who were hospitalized showed characteristic Vitamin D deficiency (i.e, vitamin D levels less than 12 ng/mL) as compared to the 50 % outpatients. This inpatient cohort also sustained more cases of oxygen therapy along with invasive mechanical ventilation and death. The study concluded that there was noted a 6 fold higher hazard of developing severe disease and a whopping 15 fold higher risk of death due to disease (Radujkovic et al., 2020). Another study by Meltzer et al. concluded that the risk of contracting the virus was 1.77 times higher in patients with vitamin D Deficiency (Meltzer et al., 2020a). Kaufman and colleagues elucidate an inverse relationship between the level of vitamin D and SARS-CoV-2 positivity rate. People with less than 20 ng/mL of Vitamin D showed 54 % higher SARS-CoV-2 positivity rates when compared with the test population having Vitamin D levels higher than 55 ng/mL (Harvey et al., 2020). The study concludes that an increase in the serum levels of 25(OH)D in patients decreased the risk of developing severe ramifications of the coronavirus.

2. IMMUNOPATHOGENESIS IN SARS-CoV-2

Immunopathogenesis of SARS-CoV-2 begins with its attack on the epithelial cells of the respiratory tract followed by its carriage to the nasal, bronchus, and mucosa-associated lymphoid tissue (NALT, BALT, MALT) for colonization and infiltration. The most highlighted

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complications of COVID-19 arise due to an increased amount of cytokines in the body. This exceptional release of pro-inflammatory cytokines is known as a cytokine storm.

According to Fiorino et al., the release of cytokines can be studied as a property of the virus' N Protein (Fiorino et al., 2020). Direct binding of spike viral protein to the NF-kB subdomains can induce synthesis of interleukins 17, 6, 8,1, and TNF alpha. Binding of virus to TLR of immune cells releases pro-IL-1β. Fever, fibrosis, and inflammation result from the cleavage-based activation of this interleukin. Whereas, binding of viral N protein AP-1 (Activator protein 1) can activate the IL-1 gene transcription which leads to the release of the pro-inflammatory IL-1 alpha. By activation of the COX-2 genes, SARS-CoV-2 can induce IL-8 which can create a local inflammatory environment and elevate the inflammatory response. This entire process has been pictorially described in Fig. 1

An exceptional correlation can be traced between the higher mortality due to COVID-19 in males above 50 years of age and difference in sex hormones between the two genders. Papadopoulos concluded a clear gender-based miasm to COVID-19 which may have roots in presence of low testosterone levels characteristic of older aged males. They suggest that the low levels of testosterone in older males developed severe ARDS, sepsis and hence account for more fatalties. (Papadopoulos et al., 2021) Salah et al. hypothesise that the worse outcomes of COVID-19 observed in males suffering from hypertension or heart conditions are due to the higher activity of serum ACE2 (Salah and Mehta, 2021). Another conclusion notes the anti inflammatory role of estrogens found in higher quantities in women by virtue of sex. They also hint at a potential shielding role of estrogen as it decreases the COVID-19 infection by modulating the pro-inflammatory signaling pathways (Al-Kuraishy et al., 2021). Bennink et al. note that the most pronounced difference between female and male patients (especially over the age of 50 years) is the manifold increased testosterone in men as compared to women. The reason for considering testosterone suppression as therapy for COVID-19 is due to its role in entry of virus via host cellular protein TMPRSS2 which is an androgen-regulated protease that primes the viral spike protein. Another alternative is to explore the potential of estrogen therapy as it is linked to stimulation of antibody production along with the reduction of innate immunity and cytokine storms (Coelingh Bennink et al., 2021).

3. The immunomodulatory function of Vitamin D on CYTOKINE STORM

SARS-CoV-2 is an infective agent that attacks the human body by manipulating the cytokine components of its immune system. Overwhelming levels of pro-inflammatory cytokines such as the IL-1, IL-6, and TNF alpha have been noted to cause severe complications of COVID-19 in form of ARDS (acute respiratory distress syndrome.) Mohan and colleagues explicate that the activity of vitamin D is much like a double-edged sword as it lowers acquired immunity while elevating innate immunity as their dominant function (Mohan et al., 2020). Subsidiary to this dominant enhancement of the innate immune system, it has also been opined that Vitamin D plays an efficient role in the regulation of adaptive immunity (Bishop et al., 2020; Kumar et al., 2021). This is achieved mainly due to the involvement of 1,25D in the regulation of T cell phenotypes, principally the naive Th cells. They also act on cytotoxic cells like the CD8+ cells and also promote the suppressor T regulatory cells (Chun et al., 2014). Murdaca concluded that the upregulation or increased production of anti-inflammatory cytokines and Th2 cytokine ultimately leads to Th1 inhibition. They also propose the down-regulation of Th1 cytokines like TNF-alpha and IFN-gamma which are pro-inflammatory in nature (Murdaca et al., 2020). On one hand, it reduces the levels of pro-inflammatory cytokines by shifting proliferating T cells from Th1 to Th2 which protects the system from causing immune-mediated injury. Vitamin D has been studied to downregulate the TH1 cytokines such as the IFNγ along with repressing the effector T cell differentiation which results in decreased release of IL-12. Daniel and colleagues note that this micronutrient also restrains differentiation of naive TH-o cells into TH-17 cells, therefore, preventing the release of pro-inflammatory cytokines (Daniel et al., 2008). On the other hand, Vitamin D causes inflammatory Th17 cells to convert into anti-inflammatory regulatory T Cells which augments anti-inflammatory cytokines such as IL-10. Hetta et al. suggest that vitamin D deficiency may show manifestations in form of coagulopathy, heart failure, or ARDS. They also conclude that the circulating calcitriol inflates the expression of vitamin D receptors in B cells which brings about the enhanced production of IL-10 by the suppression of IgE release (Hetta, 2021). Etten et al. noted that the decrease in IFNγ is characterized by a subsequent increase in IL-4. Similarly, the decrease in IL-12 levels is followed by an increased concentration of IL-10 (Etten and Evelyne, 2019). As elucidated by Penna et al. it also enhances the proliferation of FOXP3 and T regulatory cells which are immunosuppressive in nature, i.e., they decrease inflammation (Penna et al., 2005).

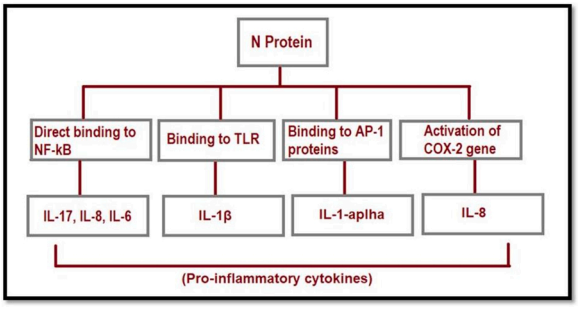

Fig. 1. Pathways of cytokine release due to binding of N viral spike protein.
The viral genome of the corona virus shows presence of four structural proteins, which are the Envelope Protein (E), Membrane Protein (M), Spike Protein (S) and the Nucleocapsid Protein (N). Out of these four integral proteins, the binding of N Protein to different bodily targets marks a prominent release of pro inflammatory cytokines such as the IL-17, IL-8, IL-1-alpha, and the IL-1 beta.

4. Effect of Vitamin D on Ace 2 RECEPTORS

Angiotensin-converting enzyme (ACE) 2 is a homolog to the carboxypeptidase ACE, which generates angiotensin II, the main active peptide of renin-angiotensin system (RAS). It has been determined that ACE2 receptors have a key role in the pathogenesis of SARS-CoV-2. It is postulated that by the use of its spike proteins, the virus gains access to the host body in the epithelial lung cells. The binding of the virus to ACE2 decreases receptor expression and leads to pneumonia and lung injury. Hence the blocking of this receptor is under consideration as a therapeutic strategy. In a study by Xu et al., vitamin D has been shown to modulate and downregulate the activity of ACE2 receptors (Xu et al., 2017). Arboleda and colleagues conclude vitamin D which acts as a negative modulator of the Renin-Angiotensin System (RAS) suppresses the RAS via the canonical Vitamin D receptor pathway (Arboleda and Urcuqui-Inchima, 2020). Mahdavi et al. affirm that vitamin D inhibits the AT1R/Classical Axis pathway while promoting the MasR/ Alternative Axis pathway of RAS. As a result, it increases the expression of ACE2 along with Ang-(1–7) and MasR (Mahdavi, 2020). The inflation of these key players of the RAS prevents acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). The outcomes of both axes are delineated in Fig. 2. Arboleda and colleagues noted that the administration of vitamin D supplements can prove to hamper SARS-CoV-2 pathogenesis in the body by downregulating the ACE-2 receptors (Arboleda and Urcuqui-Inchima, 2020).

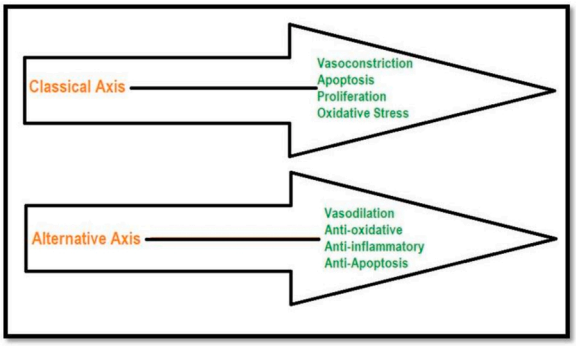

Fig. 2. Outcomes of Classical and Alterative Axis of the RAS.
The signal transduction in the renin angiotensin system is modulated by two pathways; namely the AT1R Axis and the Mas Axis. The ACE2 receptors are a vital part of both these pathways and hence can be treated as potential targets. While the classical axis leads to outcomes like oxidative stress and neuro-inflammation which can further worsen the covid situation, the alternative axis leads to decrease in inflammation and fibrosis.

5. Effect of vitamin D deficiency on C reactive protein

C reactive protein is a pentameric protein indicative of inflammation in the body when found in higher than normal levels in the blood. CRP is a hepatic origin protein, the levels of which have been seen to remain inflated in cases of H1N1 influenza, avian flu H7N9 (Wu et al., 2016), as well as COVID-19 (Zhang et al., 2021). Low-grade inflammation and thus increase in CRP levels are usually observed in people who suffer from vitamin D deficiency. A clearer outline of this inter-connected mechanism running between CRPs and Vitamin D has been outlined in Fig. 3. Daneshkhah and colleagues have postulated that due to increased low-grade inflammation in vitamin D deficient patients of ages 60 and above show 34 % more incidences of high CRP (Daneshkhah et al., 2020). It is hence predicted that enhancement in levels of vitamin D can reduce risks associated with cytokine storm and CRP in severe COVID-19 patients.

6. Vitamin D as potential drug supplement to COVID-19 patients

A systemic study of over 36 individual studies by Kazemi et al. reflected a clear link between Vitamin D deficiency (VDD) and composite severity of the disease. These individual studies evaluated the statistical correlation by studying VDD in Covid patients, comparing Calcifediol concentrations in healthy and diseases subjects, relations between the requirement of ICU facility and VDD, or the link between VDD with indicators of pulmonary complication, etc. All studies showed that the severity increased in groups that had Vitamin D deficiency (Kazemi et al., 2021). Several studies have demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia. It has been reported that vitamin D is involved with direct inhibition of viral replication or with anti-inflammatory or immunomodulatory ways. In the meta-analysis, vitamin D supplementation has been shown as safe and effective against acute respiratory tract infections. It has been observed that vitamin D-deficient individuals have increased COVID-19 risk and mortality (Sanders et al., 2020; Illie et al., 2020; Meltzer et al., 2020b). This statement can be supported by the findings of Merzon et al. in their study on a test population of 7807 people all of whom had been tested for vitamin D plasma levels at an earlier time and then for covid-19. It was noted that in the 10.02 % population that tested positive, the plasma level of Vitamin D was significantly reduced as compared to the 89.98 % population that tested negative (Merzon et al., 2020). French et al. also propose that the proportion of vitamin D found circulating in a person's body could be affected by diurnal rhythms (showing variance with the time of sample collection) and acute illnesses (which lower serum levels of 25-hydroxyvitamin D) (French et al., 2019). Jain et al., have analyzed the vitamin D level among asymptomatic and critically ill COVID-19 patients and have also studied its correlation with inflammatory markers (Jain et al., 2020). They have shown that the vitamin D level is markedly low in severe COVID-19 patients. It has also been noticed that vitamin D deficient COVID-19 patients had a high inflammatory response. This all promotes increased mortality in vitamin D deficient COVID-19 patients. Similarly, a greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation (Rastogi et al., 2020). A pilot randomized clinical trial study by Castillo et al. showed significant effects of high dose calcifediol treatment in the patients hospitalized due to Covid-19. Of the 76 patients included, 50 were treated with calcifediol and 36 were given regular treatment without calcifediol. It was noted that in the calcifediol group, 2% of patients required ICU admission, and no deaths were recorded while in the regular group, 36 % of patients required ICU admission, and 5.5 % of patients recorded death (Entrenas Castillo et al., 2020). As per the flexible approach in the current COVID-19 pandemic, authors recommend mass administration of vitamin D supplements to populations at risk for COVID-19.

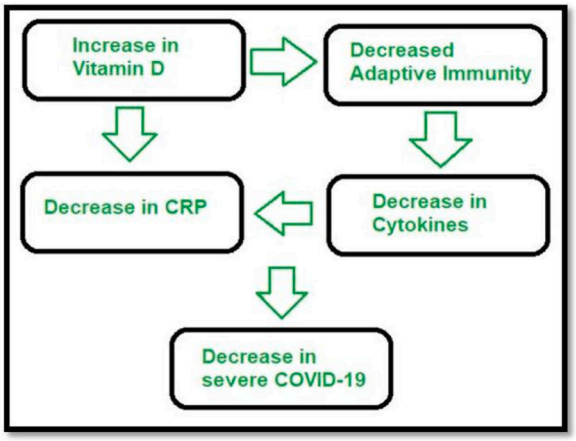

Fig. 3. Effect of Vitamin D on COVID-19 by its action on CRP.
The immune-modulatory role of vitamin D clearly shows a decrease in aspects related to the adaptive immunity. Since CRPs are indicators of inflammation, an increase in levels of Vitamin D hence leads to the decrease in cytokines which ultimately affects the degree of C reactive proteins in the patients. This entire mechanism acts as an indicator of decreased effects of Covid-19 in patients.

7. Conclusions

It is clear to see that Vitamin D does more than just making our bones stronger and preventing osteoporosis. It is in fact one of the compounds which have extensive effects on the human body whether it be in regards with manipulating the immune responses or with regards to the regulation of disease pathogenesis. The ability of Vitamin D to counteract the pro-inflammatory activity of SARS CoV makes it an impressive substitute therapy for dealing with patients of the disease. Due to lack of extensive study and research in the field of the effect of Vitamin D in corona virus patients it is yet unclear to say how extensively Vitamin D controls the disease pathogenesis. On the other hand it can be understood that with more research and exploration, this compound can be channelized into a potential drug for treating patients at least in the mild cases of COVID 19.

Data availability

Data will be made available on request.
No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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