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Role of Vitamin-D in COVID-19 Treatment

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***Abstract*: The COVID-19 epidemic has triggered a global public health emergency. Little is known about the infection's protective factors. As a result, preventative health interventions to lower the risk of infection, progression, and severity are critical. The potential function of vitamin D in lowering the risk of COVID-19 and other acute respiratory tract infections, as well as their severity, was examined in this review. Furthermore, as of May 20, 2020, this study evaluated the relationship between vitamin D levels and COVID-19 instances and deaths in 20 European nations. There was a significant negative correlation (p = 0.033) between mean vitamin D levels and COVID-19 cases per million population in European countries. In these countries, however, there was no significant connection between vitamin D and COVID-19 mortality. substantial link between vitamin D and COVID-19 mortality in these countries. Some retrospective investigations indicated a link between vitamin D level and COVID-19 severity and mortality, whereas others found no link when confounding factors were taken into account.**

***Keywords*: COVID-19, Vitamin-D, Vitamin-D supplementation, Infections, Risk factors, Antiviral mechanisms, Renin-Angiotensin axis, Biological activity.**

1. Introduction

Coronavirus illness (COVID-19) is a pandemic that began in Wuhan, China, and has already spread throughout the world. As of mid-September 2020, there have been 926,000 fatalities worldwide. The Individuals infected with this unique virus have a wide range of clinical symptoms due to a lack of evidence-based information and a very varied clinical presentation.

Vitamin D is an essential component that helps our body grow and maintain strong bones, among other things. Sunlight is the primary source of vitamin D because our skin absorbs ultraviolet photons from the sun and converts them to vitamin D. However, many people are lacking or receive insufficient amounts. This is especially true if you're older, don't eat well, or have a darker complexion. And if you get COVID-19, those low levels could put you at risk of being sick. While vitamin D improves immunity and reduces inflammation, scientists say additional research on its antiviral capabilities is needed.

In the absence of effective pharmacologic therapy or vaccines, it's critical to look into the impact of immune boosters such micronutrients (vitamins and minerals) in reducing or preventing the COVID-19's negative effects.

A growing body of evidence suggests that vitamin D may play a preventive role in lowering the risk and severity of respiratory tract infections (RTIs), particularly in the context of influenza and COVID-19. 1–5 Major clinical findings demonstrate that vitamin D insufficiency has a role in SARS-CoV-2 acute respiratory distress syndrome (ARDS) and that case fatality rates rise with age and SARS-CoV-2 serum concentrations. 6 & 7 Furthermore, the COVID-19 outbreak appears to occur primarily during the cold winter months, when serum 25-hydroxyvitamin D (25(OH) D—calcidiol or calcifediol) concentrations and ultraviolet B (UVB) doses are at their lowest, whereas the number of cases in the Southern Hemisphere near the end of summer is lower.

Infections of the respiratory tract are more common in the winter, particularly at northern latitudes, than in the summer. This definitely applies to the COVID-19 infectious disease, which briefly swept over the world and developed an andemic during the winter months. Hypovitaminosis D, which is widespread throughout the winter months in all nations north of the 42nd parallel, is a common occurrence during this time. Furthermore, the virus is more easily transferred at chilly temperatures. This raises the question of whether a deficiency in vitamin D has an impact on the onset and severity of covid-19 disease.

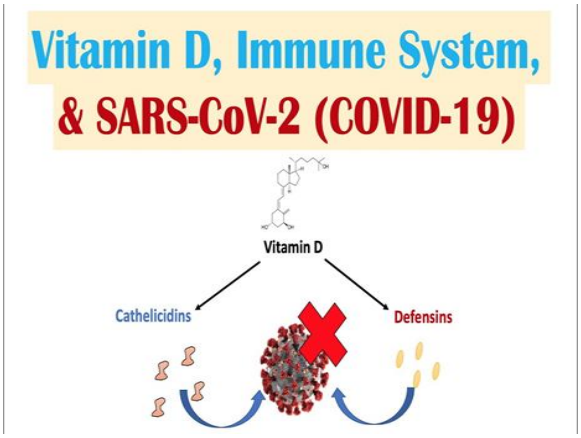

Fig. 1. Vitamin D, Immune system & SARS-COV-2 (COVID-19)

2. Definition

A. COVID-19

(CoV) is a big virus family that causes illnesses ranging from

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the common cold to more serious illnesses. A novel coronavirus (nCoV) is a coronavirus strain that has never been seen before in humans.

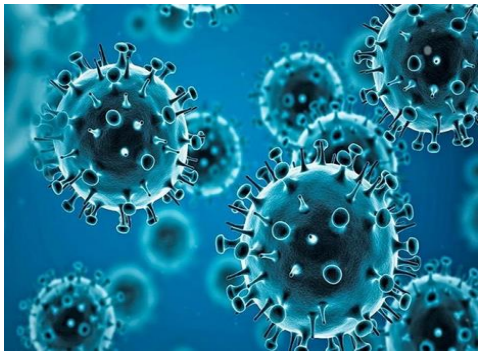

Fig. 2. COVID-19

B. Vitamin D

To function and stay healthy, the body requires little amounts of this vitamin. Vitamin D helps the body utilize calcium and phosphorus to build healthy bones and teeth. It can be found in fatty fish, egg yolks, and dairy products and is fat-soluble.

Fig. 3. Vitamin-D

3. Link between Vitamin-D and Covid-19

While the existing evidence, which is mostly from low-quality observational studies, suggests a link between low serum 25(OH)D levels and COVID-19-related health outcomes, this link was not determined to be statistically significant. Supplementing with calcifediol may help to prevent COVID-19-related ICU admissions. The current practise of administering high dosages of vitamin D to COVID-19 patients is not supported by scientific evidence. It is awaiting the results of ongoing trials to assess the efficacy, optimal dosages, and safety of vitamin D supplementation for COVID-19-related health consequences prevention and treatment.

4. Biological Activity of Vitamin-D

Among its metabolites are, Potent antibacterial and anti-inflammatory actions in vitro, among other things. Administration in animal models Vitamin D metabolites reduce the severity of a number of acute organ diseases. Complication, such as Observational study of acute lung injury information from patient groups encourage the use of these products for medicinal purposes. Lower amounts of vitamin D metabolites in the bloodstream, in particular. These numerous lines of evidence in favour of a possible vitamin D's medicinal potential has sparked interest. During the previous decade to see if huge doses of medication could be effective. Vitamin-D might improve outcomes in a variety of patient populations, includes some who are critically ill. The Revision of Deficiency in Vitamin D in Critically Ill Patients (VITdAL-ICU). The study was a multicenter randomised clinical trial that looked at the effects of the effect of vitamin D3 (540000 IU) vs. placebo treatment vitamin D insufficiency was found in 475 critically sick patients.

5. Vitamin-D and the Host Immune Response

Vitamin D helps to reduce the danger of microbial infection and death by acting on three different levels: physical barriers, cellular natural defences, and cellular natural defences. Immunity and Adaptive Immunity Cellular innate Vitamin D's activities help to boost immunity. Antimicrobial peptides are produced in part by induction containing LL-37, a human cathelicidin, and while preserving 1,25-dihdroxyvitamin D and defensins Tight, gap, and adherens junctions are three types of junctions. It's worth noting in particular the cathelicidins, which have a direct antibacterial action against a wide variety of microorganisms These Gram-positive and Gram-negative bacteria are among them. Bacteria, enveloped and non-enveloped viruses, and other pathogens as well as fungus. Cathelicidin has a variety of functions involving the activation of a number of pro-inflammatory cytokines, activation of neutrophil chemotaxis, T lymphocytes, monocytes, and macrophages entering the infection site, and accelerating the clearance via triggering apoptosis in respiratory pathogens and infected epithelial cells' autophagy.

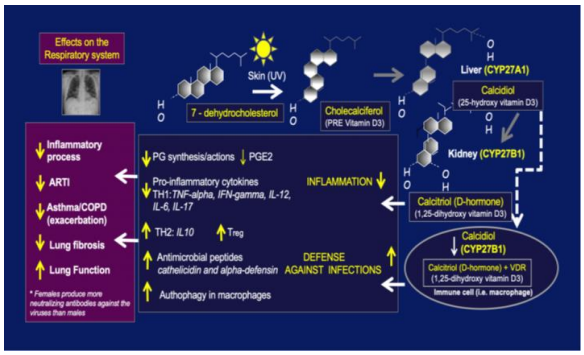

Fig. 4. Proposed mechanism whereby 1,25(OH) D -VDR (D-hormone) signalling acts on the respiratory system during the COVID-19 infection. 1,25(OH) D, 1,25-hydroxyvitamin D; ARTI, acute respiratory tract infection; IFN-gamma, inteferon gamma; IL-6, inteleukin 6; IL10, interleukin; IL -12, interleukin 12; IL-17, interleukin 17; Treg, T regulatory cells; TNF, tumour necrosis factor; UV, ultraviolet; VDR, vitamin D receptor

6. Risk Factors for Serve Courses of COVID-19

Vitamin D deficiency is associated to advanced age and co-morbidities. The synthesis of vitamin D in the skin begins to decline beyond 60 years of age, and this decline worsens with age. The precursor of vitamin D, dehydrocholesterol, decreases by about 50% in the skin from 20 to 80 years old, and the

elevation of cholecalciferol levels in serum following UVB radiation of the skin is more than 4-fold higher in people aged 62–80 years old compared to controls (20–30 years old). This helps to explain why so many older people are deficient in vitamin D. Co-morbidities are risk factors for illness severity, according to a meta-analysis involving 30 studies and 53.000 COVID-19 patients.

Table 1
Risk factors

Risk factor	Odds ratio	95% CI
Old age > 50 yrs	2.61	2.29–2.98
Male	1.38	1.195–1.521
Smoking	1.734	1.146–2.626
Any co-morbidity	2.635	2.098–3.309
Chronic kidney disease	6.017	2.192–16.514
COPD	5.323	2.613–10.847
Cerebrovascular disease	3.219	1.486–6.972

7. Vitamin-D and Role of Supplementation

Vitamin D supplementation is hypothesised to lower infection risks through increasing the expression of antioxidation-related enzymes glutathione reductase and glutamate–cysteine ligase modifier subunit. Furthermore, increased glutathione production increases the availability of ascorbic acid (vitamin C), which has antibacterial properties. Supplementing with vitamin C and zinc, among other micronutrients, has been shown to help enhance immunity. For the same reasons, vitamin D supplementation has been linked to better overall outcomes and has been shown to reduce the severity of viral infection and induce early recovery in multiple trials.

However, the optimal amounts of vitamin D supplementation, as well as the suggested dosage, are unknown. Most guidelines recommend a daily dose of 600–4000 IU/d, with a blood concentration of 20 ng/mL considered acceptable. In order to protect high-risk groups against viral infection, studies have suggested greater doses and various dosing regimes. Higher doses, on the other hand, have a different effect.

8. Vitamin D's Importance in the Treatments of Respiratory Tract Infections and Influenza

Many peer-reviewed research has shown evidence to support the concept that higher vitamin D3 levels in the blood are linked to a lower risk of microbiological infections and fatalities from RTIs including pneumonia and influenza. Furthermore, normal serum vitamin D3 levels may prevent SARS-CoV-2 infection and reduce severity and mortality. Unfortunately, no standard recommendations exist for the dose and optimal concentration of vitamin D3 required to prevent patients against RTI throughout the winter months.

Vitamin D3 plays a vital role in viral RTIs and related acute lung damage, according to epidemiological research. According to a recent meta-analysis, a daily or weekly vitamin D3 intake of 20 to 50 g resulted in a considerable reduction of RTIs. Bolus, high-dose, isolated, or added.

Furthermore, the degree of protection appears to increase as vitamin D3 concentrations reach the optimal range of 40 to 60 ng/ml. A person must take between 2,000 and 5,000 IU of vitamin D3 every day to reach this level. By altering the renin–angiotensin system in lung tissue, specifically the angiotensin–converting enzyme 2 (ACE2) enzyme, calcitriol protects against acute lung injury. The amounts of plasma 25-(OH)-Vitamin D3 and the severity of COVID-19 appear to be connected (Huang et al., 2020; Wang et al., 2020; Zhou et al., 2020). It's worth noting that a lack of vitamin D3 significantly lowers the expression of the DPP-4/CD26 receptor. In addition, adequate vitamin D3 intake tends to inhibit immunological processes that can lead to a prolonged interferon-gamma response as well as chronic interleukin.

As demonstrated in COVID-19, SARS-CoV infection causes ACE2 expression to be downregulated, which leads to acute lung injury (edoema, increased vascular permeability, and impaired lung function) and RAS dysregulation, which leads to increased inflammation and vascular permeability. COVID-19 has been linked to the generation of pro-vitamin D3, which improves cellular immunity and lowers the cytokine storm caused by the innate immune system. TNF- and IF- are pro-inflammatory cytokines that can be reduced by vitamin D3. Several studies have shown that appropriate vitamin D3 intake and plasma levels minimize the incidence of viral infections by acting on immunocytes. As a result of its effect on T cells, vitamin D3 is thought to play a role in COVID-19.

9. Role of Vitamin-D in Antiviral Mechanisms

As previously stated, the cohabitation of CYP27B1 and VDRs in immune system cells is part of an autocrine strategy for pathogen defence. Antimicrobial peptides such as -defensin 2 (BD2) and cathelicidins26 are secreted in response to this mechanism. For example, the complex formed by 1,25(OH)2D and VDR can bind to the cathelicidin gene promoter, speeding up transcription and increasing the quantity of cathelicidins available for antimicrobial activity27, 28. This ability of the vitamin was previously demonstrated in a study that discovered a higher amount of cathelicidin expression in people with high serum 25-OHD levels29, which was replicated in lung epithelial cells30.

Cathelicidins, when released, can either directly destroy pathogens of various types or neutralise poisons, performing an immeasurable role in innate immunity31. The antimicrobial peptide is effective at combating viruses and limiting their reproduction in viral infections32, 33, 34, 35. This ability is also apparent in BD-2, which has been shown to enhance the secretion and action of cytokines and chemokines involved in immune cell migration to infection sites36, 37, 38, 39. Together, BD-2 and cathelicidins are powerful bodily mechanisms for thwarting infections and preventing disease progression.

Surprisingly, the availability of pathogens, or more precisely, the quantity of Pattern Recognition Receptors (PRRs) that bind with them, influences the expression of both the CYP27B1 enzyme and VDRs, or more obliquely the amount of 1,25(OH)2D endogenously generated by immune cells.40 and 41. The immune cells can ratchet up their activity as a result of

this configuration.

Barriers are one of the most basic components of the body's defence against pathogens, and they are primarily supported by cellular junctions, particularly those of the epithelia, where Vitamin D plays an important role. The 1,25(OH)2D/VDR complex is capable of activating various signalling pathways involved in junction protein control and tissue structural integrity and functionality (for example, in transport)42. VDRs have been demonstrated to connect with the promoter region for the genes of proteins in the Claudin family that are required for tight junction formation and regulation43, 44, 45. They may also play a role in the regulation of the Occludin and ZO-1 proteins, which are important junction proteins46, 47. Vitamin D, which has been demonstrated to reduce lung permeability and enhance pulmonary epithelial barriers against pathogenic viruses, could have a positive influence on SARS-CoV-2, a virus that attacks the respiratory system.

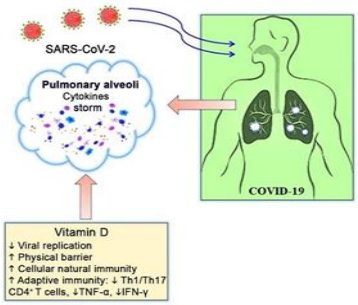

Fig. 5. Vitamin-D and the Renin-Angiotensin Axis

COVID-19 revolves on the SARS-CoV-2 infection mechanism, which is one of the most important reasons why the Renin-Angiotensin System (RAS) is so important in the issue of vitamin D.

The RAS is responsible for maintaining blood pressure and blood electrolyte equilibrium in most people. The octapeptide Angiotensin II (Ang-II) binds to type I angiotensin receptors (AT1Rs) to increase blood pressure by vasoconstriction and production of Aldosterone (which enhances renal Na+ absorption and therefore water retention). However, the binding can have negative consequences because it stimulates inflammation, platelet aggregation, mitotic agent formation, and ROS synthesis (which reduces the availability of nitric oxide, which is required for endothelial cell functionality). Thrombosis, fibrosis, oxidative stress, and endothelial dysfunction are some of the negative consequences of these effects.

Alternatively, Ang-II can interact with Angiotensin-converting Enzyme 2 (ACE2), which cleaves away the phenylalanine at the carboxy terminus of Ang-II, resulting in Angiotensin–(1–7), which can also be produced by Angiotensin-converting Enzyme (ACE) and ACE2 cleaving Ang-precursor, II's the decapeptide Angiotensin I (Angiotensin-(1-7) then binds to the Mas G protein-coupled receptor (GPCR), causing effects that are the polar opposite of those seen when Ang-II and AT1R interact—vasodilation, anti-fibrosis, anti-inflammation, and vascular protection, to name a few.

Unfortunately, SARS-entrance CoV-2's pathway into human cells is dependent on ACE2. The human serine-protease TMPRSS2 enzyme primes its spike proteins, which then bind to ACE2 on the cell membrane, initiating receptor-mediated endocytosis. As the virus multiplies, ACE2 binding becomes more extensive, and ACE2 availability plummets in the short term, owing to the enzyme's downregulation in the long term, which reduces Ang-availability.

10. Possible Benefits of Vitamin-D in COVID-19

Chronic comorbidities, such as diabetes, systemic arterial hypertension, obesity, and cardiovascular illnesses, have been linked to an elevated risk of morbidity and mortality in COVID-19 [6]. According to current research, these disorders share a chronic inflammatory pattern with high levels of proinflammatory cytokines in common. People with severe COVID-19 symptoms have an unregulated generation of proinflammatory cytokines, which has been linked to a low serum level of vitamin D and other minerals, indicating disease severity.

The most important molecules formed from 7-dehydrocholesterol (7-DHC) are the active metabolite 25-dihydroxyvitamin D, as well as its precursors ergocalciferol and cholecalciferol. When ergosterol is subjected to ultraviolet radiation, it produces ergocalciferol, often known as vitamin D2. The skin precursor of vitamin D (7-dehydrocholesterol) undergoes photochemical cleavage when exposed to UV radiation, giving cholecalciferol. Effects of giving vitamin D to adults:

Three studies with 356 participants were discovered. Two of the studies were conducted in Brazil and the other two in Spain. In two of the investigations, participants experienced severe COVID-19, while in the third, they had mild COVID-19 or no symptoms. All of the participants tested positive for COVID-19 using a lab test known as PCR, which is currently the most accurate test available.

The participants in the study were given different doses of vitamin D. In one research, they used a single high dose, whereas in another, they used numerous smaller doses spread out over 14 days. Only two studies found vitamin D insufficiency in their participants. The vitamin D status of the other trial's participants was not mentioned.

11. Unwanted Effects

We don't know if vitamin D has any disadvantages. Only one trial (in people with severe COVID-19) provided us with usable data on negative effects. One out of every 119 people vomited shortly after getting vitamin D, according to the findings.

12. Conclusions

There isn't enough data on vitamin D supplementation as a COVID-19 treatment to determine the benefits and hazards. The evidence on the effectiveness of vitamin D supplementation in the treatment of COVID-19 is equivocal. We also found a limited amount of safety data and were concerned about the consistency with which these outcomes

were monitored and recorded.

Due to differences in supplementing methodologies, formulations, participant vitamin D status, and reported outcomes, there was significant clinical and methodological heterogeneity in the included trials.

RCTs with an adequate randomization technique, comparability of study arms, and, preferably, double-blinding are urgently needed. We discovered 21 ongoing studies and three completed studies with no published results, indicating that these gaps will be filled in the future and that our findings may change. Due to the fluid nature of the work, we will update the review on a frequent basis.

References

[1] Das P, Samad N, Ahinkorah BO, Hagan JE Jr., Peprah P, Mohammed A, Seidu A-A. Effect of Vitamin D Deficiency on COVID-19 Status: A Systematic Review. COVID. 2021; 1(1):97-104.

[2] Cutolo M, Paolino S, Smith V. Evidences for a protective role of vitamin D in COVID-19. RMD Open. 2020 Dec;6(3):e001454.

[3] Biesalski H. K. (2020). Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?. Nfs Journal, 20, 10–21.

[4] Aya Bassatne, Maya Basbous, Marlene Chakhtoura, Ola El Zein , Maya Rahme , Ghada El-Hajj Fuleihan: The link between vitamin-D and covid-19:2021, Jun;119:154753.

[5] David e. Leaf; Adit A. Ginde, "Biological activity of vitamin-D," March 16, 2021 Volume 325, Number 11.

[6] Giuseppe Murdaca, Giovanni Pioggia and Simone Negrini, "Vitamin D and the host immune response," Clin Mol Allergy (2020) 18:23.

[7] Maurizio Cutolo, Sabrina Paolino, Vanessa Smith, "Vitamin D and the host immune response," December 2020.

[8] Hans K. BiesalskiHans, "Risk factors for severe courses of COVID-19," Nfs journal, 20(2020).

[9] Nurshad Ali, "Vitamin-D and role of supplementation: Journal of Infection and Public Health, 13(2020) 1373–1380.

[10] Danilo Tarsio Mota BritoLuiza Helena Coutinho RibeiroCarla Hilario da Cunha Daltro Roberto de Barros Silva, "Possible benefits of vitamin D in covid-19," May 2021.

[11] Megan Ware, Rdn, L.D. Medically reviewed by Debra Sullivan, Ph.D., Msn, R.N., Cne, COI: Effects of giving vitamin D to adults, November 7, 2019.

[12] Stroehlein J. K, Wallqvist J, Lannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem-C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta, "Unwanted effects, "May 2021.