IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

THE ROLE OF VITAMIN D SUPPLEMENTATION IN MITIGATING COVID-19 RISK: A COMPREHENSIVE SYSTEMATIC REVIEW

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Abstract:

The WHO classified COVID-19 a global pandemic, and its emergence has caused a disaster in global public health. Vitamin D is one of the main micronutrients being researched for its potential to have a preventive effect against the COVID-19 condition. Serum 25-hydroxyvitamin D (25(OH)D) concentrations and the risk or severity of coronavirus disease 2019 (COVID-19) have been found to be inversely related in observational studies. The significance of vitamin D in COVID-19 has been attributed to a number of pathways, such as the modulation of immunological and inflammatory responses, control of the renin-angiotensin-aldosterone system, and participation in glucose metabolism and the cardiovascular system. Vitamin D supplementation aids to lower the risk of severe disease progression of patients with COVID-19. In order to better understand the potential impact of vitamin D insufficiency on COVID-19 status and health outcomes in COVID-19 patients, this systematic review aims to find and consolidate the relevant literature.

Key words: COVID-19, Vitamin D, systematic review

Introduction:

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has become one of the most significant epidemiological occurrences in the previous 100 years, wreaking havoc on public health systems and socioeconomic tissue worldwide[1]. In February 2020, the World Health Organization (WHO) officially designated the pandemic caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19)[2]. Despite global efforts, the challenge of halting the disease's transmission remains daunting, given the staggering count of over 20 million cases worldwide by August 12, 2020. Current focus has shifted towards enhancing treatment and preventing factors that contribute to the increased severity of COVID-19.

COVID-19 exhibits distinct attributes, including high transmissibility and variable clinical severity. Notably, approximately 40-45% of patients exhibit no symptoms, while 30-40% experience minor ones. A mere 15% of cases progress to a severe stage. Among the various underlying health conditions, diabetes and hypertension emerge as the two most frequently associated comorbidities with the development of severe disease[3].

Meanwhile, heightened vulnerability to severe COVID-19 is observed among the elderly and individuals grappling with cardiac disease, hypertension, diabetes, chronic respiratory issues, and cancer. Moreover, the study outcomes underscore the significant correlations between severe COVID-19 cases and markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer. Furthermore, decreased levels of lymphocytes and platelets were also prominently linked to severe COVID-19 cases.

The Angiotensin-converting enzyme 2 (ACE2) receptor, a key regulator of the Renin-Angiotensin System (RAS) responsible for blood pressure and vascular equilibrium, plays a pivotal role. ACE2 expression is notably pronounced among individuals with hypertension, diabetes, coronary heart disease, and cerebrovascular conditions, offering insights into the heightened vulnerability of these patients to severe and fatal COVID-19 outcomes[4]. Recent revelations further confirm that SARS-CoV-2 can target and infect central nervous system cells via the ACE2 receptor, indicating the involvement of this neurotropic pathway in influencing disease severity and mortality[5].

This review highlights a connection between vitamin D levels and the incidence, severity, and mortality rates of COVID-19 infection. It is important to note that while the literature does not propose vitamin D supplementation as a means to entirely eradicate COVID-19, it does indicate that insufficient levels of vitamin D may heighten the vulnerability to COVID-19 infection and exacerbate the progression of the disease. Based on consensus, the recommended dosage for maintaining optimal 25(OH)D levels for adolescents and adults at risk is 1000 to 2000 IU of vitamin D on a daily basis.

Synthesis & Sources of Vitamin D:

Sources:

Vitamin D exists in two forms: D2 and D3. Vitamin D3, known as cholecalciferol, is synthesized in human skin and can be found in oily fish and cod liver oil. On the other hand, vitamin D2, or ergocalciferol, is produced through UVB irradiation of yeast and plant sterol ergosterol. Obtaining sufficient vitamin D solely from dietary sources poses a considerable challenge. Among foods, oily fish stands out as a primary source. While liver, eggs, and mushrooms contain minor amounts of vitamin D, the latter only after exposure to UV radiation. However, the primary contributor to vitamin D levels is the skin, where UVB radiation stimulates its production[6].

Synthesis:

Vitamin D shares a structural resemblance with other hormones derived from cholesterol, such as cortisol, testosterone, and estrogen. The synthesis of Vitamin D begins with 7-dehydrocholesterol, a molecule present in the skin. When exposed to ultraviolet B (UVB) radiation with a wavelength of 280-315 nm, a specific carbon-to-carbon bond (C9-C10) is broken, leading to the opening of its B ring. This process produces Vitamin D.

For Vitamin D to become its active hormonal form, 1,25 dihydroxyvitamin D (1,25(OH)2D), a series of enzymatic transformations are required. Initially, 25-hydroxylation takes place in the liver, followed by 1-hydroxylation, which occurs in the kidneys as well as various immune and epithelial cells. These conversions are mediated by the enzyme 1-hydroxylase, also referred to as CYP27B1[7].

Vitamin D deficiency and Related Disorders:

Vitamin D deficiency is associated with a range of health conditions due to its essential role in various physiological processes within the body. It's important to note that while Vitamin D deficiency is associated with these conditions, it may not be the sole cause. Other factors, including genetics, lifestyle, and overall health, also contribute to the development of these conditions. If you suspect a Vitamin D deficiency or have concerns about your health, it's advisable to consult a healthcare professional for proper evaluation and guidance.

The researchers noted that evidence suggests that the vitamin D endocrine system is involved in several biologic processes and pathways, which affect not only musculoskeletal health but also the emergence of other diseases. For instance, it has been known that vitamin D status may affect outcomes of respiratory and infectious diseases, hence, hinting at the role of vitamin D in the immune system.

Vitamin D has also been tagged in its many roles in immunity, inflammation, and epithelial repair. Specifically, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), the active metabolite of Vitamin D has long been recognized to contain immune regulatory properties. Many past studies have demonstrated that vitamin D can contribute to the defense against viral infections, specifically acute respiratory tract infections. Melanin pigments are drivers of human pigmentary status. In the course of the coronavirus pandemic, there is a disparity in the severity of COVID-19 illness in some racial groups.

Fair-skinned people only need about 20 to 30 minutes of midday sunlight exposure about 2 to 3 times a day to get a sufficient amount of vitamin D. On the other hand, darker skin people may need higher weekly ultraviolet ray doses to meet their vitamin D needs[8].

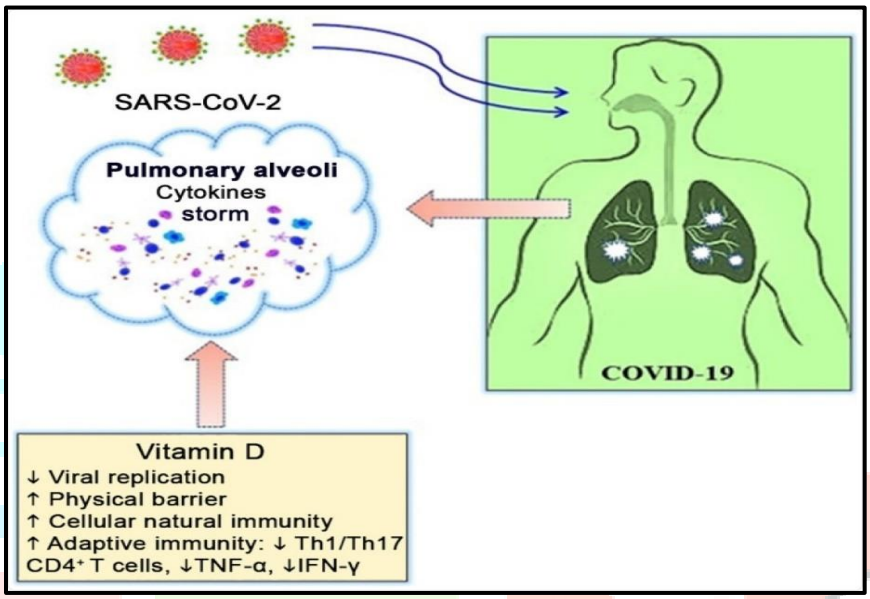

Figure:1 Potential antiviral mechanisms of vitamin D in COVID-19. COVID-19, coronavirus disease 2019; IFN-γ, interferon-γ; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th, T helper; TNF-α, tumor necrosis factor-α.

Vitamin D's Impact on SARS-CoV-2 Infection:

In the context of COVID-19, which is caused by the SARS-CoV-2 virus, severe pneumonia often arises in patients who exhibit a hyper inflammatory state. This state is triggered by a robust activation of various immune cells, resulting in the uncontrolled release of significant quantities of pro-inflammatory cytokines. This excessive immune response is commonly referred to as a "cytokine storm," and it plays a pivotal role in the progression of the disease. This storm leads to the migration of inflammatory cells into lung tissue, followed by the release of additional cytokines, proteases, free radicals, and nitric oxide. As a consequence, the microvascular and alveolar barriers sustain severe damage, culminating in the formation of hyaline membranes and excessive extravasation. These events contribute to the accumulation of alveolar edema, impairing gas exchange and ultimately causing respiratory distress. This cascade of reactions often leads to a decrease in arterial oxygen saturation, resulting in the onset of acute respiratory distress syndrome (ARDS)[9, 10].

Emerging evidence suggests a potential role for vitamin D in modulating this inflammatory phenomenon. Both the airway epithelium and alveolar macrophages have the capacity to express the enzyme CYP27B1 and the vitamin D receptor. In the context of other viral infections and respiratory pathogens, the activation of the innate immune system has been shown to promote the local production of 1,25(OH)2D3. This active form of vitamin D has been associated with enhanced viral neutralization and clearance, along with the regulation of subsequent pro-inflammatory responses[11].

Calcitriol (1,25-(OH)2D), the active form of vitamin D synthesized by the kidney's 1-hydroxylase enzyme, circulates in the bloodstream as a hormone. It assumes a crucial role in maintaining calcium and phosphate balance, fostering healthy bone remodeling, and additionally contributes significantly to cellular development, neuromuscular functions, and immune responses, including the modulation of anti-inflammatory effects. Notably, it curbs the expression of inflammatory cytokines like IL-1 and tumor necrosis factor, and its scarcity has been associated with heightened T1 cytokine expression[12].

Vitamin D, classified as a steroid hormone, is derived from dietary sources or internal synthesis, dependent on ultraviolet radiation exposure from sunlight. In-depth statistical and clinical analyses have firmly established a link between reduced vitamin D levels and an elevated susceptibility to COVID-19, marked by an increased risk of severe infections and higher mortality rates[13].

Vitamin D's mechanism of action in relation to its role in immunomodulation:

Vitamin D's interactions extend to pivotal systems involved in maintaining cellular equilibrium, including the Renin-Angiotensin-Aldosterone System (RAAS). Illustrated in Figure 2, Vitamin D demonstrates an opposing or modulating influence on RAAS signaling pathways[14]. The RAAS plays a central role in governing the body's hydroelectrolyte composition and hemodynamics. Moreover, noteworthy associations between COVID-19 and the RAAS emerge, as evidenced by the substantial elevation of serum angiotensin II (Ang II) levels in infected individuals, which directly correlate with both viral load and the extent of lung damage observed[15].

Research has established that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, facilitating its invasion of human lung epithelial cells and the initiation of infection. Intriguingly, ACE2 concurrently generates a spectrum of effects that counteract inflammation, oxidative stress, fibrosis, and hyperplasia. Furthermore, heightened activation of the RAAS at the hepatic level precipitates impaired liver function and heightens the susceptibility to developing diabetes mellitus[16].

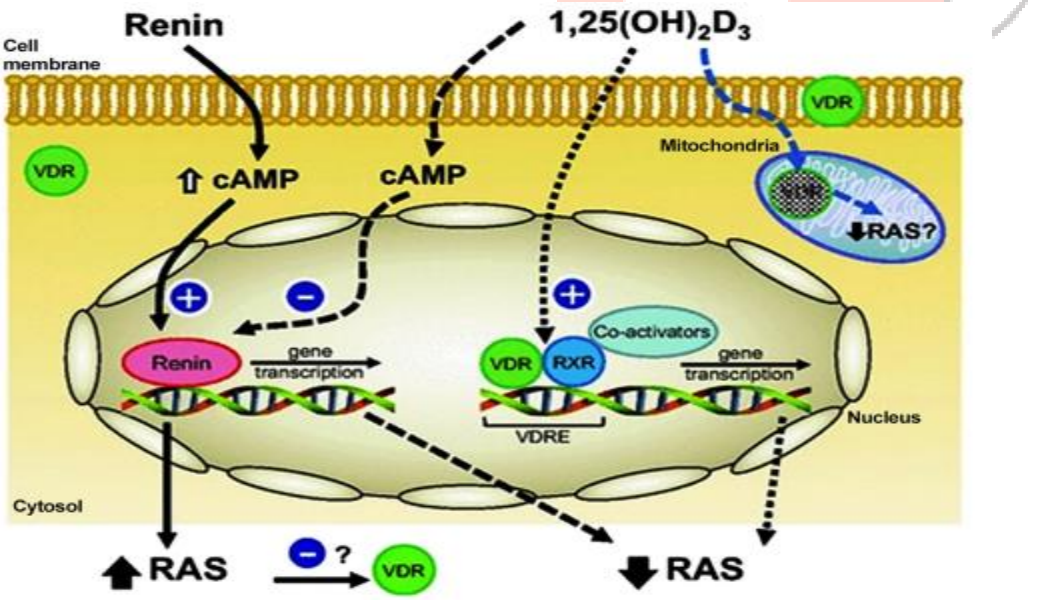

Figure-2: Angiotensin and vitamin D receptor cellular interactions. RAS stands for renin-angiotensin system; RXR stands for retinoid X receptor; VDRE stands for vitamin D response element; 1,25 (OH)2D3, 1,25-dihydroxyvitamin D3[17].

Calcitriol exerts inhibitory effects on the production and release of several cytokines originating from bronchial smooth muscle cells. Notably, platelet-derived growth factor, RANTES (regulator in the activation of expressed and secreted normal T-cells), and matrix metalloproteinase fall within this category. This inhibition contributes to diminished proliferation and inflammation in lung smooth muscle cells. Vitamin D serves as a catalyst for the

synthesis of interleukin 10 by CD4+, CD25+, Foxp3+, and T regulatory cells. In parallel, it suppresses the activation of dendritic cells through the down regulation of CD 80/86 and CD40 expression. Furthermore, vitamin D induces the expression of cathelicidin and various other anti-infective molecules[18].

Vitamin D's classical pathway, facilitated by the vitamin D receptor, emerges as a powerful negative endocrine regulator of the Renin-Angiotensin System (RAS)[19]. This pathway effectively suppresses RAS activity and decreases ACE2 expression both in vitro and in vivo. The underlying mechanism involves the inhibition of CREB, a pivotal transcription factor governing the renin gene's control. Thus, vitamin D's engagement in RAS suppression unfolds through this precise mechanism. Beyond the realm of infection, the severity of COVID-19 is intimately associated with altered and prolonged proinflammatory reactions within the lungs. This intricate interplay leads to unconventional respiratory episodes and exacerbates multi-organ dysfunction[20].

Vitamin D and Covid-19 pathology: emerging evidence:

Numerous clinical articles have acknowledged the evidence for a link between vitamin D level and COVID-19, although all of them are based on retrospective data. We have located 14 such significant clinical trials that support and one that refutes this idea are given in below table.

Table 1

Studies on association of vitamin D with COVID-19 patients[20]

S.No	Author, Year	Study title	Objectives	Method	Key findings
1.	Daneshkhah (2020)	The Possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients	Vitamin D and the severe COVID-19 inflammatory response	Global databases and literature	Decreases severity and lethality by preventing a cytokine storm
2.	Lau et al. (2020)	Vitamin D insufficiency (VDI) is prevalent in severe COVID-19	Levels of serum vitamin D in COVID-19 patients in a New Orleans ICU	Retrospective analysis of a tertiary care hospital database (n ¼ 20)	With severe COVID-19 development and severity, 75% of patients exhibited VDI.
3.	Ilie et al. (2020)	The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality	Average vitamin D levels in 20 European nations with COVID-19 cases and fatality	Global databases and literature	A link between vitamin D and COVID-19 instances and mortality that is detrimental
4.	Moozhipurath et al. (2020)	Evidence of protective role of ultraviolet-B (UVB) radiation in reducing COVID-19 deaths	UVB radiation and the COVID-19 morbidity	Global databases of 152 countries with fixed-effect log-linear regression model	The COVID-19 death rate can be reduced by 1.2% and the case-fatality rate (CFR) by 1% with every unit rise in ultraviolet index (UVI).
5.	Glicio (2020)	Vitamin D level of mild and severe elderly cases of	serum vitamin D concentrations	Retrospective analysis of 2 tertiary hospital	90% of the patients had serious

		COVID-19: a preliminary report	and lung immunity	databases in South-Asian (n ¼ 176)	infections, and 80% of the patients had vitamin D insufficiency (VDD).
6.	Raharusuna et al. (2020)	Patterns of COVID-19 mortality and vitamin D: an Indonesian study	Mortality from COVID-19 and serum vitamin D levels	Retrospective analysis of Indonesian Government hospital databases with two cohorts: active and expired (n ¼ 780)	With an elevated risk in older and male individuals with comorbidities, vitamin D level is closely related with COVID-19 mortality.
7.	D'Avolio et al. (2020)	25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2	Serum vitamin D levels in Swiss COVID-19 patients	Retrospective analysis of COVID-19 positive (n ¼ 20) and negative (n ¼ 80) cases	Serum vitamin D levels were considerably lower in COVID-19 positive subjects.
8.	Laird et al., (2020)	Vitamin D and inflammation: potential implication for severity of COVID-19	Vitamin D levels' effects on COVID-19 morbidity and death in 12 areas of Europe	Global databases and literature	There were more cases and higher fatality rates in areas with lower mean vitamin D levels.
9.	Meltzer et al. (2020)	Association of vitamin D deficiency and treatment with COVID-19 incidence	The impact of VDD on COVID-19	Retrospective analysis of a university hospital database in Chicago (n ¼ 489)	A higher risk of COVID-19 is connected with untreated VDD.
10.	Alipio (2020)	Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (Covid-2019)	Serum vitamin D levels and COVID-19 clinical outcomes	Retrospective analysis of 3 hospital databases in South-Asian (n ¼ 212)	When levels grow, the likelihood of a moderate outcome increase, suggesting that vitamin D may enhance outcomes.
11.	Herwig et al. (2020)	Sedeprovid, a novel vitamin D based substance, plus Alpha Hp lead to complete recovery from COVID-19 within 48 h after application in a 7-	Sedeprovid and AlphaHP's analysis of COVID-9 results	Prospective study with positive patients (n ¼ 5) with symptoms	By 24 hours, the symptoms of COVID-19 greatly improved, and they were fully gone by 48 hours

		mo old baby, a 1.5-year-old toddler and three further adults			
12.	Sun et al. (2020)	Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019	Serum calcium levels and COVID-19 patient's disease severity and prognosis	Retrospective analysis of a hospital database in Wuhan (n ¼ 241	In COVID-19 individuals, hypocalcaemia was linked to disease severity and a poor prognosis. The concentrations of vitamin D and serum calcium were found to be positively correlated.
13.	Lansiaux et al. (2020	Covid-19 and vit-D: disease mortality negatively correlates with sunlight exposure	SARS-CoV-2 infection and the relationship between sunshine exposure	Cross-sectional study French databases (n¼ 64,553,275)	There may be a protective effect of sunlight against COVID-19 mortality.
14.	Hastie et al. (2020)	Vitamin D concentrations and COVID-19 infection in UK biobank	Relationship between vitamin D status and COVID-19 risk	Retrospective analysis of UK biobank database (n ¼ 348,598)	There is no proof that you could get COVID-19 infection.

VDI: Vitamin D insufficiency; UVB: Ultraviolet-B; UVI: Ultraviolet index; CFR: Case-fatality rate; VDD: Vitamin D deficiency

Benefits of Vitamin D supplementation:

The World Health Organization has classified COVID-19 as a global pandemic. The infection's potential protective factors, however, are largely unknown. There is currently no conclusive proof that vitamin D supplementation lessens COVID-19's severity and fatality. Some randomized trials that have been registered to assess the part vitamin D plays in COVID-19 infections and severity haven't yet published their findings. The combination of vitamin D, magnesium, and vitamin B12 has been shown to be protective against the clinical deterioration of COVID-19 in the small cohort research mentioned above[21].

Supplementing with vitamin D has been demonstrated to be both safe and beneficial in preventing acute respiratory tract infections. The scientists also discovered that participants with baseline blood 25(OH) D levels of 25 n mol/L had a substantial protective role for vitamin D[22]. Subgroup analysis in the same trial found that daily or weekly vitamin D intake (without additional bolus doses) protected against acute respiratory tract infection, particularly in people with vitamin D deficiency. D supplementation was also reported to boost antioxidative gene expression (glutathione reductase modifier subunit). The enhanced glutathione production eliminates the need for vitamin C, which has potential antibacterial properties and has been proposed to prevent and treat COVID-19 infection. Vitamin D supplementation at doses of up to 100 g/day is safe for adults and several expert groups now recommend supplementation in older people, although at lower levels. A study found that taking 100-250 g of vitamin D per day for 6 weeks improves the baseline serum concentration of 25(OH)D by 2 to 3 folds, with no significant health effects.

Dosage Advice:

It is advised to take up to 250 g per day for a month to raise serum levels of 25(OH)D to the ideal range between 75 and 125 n mol/L. After a month, the dose can be decreased to 100 g/day in order to keep the levels of 25(OH)D in the blood stable[23].

Combining Vitamin D and Magnesium:

A recent analysis also recommended taking magnesium supplements together with vitamin D pills since magnesium aids in maintaining the balance of phosphate and calcium in the body. Magnesium, a crucial component in enzymatic processes, notably in the kidney and liver, appears to be necessary for the enzymes involved in vitamin D metabolism[24].

Precaution:

High-portion oral Vitamin D3 treatment has been shown to reduce transitory mortality in revival patients with severe hypovitaminosis D (17% overall risk decrease). Up to 10,000 IU of oral vitamin D supplementation per day is considered safe.

Vitamin D recommendations:

Current evidence-based recommendations for preventing vitamin D insufficiency include:

1. **Vitamin D supplementation in accordance with government guidelines:**

Supplementation of vitamin- D in accordance with government guidelines (e.g., 400 IU/day (10g/day) for the UK; 600 IU/day (15g/day) for the USA (800 IU/day (20g/day) for people over the age of 70) and Europe[25]. These recommendations were developed to ensure that the majority of the population has 25OHD concentrations above 25nmol/L (UK) to protect musculoskeletal health or above 30nmol/L (USA) to reduce the risk of vitamin D deficiency (the USA recommendation was also developed to optimize musculoskeletal health in the population using a 25 OHD concentration of 50nmol/L).

2. Consumption of a nutritionally balanced diet:

Balanced nutritional diet such as that recommended by the UK Eatwell Guide and the US Food Pyramid, which includes vitamin D-rich foods such as oily fish, red meat, egg yolk, and fortified foods such as morning cereals in the UK and fortified milk in the United States and Canada[26].

3. Safe sunlight exposure to increase vitamin D levels:

Dermal vitamin D production is most efficient with short, frequent (daily) exposures when the sun is at its greatest (during the day). The effectiveness of vitamin D synthesis drops well before the sunburn threshold is reached, but the acceptable dose is skin-type dependent, so the exposure times required change for different skin types. For white-skinned people in the UK, roughly 10 minutes of exposure at lunchtime in season appropriate clothing can meet vitamin D needs; for those with skin type V (eg, South Asian, brown skin tones), this increases to about 25 minutes[27].

4. **Appropriate food and lifestyle practices:** As emphasized by the WHO at this time, including enough nourishment to support the immune system[28].

5. **Targeted nutritional guidance**, such as that provided by the Defense Nutrition Advisory Service for UK military personnel, with specific reference to COVID-19[29].

6. **Advice on vitamin D for bone health:** The Royal Osteoporosis Society has developed particular guidelines for managing vitamin D deficiency in persons who have or are at risk of developing bone disease[30].

Conclusion:

The existing evidence that underscores vitamin D's role in immune system modulation strongly suggests its significant role in viral infections. The supplementation of vitamin D might potentially mitigate the gravity of COVID-19 symptoms and reduce mortality. We believe that the conventional approach of oral vitamin D supplementation could serve as a simple strategy to: (i) decrease the susceptibility to SARS-CoV-2 infection by down regulating ACE2 receptors; and (ii) alleviate disease severity by regulating the inflammatory pulmonary response or the cytokine storm that contributes to the severity of COVID-19. The researchers noted that increased melanin levels in the skin are known to be inversely proportional to the vitamin D status. Thus, this may account for the observed differences in vitamin D deficiency.

In summary, the review aimed to expand the current knowledge of vitamin D status and melanin and their effects on COVID-19 outcomes. The team noted that vitamin D may be an effective way to reduce the impact of COVID-19 on high-risk populations. Overall, the researchers suggest that vitamin D may prove an effective adjuvant to vaccines and antiviral therapeutics in the fight against COVID-19.

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