MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Open Access Journal of Endocrinology
ISSN: 2578-4641

Possible Role of Vitamin D3 in the Prevention of COVID-19 Infection and Mortality

Hasanabadi PS[1], Farmad ME[2] and Ramin A[3]*

[1]Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Iran
[2]Orthopedic Surgeon Center at the 9th Dey of Torbat Heydariyeh Hospital, Mashhad University of Medical Sciences, Iran
[3]Medicianl Plants Research Center, Mazandaran University of Medical Sciences, Iran

***Corresponding author:** Ramin Ataee, Thallassemia Research Center, Mazandaran University of Medical Sciences, Sari, Iran, Email: raminataee1349@gmail.com

Review Article
Volume 6 Issue 1
Received Date: April 11, 2022
Published Date: June 15, 2022
DOI: 10.23880/oaje-16000163

Abstract

Despite many efforts around the world to control the outbreak of COVID- 19 virus, this issue has become a pandemic. According to the latest research on the global spread of COVID- 19, researchers have found that adequate vitamin D3 increases resistance to viral infections, reduces the severity of symptoms of the disease, and ultimately mortality rate. However, the results are still contradictory. There are receptors in the human body called ACE2. The COVID- 19 virus can enter the body by binding to these receptors, and the symptoms of the disease develop gradually. Meanwhile, vitamin D3 can attach to these receptors and prevent the corona virus from attaching to the body's organs. Thus, people who have lower levels of vitamin D3 absorbed during this epidemic should take vitamin D supplements to maintain an optimal level of 25 (OH) D in the blood. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations. There is insufficient evidence between level of vitamin D3 intake and mortality rate of COVID-19 in patients. This review summarizes some of the latest findings about the role of vitamin D3 in COVID-19 infections, severity, and mortality.

Keywords: COVID-19; Infections; Clinical observations; Vitamin D3; ACE2

Introduction

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1, 25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol (Table 1) [1]. Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert 25(OH)D to 1,25(OH)2D. Serum concentration of 25(OH)D is the best indicator of vitamin D status [2,3].

Vitamin D and its metabolites may be classified as calciferol (vitamin D3) or ergocalciferol (vitamin D2). Calcipherol (vitamin D3) is a compound in the vitamin D family that is naturally produced in the skin from 7-dehydrocholesterol by exposure to ultraviolet rays of sunlight. The liver converts vitamin D3 to 25-hydroxycholecalciferol, which is weakly active. The kidneys then convert this to either 24, 25-dihydroxycholecalciferol, which is also weakly active, or to 1α, 25-dihydroxycholecalciferol, and the most active form of vitamin D (Figure 1). In the past decade, several studies demonstrated a potential link between vitamin D3 deficiency

and various diseases, including systemic infection. In clinical studies, low levels of serum vitamin D were associated with acute respiratory tract infections including epidemic influenza [4,5].

In the COVID-19 epidemic, it is best to fully identify and categorize the effect of receiving vitamins, minerals, and other micronutrients in preventing as well as reducing the effects of the virus on the body. One of the most important ways to increase the body's immune function against disease is to use essential micronutrients, including vitamins related to the vitamin D family. Vitamin D3 deficiency effects on proper functioning of the immune system. Vitamin D derivatives, including vitamin D3 improve the mucosal defense system by secreting antiviral peptides, and its deficiency can exacerbate the symptoms of respiratory disease Martineau AR, et al. [6-11]. Reviewed 25 recent meta-analysis incorporating data from observational studies. They found that the derivatives of vitamin D are able to increase the strength of the immune system against viral infections [11]. The results of these studies showed that people at high risk for COVID-19 should consider taking 10,000 IU of vitamin D3 daily for a few weeks in order to rapid increase of 25 (OH) D in blood. Some studies have shown that people with severe COVID-19 symptoms and hospitalization have low serum levels of vitamin D3 (vitamin D deficiency). However, the risk factors for severe COVID-19 are the same as those for vitamin D deficiency, so it is difficult to tell if vitamin D deficiency itself is a risk factor for severe COVID-19. Risk factors include the patient's general condition, poor diet and underlying diseases, such as diabetes, and liver and kidney disease [12-14]. There was significant clinical heterogeneity and methodology in the studies, mainly due to different supplementation strategies, formulations, vitamin D uptake status in participants, and reported outcomes.

In this review, we want to address the question of whether vitamin D3 administration is an effective and safe pre-treatment for COVID-19. We will summarize the latest studies in this review.

SL No	Compounds in the group of D vitamins
1	Ergocalcoferol (calciferol or vitamin D_2)
2	Cholecalciferol (vitamin D_3)
3	Dihydroergocalciferol (vitamin D_4)
4	Sitocalciferol (vitamin D_5)
5	Dihydrotachysterol
6	25-hydroxycholecalciferol (calcifediol)
7	1α-hydroxycholecalciferol (alfacalcidol)
8	1α,25-dihydroxycholecalciferol (calcitriol)
9	24,25-dihydroxycholecaciferol

Table 1: Compounds classified in the group of vitamin D [15].

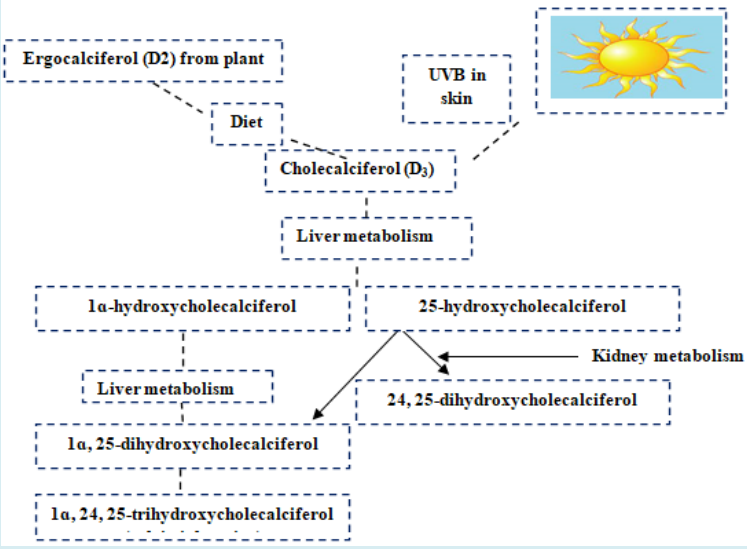

Figure 1: Metabolic pathways of vitamin D [16].

ACE-2: an Entry Receptor for SARS-CoV-2

The study was put on the health researchers' agenda because it was found that people with severe symptoms of COVID-19 had low levels of vitamin D3 in their blood. Among them, the elderly and the sick were the ones who either rarely left the house or because of the dark color of the skin, less sunlight is absorbed by their body and as a result, less vitamin D is made in their body. Angiotensin-2 converter, or ACE2 is an enzyme that binds to the outer surface (outer

membrane) of cells in the blood vessels, lungs, kidneys, heart, and intestines. This enzyme lowers blood pressure by breaking down angiotensin-2 (a vasoconstrictor peptide) into angiotensin-7-1 (a vasodilator). Angiotensin-converting enzyme 2 is the entry point for some types of coronaviruses into the body's cells. The human species of this enzyme is called hACE2 for short [17]. Unfortunately, the entry of coronavirus into cells through membrane attachment significantly reduces ACE2 receptors and loses the degradation effect of these receptors on the outer membrane. Two indicators of increased pulmonary inflammation and coagulation are as side effects of this entry [18].

This disease has a great power of transmission from person to person and seems to be due to the high ability and tendency of Spike protein to human cellular receptor ACE2 that damage organs such as lungs, heart, liver, and kidneys that have high levels of this receptor. Therefore, these organs are considered as hosts for this virus and the side effects of this disease affect these organs. However, the main target tissue of this virus is the lungs [19,20]. Both ACE inhibitors and angiotensin II receptor blockers that are used to treat high blood pressure have been shown in rodent studies to up regulate ACE2 expression hence may affect the severity of coronavirus infections. The beneficial role of ACE2 inhibitors in reducing the risk of respiratory infections by about 30% compared to the control group has been investigated in some articles. In addition to the above, it should be noted that the risk of pneumonia in patients treated with ACE inhibitors who were more prone to respiratory infectious diseases, especially in two groups of patients with stroke and heart failure was reduced. Use of ACE inhibitors was also associated with a reduction in pneumonia related mortality, although the results were less robust than for overall risk of pneumonia [21,22].

Acute respiratory failure can be due to low modulation and loss of ACE2 expression in the respiratory tissues and especially the lungs due to the entry of coronavirus into it [23]. The process of preparation, purification, as well as immunological studies of the soluble ACE2 on humans in the future also has limitations that are not addressed in this review.

Vitamin D3 Function

In general, in addition to its role in calcium homeostasis and bone metabolism, vitamin D3 is also important in strengthening and regulating the immune system. Therefore, vitamin D3 can play an effective role in preventing COVID-19 by strengthening the immune system and increasing the production of antioxidants and antimicrobial factors. Also, this vitamin can be effective in reducing the symptoms of COVID-19 disease by modulating the activity and increasing the efficiency of natural and specific immune cells, as well as reducing the inflammation caused by their excessive stimulation [24]. Several systematic studies consider the ways in which vitamin D reduces the risk of viral infections [25-30]. In a study conducted by Guven M, et al. [30] the effect of high-dose parenteral vitamin D3 on COVID-19-related in hospital mortality in critical COVID-19 patients was evaluated during intensive care unit admission through an observational cohort study. The obtained results showed that high-dose parenteral vitamin D3 administration in critical COVID-19 patients with vitamin D3 deficiency during admission to the ICU did not reduce the need for intubation, time of hospitalization, and hospital mortality rate [30]. One of the reasons why vitamin D3 administration did not show a difference in mortality in this study may be that vitamin D3 administration could not find enough time to function in the body due to the rapid progression of COVID-19. This cause can lead to death in a short time.

Vitamin D3 can increase the expression of ACE2 mRNA & protein in some tissues such as pulmonary micro vascular endothelial cells. In this case, increasing the number of ACE2 attached to the cells can act as a double-edged sword; on the one hand, it can increase the number of receptors for the virus to enter the cell in patients with COVID-19 and on the other hand the excessive ACE2 may competitively bind with the virus and neutralize it on the one hand and it saves cellular activity of ACE2 on the other hand which protect the lung from damage [31,32]. In short, vitamin D3 affects innate and adaptive immunity in a number of ways. Vitamin D3 receptors are continuously expressed on the surface of epithelial cells as well as immune system cells such as monocytes and macrophages. In addition to the above, one of the roles of vitamin D3 is to suppress the over-release of inflammatory cytokine that may lead to cytokine/chemokine storm.

Decreasing of Viral Infections Mechanisms

Vitamin D receptors are widely present in all cells of the innate immune system including B and T lymphocytes, monocytes, macrophages, and the respiratory epithelium. Calcifediol, a prohormone of the active form of vitamin D3, is calcitriol, which is mainly catalyzed to calcitriol by the enzyme 1-alpha-hydroxylase, CYP27B1, in the kidney. Calcitriol binds to vitamin D receptors in target tissues and activates vitamin D-responsive pathways, leading to increased intestinal absorption of calcium and phosphorus and decreased parathyroid hormone synthesis [15].

In this line, Castillo ME, et al. [16] conducted a pilot clinical trial in order to evaluate the effect of calcifediol treatment and best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19.

Their pilot study demonstrated that administering high doses of calcifediol to 76 consecutive patients hospitalized in the non-ICU diagnosed of COVID-19 reduces the need for ICU admission [16]. In other case, Gomez JMQ, et al. [17] stated that vitamin D receptor stimulation to reduce acute respiratory distress syndrome in patients with coronavirus COVID-19 infections [17]. They said several randomized clinical trials were being performed using orally absorbed vitamin D or calcifediol (25OHD). According to one study, oral calcifediol may be the best method. The results of these studies are expected to be published in a few months.

Many studies have suggested a link between vitamin D deficiency and the incidence of respiratory infections. Seasonal prevalence of diseases such as influenza as well as decreased serum levels of vitamin D in the cold season can also indicate an association between vitamin D deficiency and its derivatives and an increased risk of respiratory disease. A study has shown that concentrations of less than 16ng/ml of vitamin D in the body have been associated with an increased incidence of respiratory infections. Another study found that 27 Indian children with respiratory infections and vitamin D deficiency showed a significant reduction in the complications of respiratory infections when they took vitamin D supplements for six weeks [22,23].

Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration [33,34] (Figure 2).

To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000IU/d. The goal should be to raise 25(OH)D concentrations above 40-60ng/mL (100-150nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful [35,36]. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations. Vitamin D also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates both pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients [37]. Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ. administering vitamin D reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages [38].

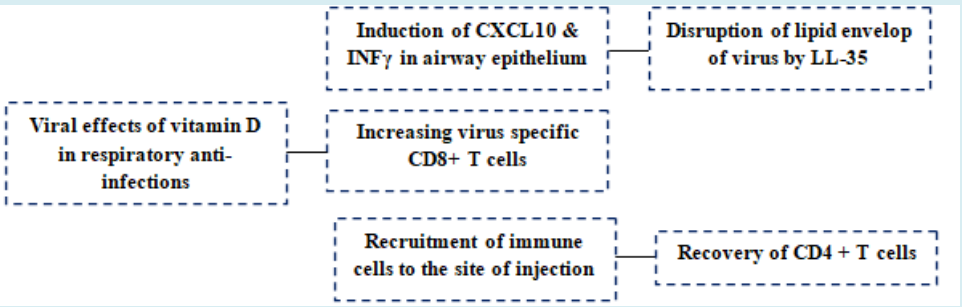

Figure 2: The regulatory effect of vitamin D on the immune system involved in respiratory infections [39].

ACE-2 is the host cell receptor responsible for mediating infection by SARS-CoV-2. Starting from this, it might suggest a higher risk of infection [40]. A recent review also supported the possible role of vitamin D3 in decreasing the risk of HIV and COVID-19 infections and mortality [41]. These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon γ and tumor necrosis factor α and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating of T cells induction. Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection [42]. Many studies have been done on the role of vitamin D and its balancing properties along with other supplements such as vitamin D3 in maintaining immune homeostasis [43-45]; well-designed randomized controlled trials are required to elucidate the plausible role of vitamin D in protective immune responses against respiratory microbes and in preventing various types of acute respiratory tract infections.

According to performed studies by Spector et al., T lymphocyte, CD4+, and macrophages infection results from

a reduction in autophagy that allows the virus to transcribe. By inducing autophagy, Rapamycin inhibits transcription of infection in monocytes. Similarly, calcitriol (D3), an active form of vitamin D, can inhibit virus transcription [46]. In a study conducted by Campbell et al., the role of autophagy in the early stages of HIV infection and the relationship between Rapamycin-induced autophagy and vitamin D3 with inhibition of infection transcription in macrophages was demonstrated [47]. According to a survey, it should be necessary to measure serum 25(OH)D levels in all inpatient and outpatient populations with COVID-19 and in different stages of the disease to identify the importance of maintaining or promptly increasing circulating levels of 25(OH)D into the optimal range of 40-60 ng/ml (100-150nmol/L) [48]. Using this measuring tool, patients with vitamin D deficiency can be identified and intensive care can be applied to these people.

Angiotensin-Converting Enzyme 2 (ACE2)

ACE2, as the key SARS receptor, does play a protective role in the cardiovascular diseases and acute respiratory distress syndrome from developing lung failure [49]. As a mentioned, the human version of the ACE2 enzyme is often referred to as hACE2. This has led some to hypothesize that decreasing the levels of ACE2, in cells, might help in fighting the infection. On the other hand, ACE2 has been shown to have a protective effect against virus-induced lung injury by increasing the production of the vasodilator angiotensin 1-7 (Figure 3) [50].

Renin-Angiotensin System

The molecular mechanism underlying the down-regulation of the intracranial Renin-Angiotensin System (RAS) induced by vitamin D is yet to be fully understood. It has been reported that the formation of the cyclic AMP response element-binding protein (CREB) and the related partner complex is blocked by 1,25(OH)2D3 9. Moreover, the other key player involved in the downregulation of the intrarenal RAS includes the transcriptional regulatory complex, comprised of nuclear receptor corepressor 1 (NCOR1), CREB1, and the vitamin D receptor, which bind to the cyclic AMP response element-like domain in the renin enhancer 9Therefore, vitamin D may suppress RAS activity through inhibition of renin and the ACE/Ang II/AT1R cascade. It has been reported that over-expression of ACE2 angiotensin converting enzyme 2 resulted in improvement of irregularities in expression related to of ACE/ACE2 and Ang II/Ang-(1-7) and alleviated lung injuries, whereas ACE2 knockout further attenuated the irregularities in expression levels of ACE/ACE2 and Ang II/Ang-(1-7), causing in exacerbated lung injuries (Figure 3) [12,51].

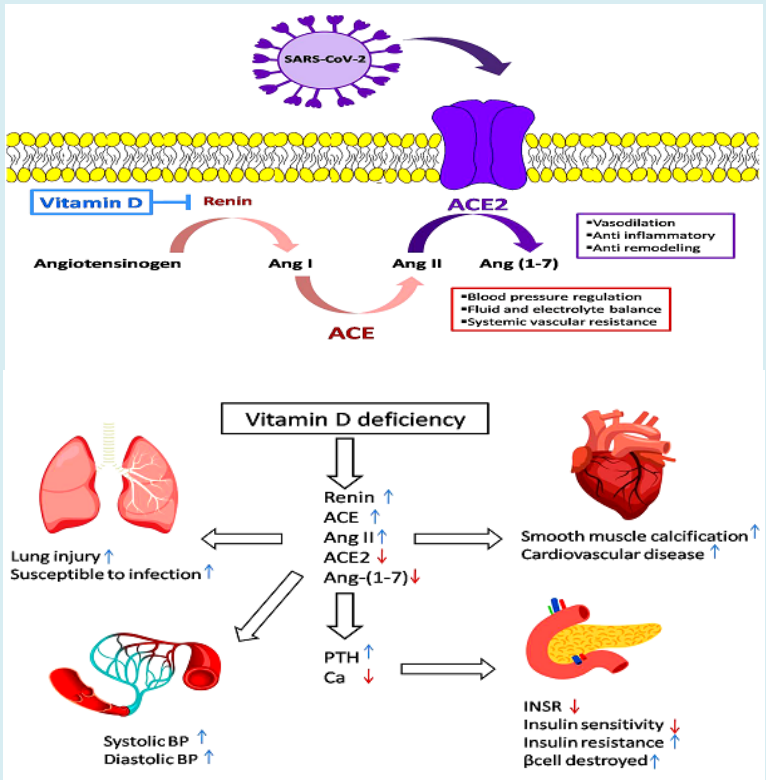

Figure 3: (a) Complications of decreased vitamin D levels in the body in the face of COVID-19 virus b) The activity of renin-angiotensin system through inhibition of renin of vitamin D [12, 51].

The Relevance of Vitamin D3 to COVID-19

Due to the rapid proliferation of the virus in a short time and the high viral load at the onset of symptoms, a combination of antiviral drugs and immune system boosters are likely to reduce the load of the virus and be effective in reducing the severity of the disease. Vitamin D as an immune booster is likely to reduce the risk of viral infection and lung damage [52]. Studies have shown that a decrease in the ratio of CD4+ to CD8+ cells, which is an indicator of the state of activation of the immune system, is associated with a decrease in calcitriol (1,25-dihydroxyvitamin D3) levels. According to a study published, patients with serum vitamin D3 levels of less than 30ng/ml were significantly less likely to experience anesthesia, hypoxia, and even death [17,53-55] (Table 2).

Another study included 25 randomized controlled trials, with 10,933 participants in total from 10 different countries indicated the beneficial effects of vitamin D3 in reducing the risk of at least one acute respiratory tract infection [8,10]. Increased production of oxygen free radicals and oxidative stress in inflammatory conditions and respiratory infections lead to damage to cell membranes and DNA. Many of the positive effects of vitamin D3 on strengthening the immune system are related to its role in the production of antioxidants to neutralize the harmful effects of oxygen free radicals on respiratory infections such as COVID-19. This role of vitamin D3 is attributed to the increased expression of enzymes that produce antioxidant agents such as superoxide dismutase 1 and 2, peroxiredoxin-3 and glutathione. [8,10]. The entry of SARS-CoV-2 into the human cells is via angiotensin-converting enzyme 2. Vitamin D inhibits renin, angiotensin-converting enzyme and angiotensin II expression, and induces ACE2 levels in air-liquid interface. Therefore, vitamin D may attenuate acute lung injury by inducing ACE2/Angiotensin [1-7] axis and inhibiting renin and the angiotensin-converting enzyme/Angiotensin II/angiotensin II receptor cascade. In conclusion, considering the protective function of vitamin D in air-liquid interface, supplementing vitamin D deficient individuals may boost the immune system to fight COVID-19 infection and reduce its severity, especially in people with associated co-morbidities. In patients with chronic heart disease, the mortality rate from respiratory infections is significantly higher than in others [56,57].

SL No	Country	Population of study	25(OH) D status	Reference
1	Iran	Meta-analysis of 48 studies including 1911 men and more than 3,600 women	Deficiency: <50nmol/L Insufficiencies: 50-75nmol/L	[58]
2	China	364 Chinese men aged 60-75	Deficiency: <50nmol/L	[59]
3	Italy and Spain	420 patients ≥65 years old admitted to rehabilitation centers	Deficiency: <50nmol/L Insufficiency: 50-75nmol/L	[60]
4	United States	26010 adults	Deficiency: <50nmol/L Insufficiency: 50-75nmol/L	[61]
5	France	297 subjects studied	Deficiency: <50nmol/L	[62]
6	UK	more than 250 patients with chronic obstructive pulmonary disease, aged 41-92 years	Insufficiencies: <50nmol/L	[63]
7	Singapore (a tertiary academic hospital) 1000 IU, Mg	43 patients (15 Jan-15 April 2020	Vitamin D 150 mg, and vitamin B12 500g (oral)	[64]
8	Belgium (Central network hospital)	186 cases, 2717 controls NA	NA	[65]
9	USA (a single tertiary academic medical center)	Adults, mean age 65.2 years	NA	[66]
10	Indonesia (Government hospital)	Adults, mean age 54.5 years	NA	[67]

Table 2: The association between vitamin D intake and COVID-19 infection in some studies.

Additional Tips

Effective regulatory effects of vitamin D3 on improving immune function have made it a non-invasive factor in the fight against infectious diseases, including COVID-19 disease [68]. Active and active X-receptor drugs during pregnancy can impair the metabolism and function of vitamin D3. Despite these points, drug-based vitamin D supplements can improve part of the systematic performance of drug treatment in some drugs, such as bisphosphonates, cytostatics, and statins. Such drugs include nonsteroidal anti-inflammatory drugs, antiepileptics, antibiotics, and blood pressure medications, drugs affecting the endocrine system, antiretrovirals, and some medicinal herbs [69]. In an open-label study, Annweiler C, et al, [70] investigated the effect of a single oral high dose of cholecalciferol versus a single oral standard dose of cholecalciferol within 14 and 28 days of inclusion on mortality rate in older adults infected with SARS-CoV-2 at higher risk of worsening. Finally, they stated that a high-dose vitamin D supplement may be an effective, convenient, and affordable treatment for COVID-19. However, there is currently insufficient scientific evidence for this [70].

In another study, Thacher TD, et al. [71] evaluated the evidence in clinical trials of vitamin D during COVID-19. Vitamin D doses greater than 100mcg (4000IU) daily should not be used without monitoring serum 25(OH)D and calcium. The highlighted point of this review article was that vitamin D doses greater than 100 mcg (4000IU) daily should not be used without monitoring serum 25(OH)D and calcium. They concluded that randomized and controlled trials are necessary to confirm the beneficial effects of vitamin D suggested by observational studies. Many observational studies and meta-analyses of clinical trials should be conducted in order to determine the exact the dose, timing, and interaction of vitamin D with other treatments. They concluded that high-risk populations for COVID-19 also suffered from vitamin D deficiency. Therefore, it seems quite reasonable to recommend accurate doses of vitamin D supplementation for the general population during the COVID-19 pandemic. However, consuming large amounts of this vitamin can lead to problems such as toxicity, manifested as hypercalcemia and nephro-calcinosis in vulnerable groups [71].

In this line, Iacopetta D, et al. [72] reviewed the latest medications and treatments updated during the treatment of COVID-19 disease. In part of this review, the effective role of vitamin D in the healing process through the ways of strengthening the immune system was mentioned [72]. In vivo and in vitro studies show that vitamin D elicits biological effects on both adaptive and the innate immune systems including macrophages, T cells, dendritic cells, monocytes, and B cells [73].

Conclusions

The results of this study indicate that vitamin D deficiency and related supplements can be considered as an important factor in the development of the risk of respiratory infections. As a mentioned, the role of vitamin D3 in patients with respiratory failure is not limited to this issue but also due to significant effects such as reducing or modulating the activity of the nonspecific and acquired immune systems and the characteristics associated with the occurrence of cytokine storms guided by the innate immune system, it can play a protective role against lung tissue damage in this disease.

We did not find many literatures that clearly and conclusively confirm the role of vitamin D3 in the recovery of respiratory patients with COVID-19 infection. However, this role can be considered as a supportive treatment method for various drug therapies. We would need evidence from well-masked randomized trials to determine if there are effects, before recommending vitamin D3 supplements for treating or preventing COVID-19 infection.

There is some evidence that vitamin D3 may have a role in preventing other respiratory infections, particularly for people with low or very low vitamin D3 status. Whilst this evidence comes from systematic reviews of randomized trials, it has many limitations, including heterogeneous definitions of respiratory infections, study populations, interventions, and definitions of vitamin D3 deficiency.

The ability of this vitamin to stimulate macrophages, neutrocytes, and natural killer cells in infection and inflammation of the lungs, as well as the epithelial tissue line, to produce antimicrobial peptides, including defensins and catalysts, is another issue that may be of interest to researchers. Studies with larger sample sizes and interventions especially the examination of the animal models can help to more accurately assess the role of vitamin D3 in COVID-19 disease and its relationship to disease severity.

References

1. (2005) Dietary Reference Intakes: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. Institute of Medicine, Food and Nutrition Board, pp: 1-1357.
2. Cranney A, Horsley T, ODonnell S, Weiler H, Puil L, et al. (2007) Effectiveness and safety of vitamin D in relation to bone health. Evidence report/technology assessment 158: 1-235.
3. Holick MF (2007) Vitamin D deficiency. New England

Journal of Medicine 357(3): 266-281.

4. Ovesen L, Brot C, Jakobsen J (2003) Food contents and biological activity of 25-hydroxyvitamin D: a vitamin D metabolite to be reckoned with?. Annals of Nutrition and Metabolism 47(3-4): 107-113.

5. Byrdwell WC, DeVries J, Exler J, Harnly JM, Holden JM, et al. (2008) Analyzing vitamin D in foods and supplements: methodologic challenges. The American journal of clinical nutrition 88(2): S554-S557.

6. Ali N (2020) Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health 13(10): 1373-1380.

7. Ebadi M, Loza AJM (2020) Perspective: improving vitamin D status in the management of COVID-19. European Journal of Clinical Nutrition 74(6): 856-859.

8. Grant WB, Lahore H, Mcdonnell SL, Baggerly CA, French CB (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12(4): 988.

9. Kow CS, Hadi MA, Hasan SS (2020) Vitamin D Supplementation in Influenza and COVID-19 Infections Comment on: Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 12(6):1626.

10. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, et al. (2020) Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 12(4): 988.

11. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. bmj 356: 6583.

12. Ghavideldarestani M, Honardoost M, Khamseh ME (2020) Role of Vitamin D in Pathogenesis and Severity of COVID-19 Infection. Arch Physiol Biochem 30: 1-7.

13. Rivera MC, Medina A, Vargas J, Gomez AM, Gonzalez E (2020) Immunological effects of vitamin D in COVID-19. Revista Colombiana de Endocrinologia, Diabetes & Metabolismo 7(S2): S94-S98.

14. Martineau AR, James WY, Hooper RL, Barnes NC, Jolliffe DA, et al. (2015) Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. The lancet Respiratory medicine 3(2): 120-130.

15. Hilger J, Friedel A, Herr R, Rausch T, Roos F, et al. (2014) A systematic review of vitamin D status in populations worldwide. British journal of nutrition 111(1): 23-45.

16. Castillo ME, Costa LME, Barrios JMV, Diaz JFA, Miranda JL, et al. (2020) Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. The Journal of steroid biochemistry and molecular biology 203: 105751.

17. Gomez JMQ, Castillo ME, Bouillon R (2020) Vitamin D Receptor stimulation to reduce Acute Respiratory Distress Syndrome (ARDS) in patients with Coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166. J Steroid Biochem Mol Biol 202: 105719.

18. Merzon E, Tworowski D, Gorohovski A, Vinker S, Cohen AG, et al. (2020) Low plasma 25 (OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS 287(17): 3693-3702.

19. Ilie PC, Stefanescu S, Smith L (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clinical and Experimental Research 32(7): 1195-1198.

20. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C (2020) Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN, pp: 1-14.

21. Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine 8(4): 420-422.

22. Lee J, Van Hecke O, Roberts N (2020) Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19. Centre for Evidence-Based Medicine Website.

23. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, et al. (2007) An association of serum vitamin D concentrations< 40 nmol/L with acute respiratory tract infection in young Finnish men. The American journal of clinical nutrition 86(3): 714-717.

24. Carter SJ, Baranauskas MN, Fly AD (2020) Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID-19 Pandemic. Obesity 28(7): 1176-1177.

25. Mccartney DM, Byrne DG (2020) Optimisation of vitamin D status for enhanced Immuno-protection against Covid-19. Ir Med J 113(4): 58.

26. Panarese A, Shahini E (2020) Letter: Covid-19, and vitamin D. Alimentary Pharmacology & Therapeutics 51(10): 993-995.

27. Hastie CE, Mackay DF, Ho F, Morales CAC, Katikireddi SV,

et al. (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes & Metabolic Syndrome 14(4): 561-565.

28. Alipio M (2020) Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19).

29. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA (2020) Perspective: Vitamin D deficiency and COVID-19 severity-plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2, and thrombosis (R1). Journal of internal medicine 289(1): 97-115.

30. Guven M, Gultekin H (2021) The effect of high-dose parenteral vitamin D3 on COVID-19-related inhospital mortality in critical COVID-19 patients during intensive care unit admission: an observational cohort study. European Journal of Clinical Nutrition 75(9): 1383-1388.

31. Panfili FM, Roversi M, Dargenio P, Rossi P, Cappa M, et al. (2020) Possible role of vitamin D in Covid-19 infection in pediatric population. Journal of Endocrinological Investigation 44(1): 27-35.

32. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C (2020) Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN.

33. Khemka A, Suri A, Singh NK, Bansal SK (2020) Role of Vitamin D Supplementation in Prevention and Treatment of COVID-19. Indian Journal of Clinical Biochemistry 35(4): 502-503.

34. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C (2020) Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN.

35. Silberstein M (2020) Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?. Medical Hypotheses 140: 109767.

36. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, et al. (2020) The possible role of Vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. MedRxiv.

37. Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, et al. (2020) Vitamin D insufficiency is prevalent in severe COVID-19. MedRxiv.

38. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, et al. (2020) The possible role of Vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. MedRxiv.

39. Rad MT, Shokri F, Salimi V, Marashi SM (2019) The interplay between vitamin D and viral infections. Reviews in medical virology 29(2): e2032.

40. Rigby WF, Stacy T, Fanger MW (1984) Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). The Journal of clinical investigation 74(4): 1451-1455.

41. Kizaki M, Ikeda Y, Simon KJ, Nanjo M, Koeffler HP (1993) Effect of 1, 25-dihydroxyvitamin D3 and its analogs on human immunodeficiency virus infection in monocytes/macrophages. Leukemia 7(10): 1525-1530.

42. Deeks SG, Kitchen CM, Liu L, Guo H, Gascon R, et al. (2004) Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. Blood 104(4): 942-947.

43. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi Aet al. (2008) The complex role of vitamin D in autoimmune diseases. Scandinavian journal of immunology 68(3): 261-269.

44. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C (2010) Vitamin D: modulator of the immune system. Current opinion in pharmacology 10(4): 482-496.

45. Costantini E, Sinjari B, Piscopo F, Porreca A, Reale M, et al. (2020) Evaluation of salivary cytokines and Vitamin D levels in periodontopathic patients. International Journal of Molecular Sciences 21(8): 2669.

46. Mazloom S, Kalayeh SMO, Najafpour A, Naeini SM, Esfandani A (2020) The Role of Vitamin D in Body Organ Systems: A Systematic Review. Archives of Pharmacy Practice 11(1): 169-182.

47. Bearden A, Van Winden K, Frederick T, Kono N, Operskalski E, et al. (2020) Low maternal vitamin D is associated with increased risk of congenital and peri/postnatal transmission of Cytomegalovirus in women with HIV. PloS one 15(2): e0228900.

48. Aissou CA, Dupre T, Grangaud JP, Assami MK (2020) Impact of vitamin D supplementation model on the circulating levels of 25 (OH) D in Algerian children aged 1-23 months. The Journal of steroid biochemistry and molecular biology 196: 105487.

49. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, et al. (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181(4): 905-913.

50. Hoffmann M, Weber HK, Schroeder S, Kruger N, Herrler T, et al. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181(2): 271-280.

51. Wu Y (2020) Compensation of ACE2 Function for possible clinical management of 2019-nCoV-induced

acute lung injury. Virologica Sinica 35(3): 256-258.

52. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, et al. (2020) Hematologic parameters in patients with COVID-19 infection. American journal of hematology 95(6): E131-E134.

53. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, et al. (2020) Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. Jama 323(15): 1488-1494.

54. Phua J, Weng L, Ling L, Egi M, Lim CM, et al. (2020) Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. The Lancet Respiratory Medicine 8(5): 506-517.

55. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, et al. (2020) Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PloS one 15(9): e0239799.

56. South AM, Brady TM, Flynn JT (2020) ACE2, COVID-19, and ACE Inhibitor and ARB Use during the Pandemic: The Pediatric Perspective. Hypertension 76(1): 16-22.

57. Meng J, Xiao G, Zhang J, He X, Ou M, et al. (2020) Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerging microbes & infections 9(1): 757-760.

58. Tabrizi R, Moosazadeh M, Akbari M, Dabbaghmanesh MH, Mohamadkhani M, Asemi Z, et al. (2018) High prevalence of vitamin D deficiency among iranian population: a systematic review and meta-analysis. Iran J Med Sci 43(2): 125-139.

59. Zhang W, Zheng X, Wang Y, Xiao H (2016) Vitamin D deficiency as a potential marker of benign prostatic hyperplasia. Urology 97: 212-218.

60. Lelli D, Bazan LMP, Egusquiza AC, Onder G, Morandi A, et al. (2019) 25(OH) vitamin D and functional outcomes in older adults admitted to rehabilitation units: the safari study. Osteoporos Int 30(4): 887-895.

61. Liu X, Baylin A, Levy PD (2018) Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications. Br J Nutr 119(8): 928-936.

62. Deplanque X, Wullens A, Norberciak L (2017) Prevalence and risk factors of vitamin D deficiency in healthy adults aged 18-65 years in northern France. Rev Med Interne 38(6): 368-373.

63. Jolliffe DA, James WY, Hooper RL, Barnes NC, Greiller CL, et al. (2018) Prevalence, determinants and clinical correlates of vitamin D deficiency in patients with chronic obstructive pulmonary disease in London, UK. J Steroid Biochem Mol Biol 175: 138-145.

64. Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, et al. (2020) Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B 12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition 79-80: 111017.

65. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA (2020) Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. Medrix 2: 1-23.

66. Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, et al. (2020) Vitamin D insufficiency is prevalent in severe COVID-19.Medrix 1: 1-14.

67. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C (2020) Patterns of COVID-19mortality and vitamin D: an Indonesian study. SSRN.

68. Guthrie G, Stoll B, Chacko S, Lauridsen C, Plat J, Burrin D (2020) Rifampicin, not vitamin E, suppresses parenteral nutrition-associated liver disease development through the pregnane X receptor pathway in piglets. American Journal of Physiology-Gastrointestinal and Liver Physiology 318(1): G41-G52.

69. Carroll M (2020) Optimizing Medication Management In COVID-19 Pandemic.

70. Annweiler C, Beaudenon M, Gautier J, Simon R, Dubee V, et al. (2020) Covid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. Trials 21(1): 1031.

71. Thacher TD (2022) Evaluating the Evidence in Clinical Studies of Vitamin D in COVID-19. Nutrients, 14(3): 464.

72. Iacopetta D, Ceramella J, Catalano A, Saturnino C, Pellegrino M, et al. (2022) COVID-19 at a Glance: An Up-to-Date Overview on Variants, Drug Design and Therapies. Viruses 14(3): 573.

73. Giannini S, Giusti A, Minisola S, Napoli N, Passeri G, et al. (2022) The Immunologic Profile of Vitamin D and Its Role in Different Immune-Mediated Diseases: An Expert Opinion. Nutrients 14(3): 473.