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REVIEW ARTICLE

Maintaining Vitamin D Balance to Mitigates COVID-19 Infection and Boosting Immune System

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ABSTRACT

The COVID-19 outbreak can be termed as a biological disaster, which has taken many lives all over the globe. Almost the entire global population has been affected by the virus, and the impact ranged from mild to severe. Still, there is no such targeted medication to prevent its severity. Some protective factors help to suppress the virus intensity, but the exact mechanism is unknown. Hence, to reduce the severity of the infection, preventive health measures is required as early as possible. Vitamin D plays an immunomodulatory role and helps to increase the innate and adaptive immune function and secretion of antiviral peptides. The serum's insufficient vitamin D level is directly linked with acute respiratory tract infections (RTI), including epidemic influenza. Randomized clinical trials showed that vitamin D supplementation against the fast-spreading of SARS-CoV-2 infected patients reduced the risk compared with those at higher risk of vitamin D deficiency during this global pandemic. Thus clinicians stated that patients those have insufficient vitamin D level in blood during this global pandemic, have recommended vitamin D supplement to maintain the circulating 25-hydroxycholecalciferol [25(OH) D] in the optimal levels (75–125 nmol/L). With this view this review elaborately discussed the probable preventive roles of vitamin D in reducing the risk of COVID-19.

Keywords: Vitamin D supplementation; COVID-19; SARS-CoV-2 Infections; innate immunity; adaptive immunity

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INTRODUCTION

The world is still fighting the COVID-19 pandemic, and the fear is still looming despite the vaccination drive throughout the world. The emerging strains have become the cause of concern as the virus changes its form for its survival.[1] Many researchers worldwide have put forward evidence supporting a strong correlation of the immune system and responses of the body against the SARS-CoV-2 infection.[2] Observational studies have suggested that the development of respiratory infections can be lowered by vitamin D supplementation.[3] Vitamin D plays a critical regulatory role in both types of immunity. Some researchers have shown that vitamin D given as a supplement to COVID-19 patients showed less severity in disease manifestation.[4,5] A pilot randomized clinical study showed that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, the main metabolite of the vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease.[6]

COVID-19 pandemic has inequitably impacted people who showed insufficiency or deficiency of vitamin D, especially in minority ethnic populations, elderly, and nursing home residents. Moreover, because of lockdown restrictions worldwide, people were forced to spent time indoors which also impacted the physiological levels of vitamin D synthesized from sunlight. Vitamin D is a multifunctional hormone and has an important role in phosphorus–calcium metabolism and immune responses.[7-9] It shows anti-inflammatory, antiviral, and antioxidant activity. The importance of nutritive food and supplements cannot be overruled, not just during the infection but before and after. The infected body becomes weakened especially when these cause fever. The body needs extra energy and nutrients to regain strength.

Vitamin D and Health

Ergocalciferol (Vitamin D_2) is a fat-soluble vitamin essential for strong bones. It is not a vitamin, but a prohormone, or precursor of a hormone. It helps in the regulation of calcium metabolism, which leads to bones growth and development.[10,11] Deficiency of vitamin D causes rickets, a disease marked by a lack of mineralization of bone. Naturally, when skin is exposed to ultraviolet

light its synthesized vitamin D. Vitamin D containing dietary supplements fulfill the daily requirement. 1, 25-dihydroxycholecalciferol (calcitriol) is the active form of Cholecalciferol (Vitamin D_3) takes a vital role in maintaining blood calcium and phosphorus balance and helps in bone mineralization (Figure 1). This active form binds to the receptors of vitamin D and modulates gene expression.[12] The process helps to elevate blood calcium concentration by increasing intestinal absorption of *phosphorus* and *calcium*, facilitating renal distal convoluted tubular (DCT) reabsorption of calcium and increasing osteoclastic resorption.[13]

Apart from Bone development and mineral metabolism, vitamin D has multiple important roles in the body, such as supporting the immune system, brain & nervous system health and regulating insulin levels. It also has a role in supporting diabetes management, supporting lung function & cardiovascular health and influencing the expression of genes involved in cancer development.[14,15] Normally, from dietary sources, people take the daily recommended requirement i.e. 800 IU (20 mcg). But it is observed that up to 50% of the world's population may not get enough sun so, it required more dietary intake i.e. 1000 IU (25 mcg) to maintain the daily requirement. Common foods such as leafy vegetables, cereals, egg yolks, oily fish and whole milk are the chief sources of vitamin D. Intake of proper nutritional diet maintain vitamin D level in the blood and makes the body functional.[16]

Innate and adaptive, the two types of the immune system, are responsible and equally important for fighting infection.[17] Innate immunity is mainly responsible for quickly killing the diseases causing pathogens whereas adaptive immunity is responsible for generating antibodies against abruptly increasing antigens. During infection, vitamin D plays a crucial role in maintaining immune stability.[18-20] The body's immune systems stay balanced during the cold and flu season with this interaction of vitamin D. Insufficient level of vitamin D developed upper respiratory tract infection. The scientific study stated that lower vitamin D levels are prone to various infections, including influenza. A study on children showed that 42% of influenza-infected patients have a decline in vitamin D levels in the body. There is a tendency for severe infection if the body has insufficient vitamin D levels, which means a direct correlation between immunity and vitamin D level.[21-23]

Food Sources of Vitamin D Supplement

People get vitamin D through food and by exposure to sunlight. Proper growth, development, and immune function require sufficient vitamin D. It helps calcium metabolism, one of the main building materials of strong bone.[24] Calcium and vitamin D jointly protects osteoporosis, rickets, and osteomalacia, which helps proper muscular movement and neuromuscular transmission. The body's immune system also needs required vitamin D to fight against bacteria and viruses.[25]

Fortified foods like cow's milk, orange juice, various breakfast cereals are provided most of the vitamin D. Fatty fish like trout, salmon, tuna, and mackerel, and fish liver oils are among the best natural animal sources vitamin D (Table 1). Beef liver, cheese, and egg yolks have small amounts of vitamin D. Mushrooms provide a little vitamin D.[26,27] Some mushrooms have been exposed to ultraviolet light to increase their vitamin D content.

The Required amount of vitamin D to maintain the various function depends upon age and physical conditions. Average daily recommended amounts are presented in Table 2.

Deficiency of Vitamin D

Vitamin D is extremely important for various health benefits. It acts like a hormone and maintains homeostasis while playing an key role in immune function. Both innate and adaptive immune functions are directly connected with this vitamin.[28] A decreased level of vitamin D increases the risk of illness and infection. A low level of vitamin D caused excessive fatigue and tiredness. Intake

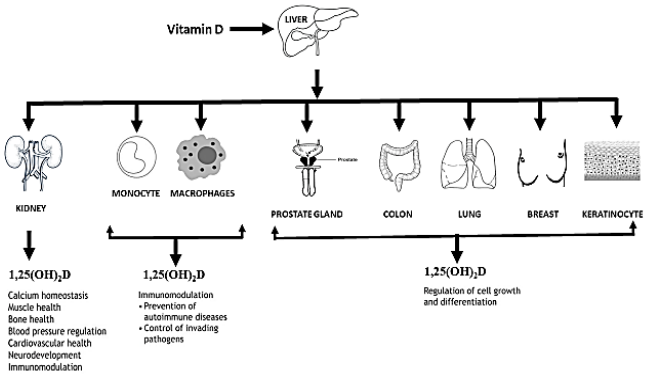

Figure 1: Role of vitamin D on human health

Table 1: Vitamin D enrich food ingredients

S. No.	*Food Ingredients*	*Vitamin D (IU)*
1	Cod Liver Oil	1,360
2	Salmon fish	360
3	Mackerel fish	345
4	Tuna fish	200
5	Sardines fish	250
6	Orange juice	100
7	Milk	98
8	Cereal	40
9	Egg	20
10	Liver	15
11	Cheese	10

Table 2: Recommended doses of vitamin D in different ages including Pregnant and lactating woman

Sl. No.	*Age*	*Recommended dose*
1.	0 to 12 months	10 mcg (400 IU)
2.	1 years to 13 years	15 mcg (600 IU)
3.	14 years to 18 years	15 mcg (600 IU)
4.	19 years to 70 years	15 mcg (600 IU)
5.	Above 71 years	20 mcg (800 IU)
6.	Pregnant and lactating woman	15 mcg (600 IU)

Table 3: Various health complications due to vitamin D deficiency

S. No.	*Vitamin D deficiency symptoms*
1.	Decline Bone growth and development
2.	Prone to infection
3.	Fatigue and tiredness
4.	Back pain
5.	Abdominal pain
6.	Depression
7.	Stress and anxiety
8.	Impaired wound healing
9.	Bone loss and effects on calcium metabolism
10.	Hair loss
11.	Hypertension
12.	Cardiovascular complexity

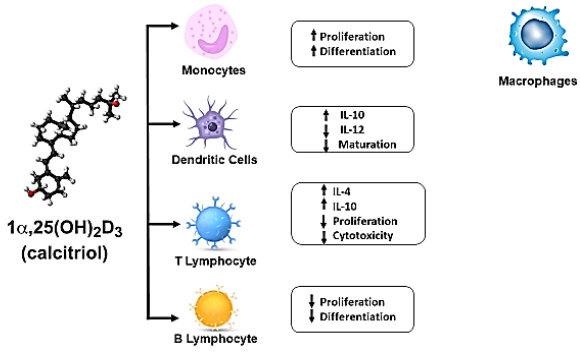

Figure 2: Immunomodulatory role of vitamin D

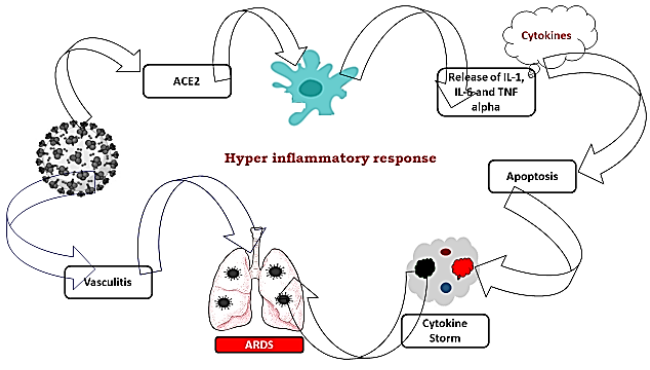

Figure 3: Hyper inflammatory response of vitamin D during COVID infection

of vitamin enriches dietary supplements improve energy levels and decline fatigue and tiredness.[29]

On the other hand, insufficient vitamin D weakens bone development and decreases calcium metabolism. It also develops depression and creates stress-like symptoms (Table 3). Inadequate vitamin D levels may lead to poor wound healing following injury and infection.[30,31] In elderly people and menopause women, insufficient vitamin D developed osteoporosis. Excessive hair loss in a woman was caused by inadequate vitamin D levels.[32] Deficiency of vitamin D developed chronic pain and a decline in normal neural function.

Immuno-modulatory Role of Vitamin D

Vitamin D is a fat-soluble steroid hormone precursor that arises from ultraviolet B (UVB) radiation exposure of 7-dehydrocholesterol (7- DHC) in the epidermis of the skin, where it is transformed into the circulating precursor cholecalciferol.[33,34] In the liver, cholecalciferol is hydroxylated to form 25-hydroxyvitamin D, which is transformed into the active hormone 1,25-hydroxyvitamin D (1,25(OH)2D) in the kidneys (Figure 2). Vitamin D has roles in a wide range of body systems, including innate and adaptive immune responses Vitamin D enhances innate cellular immunity through stimulation of expression of antimicrobial peptides, such as cathelicidin and defensins. Defensins maintain tight and gap junctions, adherens and enhance the expression of anti-oxidative genes.[35-37] Viruses such as influenza are known to significantly damage the integrity of tight epithelial junctions, increasing the risk of infection and pulmonary oedema.[38] Vitamin D is known to maintain the integrity of these junctions with low levels of vitamin D receptor expression leading to increased expression of claudin-2 and inflammation.

Role of Vitamin D on COVID-19 Induced ARDS

Cytokines and chemokines storms and alteration of neutrophil activity are common phenomenun during viral infection. Vitamin D plays a vital role in maintaining cellular integrity. Sufficient vitamin D levels in the bloodstream decrease the storm of cytokines and chemokines and modulate the neutrophil activity and the renin-angiotensin system.[39] The activity of the vitamin D maintained the characteristic features of pulmonary epithelial cells, inhibited infection. A recent study on the murine model showed that sufficient vitamin D receptors helps to developed adaptive immunity leads to the production of antibodies.[40] The current clinical observational report stated the use of vitamin D for the prevention and/or management of ARDS (acute respiratory distress syndrome) in the setting of COVID-19. Another study also highlighted that majority of COVID-19 ARDS patients (Figure 3) have vitamin D deficiency. The

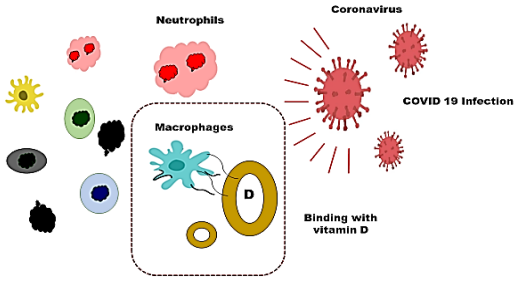

Figure 4: Molecular mechanism of vitamin D on innate immunity

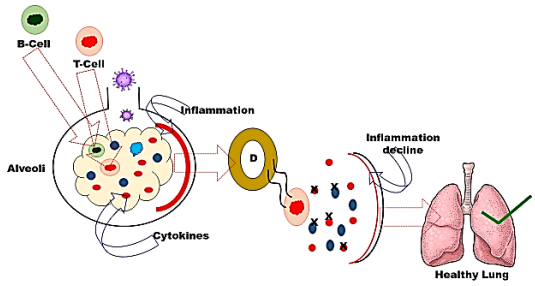

Figure 5: Molecular mechanism of vitamin D on adaptive immunity

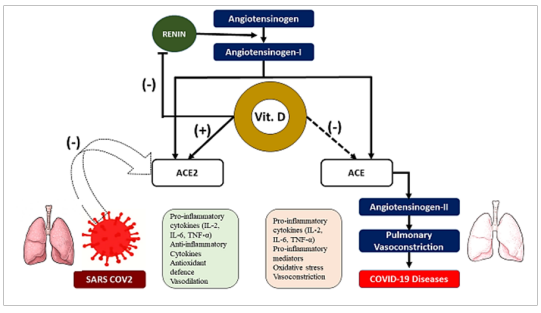

Figure 6: Immune boosting action of vitamin D during COVID infection and its mode of action

researcher stated that low levels of 1,25-dihydroxyvitamin D were associated with prolonged mechanical ventilation and low oxygen level.[41,42] The serum levels of both 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D need to be regulated in patients suffering from life-threatening COVID-19 induced ARDS, and which would give clue to the role played by both the isoforms in COVID-19 induced ARDS, and mechanistic insights into the impact of vitamin D levels on pro- and anti-inflammatory immune responses.[43]

Immune Regulation by Vitamin D

The immune system protects the body from invading foreign pathogens, and vitamin D play an important role in modulating innate and adaptive immune responses. The deficiency of vitamin D increases the body's susceptibility to infections.[44-47]

Role of Vitamin D on Innate Immunity

The first line of defense in the body is innate immunity. B and T cells play a vital role when the body attacks pathogens, bacteria, and viruses (Figure 4). After body attacks by infectious agents certainly developed more neutrophils and macrophages, play a major role in killing foreign antigens. At this stage, vitamin D binds with macrophages and facilitates gene expression that kills the pathogens.[48,49]

B) Role of Vitamin D on Adaptive Immunity

Defensive action against pathogen adaptive immune response is the second line defense system. Mainly B-cell and T-cells takes a vital role in adaptive immunity (Figure 5). These two cells produced specific antibodies that fight against unwanted foreign molecule and protects our body against infection.[50,51] During this continuous biological process, these immune cells develop antibodies to protects the body from foreign infection. When the body is severely affected by infection, the adaptive immune system releases cytokines, which creates cytokines storms. Cytokines are mainly small proteins that attract more immune cells to the affected area during infection and develop local inflammation.[52] This inflammation gradually persists and makes severe sometimes. In this condition, if the body has sufficient vitamin D in the blood that enters the cell and binds with T cells, gene expression gets more power to destroy pathogens.[53] Lungs being partially protected from the coronavirus infection with the help of vitamin D. Both Innate and adaptive takes a vital role in protecting the lungs during infection.

Role of Vitamin D in Regulating COVID-19

Researchers have reported in many countries of the world that the average vitamin D level has a strong link with the number of COVID-19 infections and the associated death due to the infection.[54,55] The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality.[56] To reduce the cases of COVID-19 infection, criticality, and mortality from COVID-19 the vitamin D supplementation (Figure 6) is recommended.[57] Vitamin D supplementation could prevent and treat influenza, coronavirus, and pneumonia infections.[58]

The data from a retrospective cohort study by Demir *et al.* also found that vitamin D deficiency was associated with greater infection probability by a coronavirus. The patients who were found to be COVID-19 positive having adequate vitamin D levels showed remarkably lesser D-dimer levels in the blood and lower CRP level, which is the inflammatory marker, decreased recurrence of ground-glass opacity in CT scan of chest region and brief hospital stay.[59] Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease.[60,61]

CONCLUSION

The patients suffering from severe coronavirus 2019 infection show severe acute distress syndrome, myocarditis, microvascular thrombosis, cytokine storms, and presence of pneumonia, and all these symptoms implicate underlying inflammation. T regulatory lymphocytes are the provider of defense against any viral infection and uncontrolled inflammation. It has been observed that many COVID-19 patients have lower levels of T regulatory lymphocytes, which can be elevated by providing supplementation of vitamin D. Moreover, if the patients are diabetic or obese, they show Vitamin D deficiency, and these patients too have high mortality risk. The suggestion is that if the severity of COVID-19 concerning inflammation, pneumonia, thrombosis, and cytokines can be reduced through vitamin D supplements, then in the large interest of society, the pandemic management could become relatively easier by vitamin D supplementation. It is always to keep in mind that the usual supplement should be taken only under medical supervision, not randomly.

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Author Contributions

All authors made a significant contribution to conducting the study, whether in the conception, literature review, drafting, preparation of data, acquisition of data, and interpretation. After critically reviewing the article, the authors gave final approval for publication, the journal of choice, and the accountability for all aspects of the work.

Data and materials availability

All data associated with this study are present in the paper.

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