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Impacts of vitamin C and D supplement on COVID-19 treatment: possible patho-mechanisms and evidence from different countries

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Abstract

Background A balanced diet and nutrition greatly influence our immune system's ability and regulate the risk and severity of infections. This review presented the possible patho-mechanisms of vitamins C and D in COVID-19 immunity.

Main body Deregulation of the immune system including the decreased level of immune boosters is invariably reported in COVID-19. Vitamin C and vitamin D are among the immune boosters; homeostasis of those was found essential for fighting against the viruses, and COVID-19 is no exception. Statistical data strengthens the statements put forth on the effects of these vitamins regarding the complications, symptoms, and mortality.

Short conclusion A comprehensive literature review revealed that vitamin C helps to reduce and in some cases eradicate the particular symptoms that pose major risks of COVID-19 while balanced vitamin D content in COVID-19 patients has been proved to possess a negative correlation with mortality.

Keywords Vitamin C, Vitamin D, COVID-19, SARS-CoV-2, Treatment, Mechanism

Background

The COVID-19 pandemic caused by SARS-CoV-2 has rampant the homeostasis of the global economy, politics, and livelihood. More than 100 million people have been affected by this infectious disease with almost 3 million deaths to date [1–4]. The clinical features of COVID-19 are varied from non-symptomatic or moderate illness to severe respiratory problems and possibly death [5]. Deregulation of the immune system including cytokine storms is found to be an important indicator of COVID-19 severity. Immune-boosting therapeutics and diet are found to play an important role to fight COVID-19. The deficiency of immune-boosting vitamins C and D is reported to increase the risk and severity of COVID-19 [6]. Vitamin C and vitamin D supplement

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stimulates antiviral activity and prevents cytokine storms in COVID-19 patients and results in a good outcome [7].

In this review, we will highlight the underlying mechanisms of vitamin C and vitamin D in boosting antiviral activity and preventing cytokine storms in COVID-19 patients. We also summarize aggregative evidence of both vitamins' work against COVID-19.

Main text

Mechanisms of vitamin C in antiviral activity and preventing cytokine storm

Vitamin C, also known as ascorbic acid, is an essential component for the growth, development, and repair of the body [8]. It acts as a multi-regulator in our body to protect and reduce the severity of various diseases. The immunomodulatory activity of vitamin C plays a role in both innate and adaptive immunity which can protect the physical tissue barrier [9]. It performs an important part in tissue repair by down-regulating the cytokines and safeguarding the endothelium from oxidant injury [9].

Vitamin C activates neutrophils including TNF and IL-1β, which activates the inhibitor nuclear transcription factor kappa B (NFkB), and stops the cytokine production in the alveolar space (Fig. 1). On the other hand, activation of TNF and IL-1β blocks NETosis (neutrophil extracellular trap) that hampers the cytokine production in the alveolar space [10]. As a result, a cytokine storm does not take place. Moreover, vitamin C helps in the development and maturation of T lymphocytes during the period of infection [9]. Matured lymphocytes and macrophages also help to decrease the number of cytokines and protect from cytokine storms (10, Fig. 1).

The antioxidant activity of vitamin C reduces oxidative stress by decreasing reactive oxidative species (ROS) [9, 11]. Moreover, the antioxidant activity of vitamin C helps to protect the epithelial barrier [11]. On the other hand, vitamin C acts as a cofactor for many enzymes and helps the biosynthesis of hormones such as norepinephrine, catecholamines, and vasopressin; methylation of DNA; and histones [11]. Vitamin C also has antimicrobial properties (such as antifungal, antibacterial, and antiviral) which protect the body from diseases [12].

Mechanisms of vitamin D in antiviral activity and preventing cytokine storm

Vitamin D is a fat-soluble vitamin, responsible for calcium homeostasis and bone metabolism. In addition, vitamin D plays an important role in boosting immunity and reducing the severity of many infectious diseases. Vitamin D helps the maturation and differentiation of

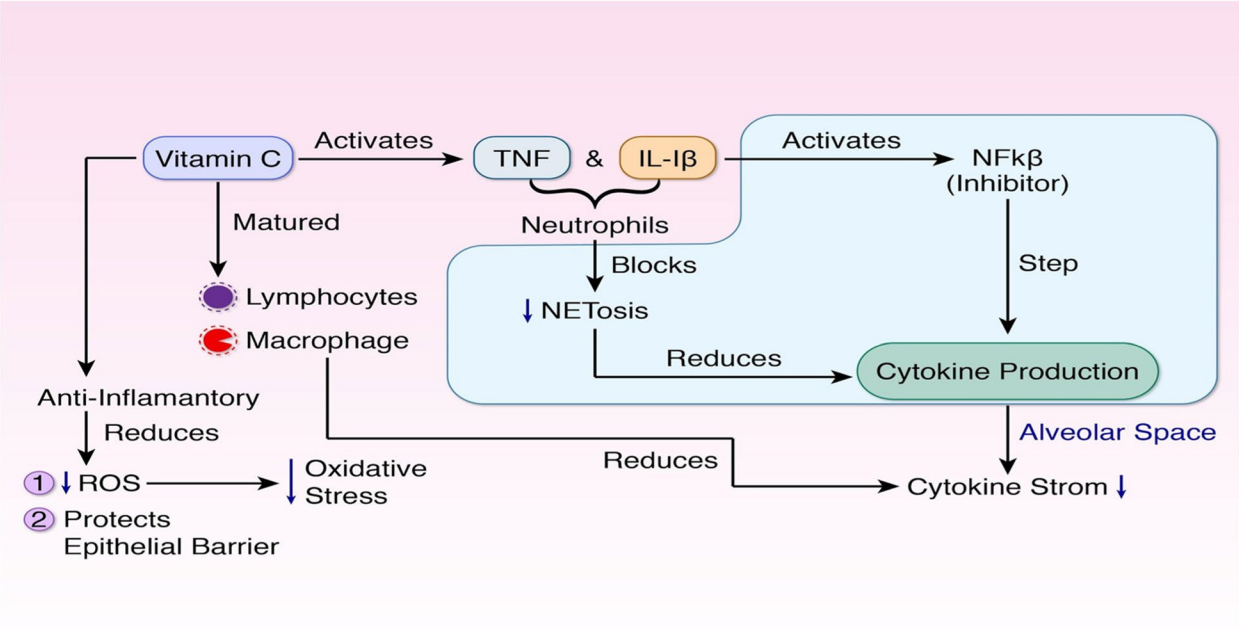

Fig. 1 Vitamin C. Its immunomodulatory activities prevent the formation of cytokine storms in two ways. **a** It activates neutrophils (TNF and IL-1β) which block neutrophil extracellular trap (NETosis) in the alveolar space. On the other hand, the neutrophils also inhibit nuclear transcription factor kappa B (NFkB). These two ways prevent the formation of cytokines in the body. **b** Vitamin C also matures lymphocytes and macrophages in the prevention of cytokine storms. Moreover, vitamin C has anti-inflammatory activities, reduces reactive oxidative species (ROS), and protects the epithelial barrier. These activities of vitamin C protect the body from diseases and also reduce the severity of diseases

monocytes and macrophages and plays a role in the production of T lymphocytes [13]. Unfortunately, billions of people around the world are reported to have a deficiency in vitamin D and are prone to many infectious diseases [14].

Vitamin D also has anti-inflammatory features and can inhibit the expression of pro-inflammatory cytokines including IL-10, IL-21, and IL-1 s with help of macrophage and T-cells, as a result, preventing cytokine storms [11, 15] (Fig. 2).

Vitamin D exhibits antiviral activity. When the viral infection increases, vitamin D gets activated and helps increase the production of antimicrobial peptide cathelicidin (LL-37) and reduce the viral infection [13, 16].

Evidence of vitamin C in reducing COVID-19 severity

The immune-modulatory and antimicrobial activity made vitamin C an important factor in many chronic and infectious diseases [17]. Most studies have reported that a high dose of vitamin C supplement correlated with reduced infection and inflammation susceptibility and lower hospitalization and requirement for mechanical ventilation, as well as reduced mortality (Table 1). On the other hand, a low dose of vitamin C has been shown to cause an insignificantly lower level of thrombosis (Table 1).

Role of vitamin D

The optimum performance of our immune system is incredibly influenced by vitamin D. Its insufficiency has been associated with a vulnerability to respiratory infections [36, 37]. The necessary amount of vitamin D for our bodies is obtained via food supplements or sunlight. 7-Dehydrocholesterol, the precursor to vitamin D, becomes active when sunlight contacts the skin, and the ultraviolet B (UVB) rays then transform it into vitamin D3. Vitamins D2 and D3 are transformed by our liver into 25-hydroxyvitamin D3 [25(OH)D3]. COVID-19 patients with vitamin D deficiency exhibited increased infection and susceptibility, higher mortality, and increased ARDS. Vitamin D supplement has been found to lower viral multiplication and lower susceptibility and inflammation and ICU need (Table 2).

Summary

Compilation of the comprehensive literature studies revealed that supplementation of vitamin C and vitamin D at an early stage of COVID-19 infection is highly beneficial for patients. Interestingly, both the vitamin C and vitamin D supplement work better if given in high doses for a long period. More critical and hospitalized COVID-19 patients were also found associated with vitamin C and vitamin D deficiency. However, studies undertaken by different groups on various populations report heterogenous outcomes of vitamin C and D supplements. Additionally, different physicians prescribed

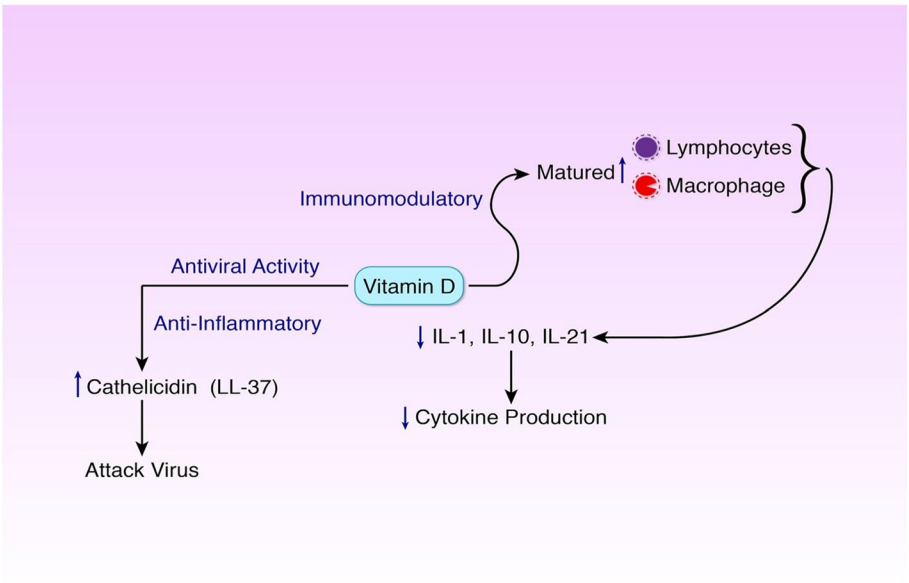

Fig. 2 Vitamin D. It has three activities. **a** It has immunomodulatory activity. Here, it matures lymphocytes and macrophage. **b** Its anti-inflammatory activity decreases the level of IL-1, IL-10, and IL-21. As a result, the level of cytokine decreases. **c** In its antiviral activity, vitamin C increases the level of cathelicidin (LL-37) which attacks viruses. Vitamin D helps to protect the body from diseases and reduce the severity of diseases

Table 1 Effectiveness of vitamin C supplement in COVID-19 treatment in different populations

Treatment	Key findings	References
High dose of vitamin C	Reduced inflammation and severity of the disease and improved oxygen saturation	[18, 19]
	No effect on the number of needed ventilation days	[20]
	Increase in oxygenation and reduction in the amount of inflammatory markers were observed	[21–23]
	Reduced overall mortality	[24]
	Lower rates of mechanical ventilation and cardiac arrest	[25]
	Lower rate of hospitalization	[26]
	No significant outcomes	[27–29]
Low dose of vitamin C	No difference was found in the case of mortality rate and the need for mechanical ventilation	[30], [5, 31–33]
	Lower level of anti-inflammatory response observed	[34, 35]
	Lower rate of thrombosis	[30]

Table 2 Effectiveness of vitamin D supplement in COVID-19 treatment in different populations

Treatment	Key findings	References
Vitamin D deficiency	Increased mortality	[36, 38]
	Increased COVID-19 susceptibility	[39]
	Intensified acute respiratory distress syndrome (ARDS)	[39]
	Increased rate of infection	[40]
Vitamin D supplement	Lower rate of ICU need	[41]
	Lower level of fibrinogen	[42]
	Lower level of ARDS	[39]
	Lower severity	[43]
	Increased level of anti-inflammatory cytokines and decreases levels of pro-inflammatory cytokines, boosts the production of natural antimicrobial peptides, and activates cells like macrophages that can kill SARS-CoV-2	[39]
	Increased human cationic antimicrobial protein (hCAP18) in pregnant women, play role in the post-SARS-CoV-2 infection treatment	[17]
	Positively impacts on the innate and adaptive immune system. Significantly reduce pro-inflammation by selectively inhibiting inflammatory cytokines, decreasing leukocyte infiltration, increasing memory and regulatory T cells, and lowering the lymphocyte ratio	[44]
	Lower viral multiplication	[45]

different doses and courses of vitamins C and D, which indicates the requirement for precise guidelines. The studied population size was also too small to make any concrete decision. Intravenous supplementation of vitamin C and vitamin D works better than taken orally. Efficacy and safety are the two major concerns for treating COVID-19 patients with vitamins C and D. As the rate of vitamin C metabolism in blood is high, larger doses along with longer courses of vitamin C are recommended. A high dose of vitamin C has been used for decades. Recently, an NIH expert panel states that a high dose of vitamin C (1.5 g/kg body weight) is safe without major adverse effects (https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq). None of the trials revealed any major side effects of using high doses of vitamins C and D in the patient's body. On the other hand, it is obvious that the result may vary with different populations and patients with other comorbidities [46–49]; thus, more detailed studies are required. Apart from the COVID-19 treatment, vitamin C is generally safe. But for some people, it may cause stomach cramps, nausea, and headache. Taking more than 2000 mg/per day is unsafe and may cause kidney stones and severe diarrhea. Similarly, a high dose of vitamin D can cause stomach discomfort, unusual symptoms, or kidney problems. Thus, COVID-19

patients are prescribed to take vitamins C and D as per doctor's advice.

Conclusions

Mode of administration, dosage, initiation time, treatment duration, disease type, and disease progression play an effective role in the results of the studies regarding the effectiveness of vitamin C and vitamin D on COVID-19. Despite not getting any significant results, there is still a possibility to find the effectiveness of these two vitamins on COVID-19 as the results were not fully negative. As no significant side effects were observed, vitamin C and D supplement may be advised specially for hospitalized critical COVID-19 patients.

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Authors' contributions
MK conceived the study. MJH designed the study. MH and DC wrote the draft manuscript. KA, MK, and MJH edited and revised the manuscript. All the authors approved the final version of the manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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