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Review Article

Vitamins and Immunity in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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Abstract

COVID-19 is known as a revolution in health system around the world. Till February 2025, it has caused 7,010,681 people to die. And thanks to vaccines and immune responses 675,619,811 people were recovered. As there is no specific treatment for this disease, it's necessary for recognizing supplements to strengthen the immune system in order to reduce the risk of infection. Food is a well-established portion with adequate amounts of macronutrients and micronutrients, which are all essential for the precise function of the immune system. Amongst the micronutrients, vitamins A, C, D, E, and B have crucial roles in the efficient response of the immune system to infections. They might have roles in T cell exhaustion reinvigoration and, through this, enhance immune responses in order to chronic infections. This study aimed to discuss the role of vitamins in the immune system and their impact on the defense against COVID-19.

Keywords: COVID-19; Immunity; Infection; SARS-CoV-2; Vitamins

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a positive-stranded RNA virus, is a member of the β-coronaviruses subfamily. In 20% of people, the SARS-CoV-2 virus causes immunopathology and severe tissue damage due to inadequate or overactive immune system response (1-3). Consequently, fighting against SARS-CoV-2 requires a proper and controlled immune response (4). Although vaccines had a major role in controlling the disease, still there is no specific treatment for this viral infection and the immune system is the main player to defend against this disease. (5, 6). In this regard, nutrition has a crucial role in regulating the immune function (7). According to the latest research, adequate amounts of macronutrients and micronutrients are pivotal for the precise functioning of the immune system to fight against infections (7, 8). Among micronutrients, vitamins A, C, D, E and B have momentous character in this regard (7, 9). So, herein, the vital role of vitamins in the functioning of the immune system and their effects on the defense against SARS-CoV-2 is reviewed. Plenty of clinical trial studies regarding the effects of vitamins A, C, D, and B3 on the treatment of COVID-19 were pursuing in Iran, Italy, France, the US, and Spain (10). An updated systematic review of clinical trials in prevention and management of COVID-19, included 37 related arti-

cles and did a meta-analysis. They claimed that most of the reviews and clinical trials should have been done with more quality (11). Based on the epidemiological (12, 13), hypothetical (14), and retrospective researches (15-22), Vitamin D has a significant role in terms of prevention, treatment, and death reduction from COVID-19. The outcome of a meta-analysis shows us, take vitamin D supplements as a safe agent will have a crucial role in the prevention of acute respiratory tract infections, especially in individuals who suffer from vitamin D deficiency (23). Findings from a clinical study in Singapore showed that taking vitamin D with magnesium and vitamin B12, improved COVID-19 patients and reduced the need for oxygen therapy (24). And studies revealed that vitamin D can be effective through (renin-angiotensin-aldosterone system) RAAS regulation and improve anti-inflammatory role of immune system (11, 25). The results of two clinical trials conducted in China and the US showed that IV injection of vitamin C in patients with COVID-19 reduced the inflammatory markers, and improved health (26, 27). A hypothetical study also suggested that due to the role of vitamin B12 in the production of anti-inflammatory agents and inhibition of RNA-polymerase, it may be predicted to be effective in reducing the symptoms of COVID-19 (28). But others claimed that vitamins A and B might not be crucial against respiratory diseases (11). Therefore, although there are promising results so far in terms of the effect of vitamins on the improvement of COVID-19 disease, their use for treatment requires extensive clinical studies. Understanding the roles of vitamins in enhancing immune responses and their impact on exhausted T cells during chronic infections is crucial for developing effective therapeutic strategies. This knowledge not only deepens our insight into immune regulation but also equips us to better prepare for future epidemics by optimizing immune function and resilience.

Vitamin A

Vitamin A is a generic name that refers to a group of fat-soluble compounds, found in two dietary sources: preformed retinoids and pro-vitamin A carotenoids. Animal food such as liver, fish and eggs are the major source of preformed vitamin, while carotenoids are naturally found in a wide range of plants, including colored fruits and vegetables (29). Deficiency of vitamin A could susceptible individuals to visual disturbances, anorexia, epithelial differentiation, and impaired function of the innate and acquired immune system (30). Animal studies have shown that vitamin A deficiency causes atrophy of lymphatic organs such as the thymus, spleen, and lymph nodes (31). Vitamin A participates in the development of goblet cells, mucus secretion, and the maintenance of ciliated epithelial covering in the respiratory and gastrointestinal tract. So, it's deficiency can increase the incidence of infectious diseases and mortality by reducing the number of goblet cells and disruption of mucosal and epithelial integrity (31, 32). Vitamin A has some vital function in the innate immune system as follows: fighting against infectious agents by regulating the number and function of NK cells, enhancing the phagocytic activity of macrophages, enhancing the neutrophil extracellular traps (33), and cytotoxic activities (32, 34, 35). In the acquired immune system, vitamin A plays a role in the development of thymocytes (36), homing of TCD4+, TCD8+ lymphocytes and B lymphocytes to mucosal tissue and their survival and function (32, 34). This vitamin differentiates B lymphocyte cells to IgA-producing plasma cells (7). In the inflammatory conditions, it maintains the stability and function of T-regulatory cells and inhibits their differentiation into inflammatory T-cells such as Th17 (37, 38). Vitamin A often differentiates Th cells to Th2 and induces anti-inflammatory immune responses (39). Therefore, due to the role of vitamin A in regulating the response of the innate and acquired immune system, vitamin A deficiency can increase the incidence of infectious diseases spread from the gastrointestinal and respiratory systems (32). Vitamin A is also a proven treatment in respiratory diseases such as pneumonia and measles (40, 41). On the other hand, reports show that this vitamin improves the antibody response after the injection of vaccines such as measles, rabies and influenza in children (32, 42, 43). Among infected patients, agents including poor appetite and deplete body stores by excessive excretion reduce the body's supply of vitamin A, which leads to more adverse complications (29, 44). It should be noted that vitamin A deficiency is more common in low and

middle-income countries, especially among preschool age children, pregnant and lactating women (45, 46). Diseases that cause fat malabsorption, such as celiac disease, Crohn's disease, and pancreatic or biliary disorders, can lead to vitamin A deficiency. Therefore, vitamin A is considered to play a critical role in regulating and strengthening the immune system. Thus, It can be useful in reducing the risk of respiratory tract infections such as COVID-19 (47). But there are no results on the particular impact of this vitamin in the treatment of COVID-19. In this regard, to ensure the effectiveness of vitamin A in the treatment of patients with COVID-19, two clinical trial studies have been done in Iran with two doses of 25,000 and 50,000 in a combination of standard treatment (10). Considering that taking vitamin A supplements in people with vitamin A malabsorption has reduced the incidence risk of respiratory tract infections while increasing the risk of people with normal intake levels (48-50). To date, studies have shown that patients with low levels of vitamin A were more susceptible to COVID-19. However, there is no conclusive evidence regarding the relationship between vitamin A levels and long COVID (11, 51, 52). We suggest that the evaluation of vitamin A status among chronically infected patients and the implementation of necessary actions may contribute to a better outcome. Plasma retinol is a useful indicator for assessing vitamin A status. The plasma level below <20 μg/dL (0.70 μmol/L) is considered a deficiency and intervention should raise the plasma level of retinol to a normal level of 1.05–3.00 μmol/L (44).

Vitamin C

Vitamin C, as a water-soluble vitamin which is mainly found in fruits and vegetables. They are present in the body in two forms: reduced (ascorbate) and oxidized forms (dehydroascorbic acid) (53). All biological activities of this factor will be done by a reduced form (ascorbate) (53). Vitamin C acts as a cofactor for some enzymes, as an antioxidant and enhancing agent for the immune system (54-56). In the innate immune system, vitamin C maintains the integrity of the epithelial barriers by enhancing collagen synthesis, enhancing fibroblast proliferation, and differentiating keratinocytes (39, 57, 58). It also boosts the chemotaxis of neutrophils and macrophages, increases their antimicrobial activity (57, 59). and increases the activity of NK cells (59). The results of preclinical and in vitro studies showed that vitamin C inhibits the production of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1, IFN-γ, and increased anti-inflammatory IL-10 production (60, 61). Additionally, it plays an important role in antiviral defense through the production of IFNα/β (62). In acquired immunity, vitamin C enhances the proliferation of B and T lymphocytes (57). However, there is disagreement about the role of this vitamin in boosting antibody responses (63, 64). It differentiates the response of Th cells to Th1 (65). Therefore, vitamin C is involved in regulating the response of the innate and acquired immune system and also prevents the overactivation of the immune system (65). The suggested daily intake of vitamin C is 90 and 75 mg for adult men and women, sequentially. Additionally, smokers require 35 mg/day more vitamin C than non-smokers. (66). However, the prophylactic effect of vitamin C appears to be associated with higher doses(67). The optimal dose of vitamin C supplementation depends on an individual's condition at the time of intake. Infection prevention appears to be achievable through a daily dietary intake of vitamin C in the range of 100–200 mg, whereas treating infections may require gram-level doses to meet increased metabolic demands. (57). Also, some studies show that Vitamin C in the megadose can reduce symptoms and even prevents the onset of symptoms in patients with flu and common cold viral infections (68). SARS-COV2 can cause sepsis, pneumonia and acute respiratory distress syndrome (69-71). So, the result of studies about the effects of this vitamin on all of them can be beneficial (69). According to the results of studies, high doses of intravascular vitamin C have led to the successful treatment of acute respiratory distress syndrome (72, 73). Vitamin C reduces the incidence of pneumonia caused by viral infections (74). A meta-analysis study confirmed a high dose of intravascular (IV) vitamin C decreased the mortality of patient with sepsis (75). Also, the administration of high-dose intravascular of vitamin C in patients with severe sepsis has reduced the multiple organ failure and injurious agents (76, 77). It is caused because of the ACE2 expression reduction by vitamin C on the cells. So, the Coro-

na virus cannot be entered to the cells (78). Other studies have shown that vitamin C deficiency increases the risk of severe respiratory infections (57, 79). Prominently, previous evidence revealed that vitamin C stores might be depleted following infection (80). As a high dose of vitamin C had not shown any side effect, therefore, it is suggested that high dose oral or IV vitamin C administration can be beneficial due to the role of immunomodulatory (57) and good protection effect on ADRS and viral infections in infected people with SARS-COV2 (69). In this regard, according to a study in the US, the administration of a low-moderate dose of IV vitamin C has reduced inflammatory markers, but the effect on mortality was modest (27). A case report study has shown infusion of high dose IV vitamin C in a 74-year-old woman rapidly improved her (81). Also, Researchers in China have shown that administration of high dose intravascular (IV) vitamin C has been promising for the treatment of patients with COVID-19, especially by cytokine release syndrome reduction (82-84). In contrast to these positive findings, some clinical trials have reported no significant association between vitamin C supplementation and improved clinical outcomes(11). Moreover, a meta-analysis concluded that ICU patients who received vitamin C had prolonged hospital stays (85). The potential benefits of vitamin C for COVID-19 patients remain a subject of ongoing debate.

Vitamin D

Vitamin D, as a steroid hormone, can be derived from either ultraviolet B radiation from sunlight in the skin, from the diet, or from supplements (80). Unfortunately, vitamin D has a few dietary sources, which include fatty fish, animal liver, fish oil, and egg yolks (81). Vitamin D from the skin and diet is converted to 25-hydroxyvitamin D in the liver, which is the dominant circulating form and an indicator of vitamin D status (82). Finally, in the kidney, 25(OH) D undergoes the second hydroxylation to produce biologically active, 1, 25 (OH) 2 D, or calcitriol (83). This vitamin has several functions, including calcium homeostasis, metabolism, regulation of immune system function, proliferation, and differentiation of hematopoietic cells (84). In innate immunity, vitamin D enhances the phagocytic activity and kills microbial agents by increasing the differentiation of monocytes into macrophages and down-regulation of TLRs 2 and 4 without tissue damage. It also inhibits the maturation of dendritic cells (DC) and creates a tolerogenic phenotype (55, 84, 85). Vitamin D inhibits the production of inflammatory cytokines, including IL-6, IL-8, IL-17, IL-12, and TNF-α, and increases the production of the inhibitory cytokine IL-10 (86). In addition to boosting innate immune systems, this vitamin also regulates acquired immune responses (85). In acquired immunity, vitamin D inhibits the proliferation of T lymphocyte cells (87, 88). differentiates Th cells into Th2 and T regulatory cells and inhibits differentiation to inflammatory Th1 and Th17 (85). Vitamin D also reduces the production of IL-2 and IFN-γ cytokines (89). and inhibits the cytotoxic activity of TCD8+ cells as well (90). In humoral immunity, vitamin D inhibits the differentiation of B lymphocytes into memory cells and plasma cells that produce immunoglobulins (7, 87, 91, 92). Vitamin D has suppressive effects on the acquired immune system, such as Th1 and TCD8+ cells (93). high levels of this vitamin may lead to susceptibility to respiratory infections. On the other hand, it strengthens the activity of macrophages without producing inflammatory cytokines (85). so low levels of vitamin D increase the risk of respiratory infections (31, 94, 95). Therefore, vitamin D is involved in regulating both innate and acquired immune systems, while its deficiency increases the susceptibility to infections (9). In a study related to the effect of vitamin D on respiratory infections, there was no significant difference between the two groups with high doses of vitamin D compared to standard doses (96). However, in another study in the elderly, the use of high doses of vitamin D reduced the incidence of respiratory infections (97). Ilie et al. reported that vitamin D can have an impact on the prevention of COVID-19 (17). A recent clinical study confirmed that patients with COVID-19 had low levels of vitamin D (98). Another study advised that the optimization of vitamin D status could reduce the risk of coronavirus infection (99). Also, studies have shown that mortality rates in geographical areas with the lowest levels of vitamin D, such as in European countries, have been the highest (12). Vitamin D deficiency increases the suscepti-

bility to influenza and exacerbates this infection by increasing the amount of vitamin A (reducing the ratio of vitamin D to A) (12). According to hypothetical studies, Adequate levels of vitamin D through mechanisms such as inhibition of virus replication, inhibition of inflammatory cytokine production, and increased production of anti-inflammatory cytokines can be an effective factor in reducing the risk of respiratory infections and death from COVID-19 (13, 100). The mortality rate of COVID-19 is significantly different among different countries (101). Based on epidemiological studies, a recently published article on the relationship between latitude and mortality from COVID-19 revealed that all countries below 35 degrees north have lower mortality from COVID-19 (11, 102). On the other hand, deprivation of sufficient exposure to sunlight among people who live in this area has challenged the synthesis of adequate vitamin D. Therefore, high-latitude countries are at higher risk of vitamin D deficiency (103). Such findings could suggest that vitamin D status may be involved in determining outcomes from COVID-19. Vitamin D deficiency has also been correlated with obesity (104), older age (105), and chronic disease (106), all of which have been shown to be associated with the worst consequence of COVID-19 (107-109). Also, retrospective studies have reported that deficiency or insufficiency of vitamin D is associated with higher mortality and more severe disease in patients with COVID-19 (14-21). A clinical trial in Singapore showed that vitamin D supplementation in combination with magnesium and b12 improved patients with ICU hospitalization and their need for oxygen therapy (23). A meta-analysis study found that while vitamin D was safe, it was effective in preventing respiratory infections, especially in people with vitamin D deficiency (110). Nonnecke et al. reported that viral infection itself reduces levels of vitamin D and E, so controlling the levels of these vitamins in people with infections can also be important (111). Therefore, the use of vitamin D for therapy for viral respiratory infections depends on the level of vitamin D in individuals (112). Regarding the optimal serum level of 25(OH) D, there is still controversy between different guidelines. Based on a recent review concerning the current status of vitamin D worldwide, a serum level of >50 nmol/L or 20 ng/mL is suggested as a primary treatment goal, even though some findings proposed beneficial effects for a higher threshold (113). However, it seems that a serum level of 20 ng/mL is adequate for maintaining calcium homeostasis, and desirable concentration for other critical roles of vitamin D, including cancer prevention, should be at least 40–60 ng/mL (114, 115). The US recommended dietary allowance (RDA) is 400-800 IU/day of vitamin D based on age group (116). Several studies concluded that daily vitamin D supplementation provides more beneficial effects than a high single dose per month (117-119). Although there is no absolute optimal dose of vitamin for supplementation, based on the previous evidence, a higher dose of vitamin D compared to RDA is needed to reduce the risk of respiratory tract infections (100, 110). Therefore, daily vitamin D supplementation by a dose of 2000 IU/day might be a good recommendation. Considering the possible role of vitamin D in the prevention and treatment of COVID-19, more attention should be paid to the evaluation of this vitamin status, especially among patients at higher risk of deficiency. Based on previous and recent data, vitamin D supplementation could be recommended to raise 25(OH) D concentrations as a probable step in preventing COVID-19 infection and its spread. To obtain more information in this field, several clinical trials to investigate the effect of vitamin D in preventing disease in susceptible individuals, length of hospitalization, improving severe complications, and reducing the incidences of related syndromes in the hands of doing (10, 45). Research indicates that vitamin D may reduce the likelihood of COVID-19 infections by influencing the renin-angiotensin-aldosterone system (RAAS). This system contains the ACE2 receptor, which plays a crucial role in allowing SARS-CoV-2 to enter host cells (25). A clinical trial that took place in Iraq, showed that using vitamin D as a supplementation reduces BioNtech and Pfizer vaccines side effects and enhances IgG titer (126). In the case of long COVID one study revealed that using daily dose of vitamin D can improve symptoms and help to recovery (127). An umbrella review study, published in 2025, suggest that low vitamin D levels are associated with higher infection rates, more severe disease, increased ICU admissions, longer hospital

stays, and higher mortality, though no significant link was found with the need for mechanical ventilation. Vitamin D supplementation may help reduce disease severity but lacks strong evidence for preventing infection or reducing mortality. The study also highlights inconsistencies and heterogeneity across analyses due to factors like patient status, vitamin D dosage, and study design. While vitamin D's role in immune regulation, particularly in mitigating cytokine storms and acute respiratory distress syndrome (ARDS), is recognized, more well-controlled studies are needed to determine its therapeutic effectiveness in COVID-19 patients (128). Finally, a guideline published in 2025 suggests that taking daily doses of vitamin D would be beneficial for preventing viral infections (129).

Vitamin E

Vitamin E is a potent lipid-soluble antioxidant that most present as α-tocopherol isoform in human tissue (130). Vegetable oils, whole grains, nuts and green leafy vegetables are the main dietary sources of this vitamin. This vitamin conserves cell membranes and lipoproteins from oxidative stress by scavenging free radicals. It has considered playing a role in regulating the immune system (130). In innate immunity, vitamin E increases the cytotoxic activity of NK cells (7, 131). With its antioxidant properties, removes the effects of free radicals on cell membranes and preserves epithelial barriers (7, 132). However, in the acquired immune system, vitamin E indirectly through macrophages and directly, enhances T cell proliferation and increases their IL-2 production (131). Moreover, this vitamin improves the function of T lymphocytes in the elderly through macrophages (133). Vitamin E is important in reducing the risk of respiratory infections, especially in the elderly, with its regulatory effects on the immune system (134), and It differentiates Th cells to Th1 as well (39). Vitamin E boosts the humoral immune response, and increases antibody production by B cells (131). The presence of oxidative stressors resulted in the acceleration of body vitamin depletion (135). Besides, the risk of vitamin E deficiency can be influenced by some factors such as age, obesity, and sex. So, the lower level of vitamin E was reported among the elderly, obese population, and male sex (136). Vitamin E deficiency impairs the function of the humoral and cellular immune systems (137) and increases the incidence of the immunopathology of viral infection (138). Regarding confirming this discovery, animal and human studies has shown that vitamin E supplementation reduces the risk of infections and lung damage, especially in the elderly (139, 140) and increases resistance to respiratory infections (141). Also, vitamin E reduced the burden of the flu virus in older mice (142). Regarding the role of this vitamin in regulating the immune system, and low levels of vitamin E in almost two-thirds of older adults (9), vitamin E along with other fat-soluble vitamins, including vitamins A, and D may have beneficial effects on patients, especially older and obese adults with SARS-CoV-2 (143, 144). Despite the beneficial roles of this vitamin in immunity, there is limited information on the effects of vitamin E in patients with COVID-19 infection. Although, patients with COVID-19 are encouraged to have adequate intakes of this antioxidant (145). It is mentioned that COVID-19 can lead to vitamin E concentration reduction and depletes antioxidant enzymes (146). A clinical study in Iran investigated the effect of vitamin E in combination with other vitamins on the recovery process and mortality rate in patients with COVID-19 hospitalized in the ICU (147). They found that in patients with COVID-19 admitted to the ICU, supplementation with vitamins A, B, C, D, and E correlated with milder disease presentation and decreased serum levels of inflammatory markers. The incidence of extended hospitalization was reduced in individuals who received the supplements; however, the probability of prolonged hospitalization in the supplemental vitamin group was not statistically significant after accounting for confounding variables (148).

Vitamin B

B complex vitamins include B1, B2, B3, B5, B6, B9, and B12. Vitamins in this family, like other vitamins, regulate the immune system. Vitamins B1, B2, B5, and B7 are often involved in the function of the immune cells by regulating cellular metabolism. Vitamins B3 and B7 have anti-inflammatory effects on the immune system by inhibiting the production of inflammatory cytokines and differentiation of Th cells into regulatory T cells

(149). Due to the critical role of vitamin B6 in the metabolism of nucleic acids and proteins, this vitamin is involved in cell proliferation and thus regulating the immune system response (150). In the innate immune system vitamin B6 enhances the cytotoxic activity of NK cells (59). Also is involved in regulating inflammation, by the production of immunomodulatory agents (151, 152). In acquired immunity, this vitamin plays a role in the differentiation of functional T lymphocytes in the thymus (153). It has also an impact on enhancing the function of B lymphocytes and antibody production, increasing the proliferation and the cytotoxic activity of T lymphocytes (154). Vitamin B12 enhances the cytotoxic activity of NK cells and TCD8+ cells and regulates the ratio of TCD4+ to TCD8+ cells (155). Vitamin B12, along with folic acid and vitamin B6, is involved in antibody production (7). Folic acid, as a synthetic form of folate, maintains the proper function of the immune cells by regulating metabolism and cell proliferation (9). Vitamin B12 deficiency reduces the immune response against the virus and bacteria (156). Mouse studies have reported that although vitamin B6 deficiency reduces antibody production (157), excessive vitamin B supplementation also reduces antibody production (158). Given the potential role of vitamin B12 as an inhibitor of RNA polymerase and the production of anti-inflammatory agents like melatonin, prescribe supplements of this vitamin may reduce the symptoms and complications of COVID-19 disease (28). In this term, the results of a clinical trial study have shown the B12 administration in a combination of vitamin D and magnesium improved the symptoms of patients with COVID-19 (24). There has been limited data on the effects of this vitamin family on SARS-CoV-2 infection. According to the role of them in regulating of the immune system, it appears the normal level of these vitamins, especially in the people with a deficiency in B complex vitamins (elderly and women of childbearing age) (159, 160), could be effective in improving the treatment of patients with COVID-19 infection and also prevention. An increased consumption of vitamin B5 may decrease the likelihood of COVID-19, whereas a moderate intake of vitamin B12 exhibits a protective effect against the virus (161). Vitamin B12 supplementation effectively manages COVID-19 by improving inflammatory factors and immune system functionality. Further research is needed to understand malnutrition's role in COVID-19 (162).

Vitamins and T cell exhaustion in COVID-19 setting

One of the primary factors contributing to the diminished responsiveness of the immune system in chronic infections is T cell exhaustion (163). In this state, repeated exposure to infectious antigens leads to a decline in T cell functions, including proliferation and cytokine production, while simultaneously increasing the expression of inhibitory receptors on their surface (164). It is evidenced that in mild, moderate and severe cases of COVID19, in spite of lymphopenia, on the remained T cells, immune checkpoints such as PD-1 and TIM-3 are upregulated (165). It might be associated to T cell exhaustion (166). COVID-19 triggers a strong and early cytokine storm, whereas patients with flu-like symptoms (FLS) experience a more gradual immune response. Unlike FLS, COVID-19 rapidly increases the frequency of exhausted and senescent T cells, particularly in the CD8+ T-cell compartment. This exhausted T cells express PD-1 and ICOS, while senescent T cells lose CD28 and express CD57 and KLRG1 (167).Although pro-inflammatory cytokines are elevated in sever COVID-19 patients, they are potentially contributing to immune dysfunction rather than effective viral clearance (168). In the setting of long COVID, the same results have been investigated and SARS-CoV-2 specific T cells expressed more inhibitory receptors than controls (169). Interesting point is that even 6 month after recovery, exhausted T cells persist and it increases risk of reinfection and comorbidities (170, 171).

To overcome this issue, strategies for T cell reinvigoration should be considered. As it is known that metabolism of exhausted T cells is impaired, hypothetically, vitamins may provide supportive benefits in preventing or alleviating T cell exhaustion in COVID-19. In this regard, some studies have assessed association between vitamins supplementation and T cell exhaustion. One study revealed that in Hepatitis B Virus, there is a correlation between T cell exhaustion and vitamin D deficiency. HBV infection leads to a decline in

Vδ2+ T cells and an increase in inhibitory receptors (PD-1, Tim-3, LAG3, CD38) on γδ T cells, contributing to poor viral control and tumor immune escape. Vitamin D deficiency was linked to higher HBV DNA loads and increased PD-1 expression on γδ T cells, suggesting a role in immune exhaustion. Notably, vitamin 1α,25(OH)2D3 was found to enhance immune function by reducing immune checkpoint expression and promoting IFN-β production in Vδ2 T cells (172). In the context of Non-Small Cell Lung Cancer, researchers showed that using vitamin D may reduce expression of inhibitory receptors and increase costimulatory ones like CD28 on the cytotoxic T cells (173). One study found that adding vitamin C during CD19-CAR T cell production enhances their stem cell memory–like phenotype, increases expansion, and improves their ability to kill target cells. VC-manufactured CD19-CAR T cells maintained their function even after repeated stimulations, whereas control CAR T cells showed signs of exhaustion. In vivo, VC-treated CAR T cells delayed tumor growth and improved survival. These findings suggest that VC prevents T cell exhaustion and enhances antitumor activity, with ongoing research exploring potential epigenetic mechanisms behind these effects (174). The researchers found that nicotinamide (a member of vitamin B group) prevents and partially reverses T cell exhaustion by addressing metabolic dysfunction, particularly mitochondrial oxidative stress. nicotinamide reduced reactive oxygen species (ROS) and downregulated TOX, a key regulator of T cell exhaustion (175). Vitamins, in general, have beneficial impacts on exhausted T cells in chronic infections, according to this limited research. However, there should be more considerations about the dose of administration, the period of usage, and the patient's status in order to ameliorate clinical symptoms.

Conclusion

According to the research on how vitamins affect the immune system, vitamins as micronutrients at healthy levels are crucial for controlling the immune response. Changing their levels as immunomodulatory agents can mess up these settings. So, high or low levels of each vitamin can increase the susceptibility to respiratory infectious diseases such as SARS-CoV-2 or may exacerbate disease by deregulation of the immune system. Due to their immune system-regulating effects, most studies suggested that vitamins could prevent and treat COVID-19. Only a small number of clinical trials have been performed to evaluate the effect of vitamins on the treatment of COVID-19. Although the results obtained so far are promising and indicate the potential therapeutic effect of vitamins in COVID-19, more studies are needed to recommend the administration of certain doses of vitamins for treatment. Based on the studies in this article, the intake of vitamins through food sources or supplements to maintain their amount at the optimum level can increase the body's resistance to lead and fight infection. Since high amounts of vitamins can disrupt the immune system regulation, it's better to measure the level of the patient's vitamins in the initial screening, and in case of vitamin deficiency, prescribing vitamin supplements to optimal levels could potentially help in the treatment of COVID-19. Recent studies have also highlighted the role of vitamins in preventing and reversing T cell exhaustion, a major contributor to immune dysfunction in chronic infections, including COVID-19. Persistent exposure to SARS-CoV-2 antigens has been shown to induce T cell exhaustion, characterized by upregulation of inhibitory receptors such as PD-1 and TIM-3, along with impaired cytokine production and reduced cytotoxic function. This phenomenon is particularly concerning in long COVID, where exhausted T cells persist even months after recovery, potentially increasing the risk of reinfection and other complications. Certain vitamins have been identified as potential modulators of T cell exhaustion. Vitamin C has been shown to enhance T cell expansion and functionality while preventing exhaustion in CAR T cell therapies. Similarly, nicotinamide (a B vitamin) has demonstrated the ability to reduce oxidative stress and downregulate TOX, a key regulator of T cell exhaustion, leading to improved T cell function. Vitamin D has also been implicated in reducing immune checkpoint expression and restoring immune balance in chronic infections. These findings suggest that maintaining optimal vitamin levels could support T cell resilience and enhance immune recovery in COVID-19 patients. However, further clinical research is needed to define specific vita-

min-based strategies for combating T cell exhaustion and improving long-term immune function in affected individuals.

Conflict of interest

The authors have no conflicts of interest.

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