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Review

Potential Roles of Vitamins in the Management of COVID-19: A Comprehensive Review

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Abstract

The coronavirus disease 2019 (COVID-19) outbreak has caused a public health crisis worldwide. However, data regarding the protective factors of the disease is limited. Consequently, preventive health measures that can decrease the risk of infection, progression, and severity are dreadfully required. It is well-documented that people with immunodeficiency, such as the elderly, people who already have comorbidities (e.g., diabetes mellitus, hypertension, respiratory and cardiovascular disorders), and underrepresented minorities, are placed in a group with a higher risk of getting infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A diet rich in vitamins, minerals, and antioxidants plays an essential role in strengthening the immune system and fighting against invading pathogens. The present comprehensive review has discussed published literature regarding the potential role of vitamins in strengthening the immune system and managing viral infections, particularly SARS-CoV-2 infection. Although there are controversial data regarding the plasma level of vitamin D and the severity of the disease, according to the limited evidence, vitamin D may lower the mortality rate. Moreover, vitamin C could reduce the development of inflammatory response; however, the results of ongoing clinical trials are required to confirm these primary findings.

Introduction

The pandemic of novel coronavirus disease 2019 (COVID-19) has been the major global health crisis of our time with high economic and social impact. The overall mortality rate per confirmed COVID-19 cases was reported as approximately 4.5%, but the actual number would be greater because of the undetected population. People with immunodeficiency, such as the elderly, people who already have comorbidities (e.g., diabetes, hypertension, respiratory and cardiovascular disorders), and underrepresented minorities, are categorized in high-risk groups.[1-3]

The severity and recovery of the disease depend greatly on the genetic, age, nutrition, and overall strength of the host immune system. Given that to date no direct medication or vaccine has been approved by the Food and Drug Administration (FDA) for the treatment of individuals with COVID-19, the rational solutions are hygiene protocols, social distancing, the global vaccination program, and a healthy diet to help function and strengthen the immune system until providing definitive treatment. Malnutrition is considered one of the most common reasons for immunodeficiency.[4,5] Hence, a healthy diet and adequate vitamin intake are critical in the management of numerous diseases such as malignancies, allergies, autoimmune diseases, and infections, such as COVID-19. Besides, the importance of immune system dysregulation in the clinical progression of the infection has been well recognized. This fact increases the interest in using vitamins and antioxidant supplements in the management of COVID-19. Considering these points, we reviewed the current evidence regarding the importance of potential vitamins in the prevention and treatment of COVID-19.

The Immune System

The immune system comprises two defense lines called innate immunity as a non-specific and rapid

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immunological mechanism and adaptive immunity as an antigen-specific mechanism for fighting against invading pathogens. So that in the phase of innate immunity, immune cells respond by producing neutrophils, mast cells, phagocytes, dendritic cells, eosinophils, and some other white blood cells (WBC). In contrast, adaptive immunity involves action from cytotoxic T cells, T helper (Th) cells, and B cells. Cytotoxic T cells are responsible for destroying infected cells, and Th cells coordinate the responses of other immune cells. In comparison, B cells are in charge of the production of pathogenic antigen-specific antibodies. The strength of our immune cell response is highly dependent on the availability of minerals vitamins as cofactors. Consequently, vitamin supplementation could boost the immune system.[6-10]

Fat-soluble Vitamins

Vitamin D (ergocalciferol-D2, cholecalciferol-D3, alfacalcidol)

Numerous studies have evaluated the effect of vitamin D on the immune system.[11-16] Vitamin D is an immune system regulator and plays a series of important roles in the replication and maturation of macrophages and monocytes, physiological functions of mineral homeostasis such as calcium, phosphate, and magnesium.[17-19] Besides, there is mounting evidence supporting the potential beneficial effects of vitamin D in the numerous viral and bacterial infections such as human immunodeficiency virus (HIV),[19,20] and tuberculosis.[21]

Notably, it has been shown that vitamin D deficiency prevalence seems to be high, particularly among individuals who are taking some pharmaceutical agents (e.g., antiepileptics and antihypertensives) because of impaired vitamin D metabolism, elderly population, and those with limited time outdoors and reduced epidermal synthesis.[22] Several preclinical and clinical studies have evaluated the efficacy and safety of vitamin D supplementation in the management of infectious diseases.

Hayashi *et al.*[23] showed that long-term administration of 25-hydroxyvitamin D3 (25(OH) D3) could relieve the clinical appearance of infectious diseases prophylactically in a mouse model by decreasing the viral replication and production of inflammatory cytokines. A diet containing a high dose of 25(OH) D3 led to significantly lower viral titers and IL-5 and interferon-γ levels in this study. Ginde *et al.*[24] conducted a randomized controlled trial to evaluate the efficacy and safety of high-dose vitamin D compared with the standard dose supplementation for the prevention of acute respiratory infection in 107 individuals older than 65 years of age from 2010 to 2014. In the standard-dose group, individuals taking <400 IU/day received 12,000 IU of vitamin D3 every month, and those taking 400-1,000 international units (IU)/day were given a placebo, while cases in the high-dose group received 100,000 IU vitamin D3 every month. Data analysis showed that 0.67 and 1.11 acute respiratory infection per person-year were reported for the high-dose the standard-dose groups, respectively (incidence rate ratio (IRR) = 0.60, 95% confidence interval (CI) = 0.38-0.94, P = 0.02). Moreover, fractures were rare in both groups (0.10 vs. 0.19 per person-year; P = 0.31). Moreover, falls were more prevalent in the high-dose group compared with the standard dose group (1.47 vs. 0.63 per person-year; IRR = 2.33, 95% CI = 1.49-3.63, P < 0.001). Finally, hypercalcemia kidney stones were not observed in the study groups.

Seventy-two continuous patients with chronic hepatitis C virus (HCV) genotype one were randomized into two groups to assess whether adding vitamin D improve the response of HCV to antiviral therapy or not. Patients in the in the treatment (n = 36, 50% male, mean age 47 ± 11 years) and control groups (n = 36, 60% male, mean age 49 ± 7 years) received peginterferon alfa-2b (1.5 μg/kg per week), ribavirin (1000-1200 mg/day) as the standard care. The individuals in the treatment group were given vitamin D3 (2000 IU/day, target serum level > 32 ng/mL) in addition to the standard treatment. A higher mean body mass index (27 ± 4 kg/m2 vs. 24 ± 3 kg/m2; P < 0.01), viral load (50% vs. 42%, P < 0.01), and fibrosis score (> F2: 42% vs. 19%, P < 0.001) was observed in treatment group than the controls. After 12 weeks of infection, 34 and 17 patients in the treatment and control groups were HCV- ribonucleic acid (RNA) negative, respectively (P < 0.001). Furthermore, at week 4, 44% and 17% of cases in the treatment and control were HCV-RNA negative, respectively (P < 0.001). At week 24, 31 patients in the intervention group and 15 in the control group were HCV-RNA negative (P < 0.001).[25]

Aglipay *et al.*[26] carried out a randomized clinical trial in patients with ages 1 to 5 years to evaluate the efficacy of high-dose vitamin D compared with standard-dose on respiratory tract infections. A total of 703 patients were randomized to receive 400 IU/day (standard-dose group; n=354) or 2000 IU/day (high-dose group; n=349) vitamin D for at least 4 months. Among them, 99.4% completed the trial. The mean number of upper respiratory tract infections were 1.03 (95% CI, 0.90-1.16) and 1.05 (95% CI, 0.91-1.19) per case in the standard-dose and high-dose groups, respectively. No significant difference was observed in the number of infections between the study groups (IRR, 0.97; 95% CI, 0.80-1.16). Moreover, no statistically significant difference was observed in the median time to the first infection ((3.29 months (95% CI, 2.66-4.14 months) vs. 3.95 months (95% CI, 3.02-5.95 months)) and the number of parent-reported upper respiratory tract diseases (600 vs. 625; IRR, 1.01; 95% CI, 0.88-1.16). Finally at the end of trial, levels of serum 25 (OH) vitamin D were 36.8 ng/mL (95% CI, 35.4-38.2 ng/mL) and 48.7 ng/mL (95% CI, 46.9-50.5 ng/mL) in the standard-dose and high-dose groups, respectively.

The advantages and disadvantages of using vitamin D in the medication regimen of COVID-19 patients should be carefully evaluated.[27] Some articles have addressed the role of vitamin D in decreasing the risk of acute upper respiratory tract infections, so the idea of using this vitamin in response to COVID-19 came to mind.[28,29]

Vitamin D has been widely investigated in intensive care unit (ICU) patients before and during the COVID-19 pandemic, and these studies have shown conflicting results. According to two ecological studies, there are inverse correlations between incidence and mortality of COVID-19 with national estimates of vitamin D status. It has been shown that patients with vitamin D deficiency are more susceptible to COVID-19 and have a higher risk for severe forms of the disease.[16,30-39]

Amrein *et al.*[36] in a randomized clinical trial, showed that high dose vitamin D supplementation could reduce the mortality rate only in patients with vitamin D deficiency. The use of vitamin D3 (10,000 IU/day for a few weeks followed by 5000 IU/day) has been suggested to decrease the possibility of infection in the population at risk of COVID-19. In contrast, Martínez and colleagues[39] concluded that vitamin D could not decrease virus replication in both animal and clinical data.

A recent systematic review and meta-analysis of four studies involving 259 patients[40] showed that vitamin D supplementation led to a statistically significant lower mortality rate in patients with COVID-19 (OR=0.264, 95% CI=0.099–0.708, p-value=0.008). Moreover, Rastogi *et al.*[41] showed that vitamin D supplementation could significantly decrease serum levels of fibrinogen and inflammatory markers; however, no major difference was observed in the levels of procalcitonin, C-reactive protein, D-dimer, and ferritin. Furthermore, Castillo *et al.*[42] showed a lower rate of ICU admission in those who received vitamin D ($p < 0.001$). Finally, there was a significant decrease in the COVID-19 ordinal scale of clinical improvement in the patients who received vitamin D.[43,44]

Vitamin E (alpha-tocopherol, tocopherol, tocotrienol)

Vitamin E is a lipid ingredient of the biological membrane, and as a lipid-soluble compound, its metabolism, regulation, and excretion occur in the liver. It plays a critical role as a major component in antioxidant defense in mammalian systems, with the capability of mitigating the membrane lipid peroxidation by neutralization reactive oxygen species (ROS) and free radicals, protecting against air pollution and ultraviolet radiations. It is also essential for recovery after a chronic viral infection by supporting the integrity of respiratory epithelial barriers; however, it seems that vitamin E has no protective effects on respiratory tract infections.[45-49] Vitamin E could decrease the inflammatory parameters.[10,50,51]

Vitamin E has the capability of boosting the immune response via the following mechanisms: starting the T-lymphocytes signals, reduction in producing nitrogen oxide, which leads to prohibition of cyclooxygenase-2 and reduction of prostaglandin E2 release by macrophages,[18,45,50,52-54] modulation of Th1/Th2 balance, production of interferon-γ, interleukin 2 (IL-2) and supporting the activation of immune synapses between Th cells and enhancing the amount of antigen-experienced memory T-cells.[16,18,52,54-57] Vitamin E effective dosage has been reported 50-200 mg per day.[58] Vitamin E deficiency is rare in humans but results in impaired humoral and cell-mediated adaptive immunity, an increased possibility of infection with high virulent strains and severe pathologies, and reduction in specific antibody production following vaccination, natural killer (NK) cell activity, neutrophils phagocytosis, and lymphocyte proliferation.[59-62]

Taking vitamin E supplementation on a regular basis enhances resistance to respiratory infections, in particular, the risk of infection by SARS-CoV-2 by improving overall immune functions and reducing virus load in lung tissues.[10,45,55,63-66] Nevertheless, data regarding the potential beneficial effects of vitamin E is limited in patients with COVID-19.[67]

Numerous animal studies have been conducted to investigate the association between vitamin E deficiency and the impairment of humoral and cell-mediated immune functions.[68] It has been shown that vitamin E deficiency leads to impaired lymphocyte proliferation in rats, lambs, dogs, chickens, and pigs and lower antibody production in rat and mouse models.[69-75]

A randomized, double-blind, placebo-controlled trial was carried out to evaluate the effects of vitamin E supplementation on lower respiratory tract infections in 617 elderly individuals nursing home residents. The patients were randomized to receive vitamin E (200 IU) for 12 months or a placebo. Results showed that vitamin E supplementation had no statistically significant effect on the number of days with respiratory tract infections and incidence of the infections. Furthermore, antibiotic use was not significantly different between the study groups. Nevertheless, the number of patients with at least one respiratory tract infection was lower in the cases that received vitamin E compared with placebo (60% vs. 68%; risk ratio, 0.88; 95% CI, 0.76-1.00; P =.048). Moreover, post hoc subgroup analysis indicated that the incidence of the common cold was in the vitamin E group compared with the placebo group. (0.67 vs. 0.81 per person-year; risk ratio, 0.83; 95% CI, 0.68-1.01; P =.06). Notably, It has been indicated that different doses of vitamin E supplementation (60 to 800 mg/day) could enhance Th-1 cell-mediated immunity and vaccination responses to hepatitis B (HBV) virus so that significantly higher normalization of hepatitis HBV-deoxyribonucleic acid (DNA) negativization and liver enzymes were obtained.[28,66,76-78]

Vitamin A (retinol, retinal, retinoic acid, beta-carotene)

Vitamin A plays a fundamental role in regulating innate and adaptive arms of immune response by supporting the production of antibodies by B cells, supporting oxidative burst and phagocytic activities of macrophages, adjusting both the function and number of NK cells, differentiating phenotypes of Th1/Th2, increasing the secretion of IL-2, and T cells development.[44,49,78]

It also preserves the normal antibody-mediated Th2 responses by downregulating of IL-2, interferon-γ, and tumor-necrosis factor α (TNF- α), which is produced by Th1

cells. Besides, vitamin A is required for natural secretion, function, structure, and differentiation of epithelial tissues (i.e., mucosa, gastric, and nasal epithelium) as well as for preserving the integrity of barriers. It is also termed "anti-inflammatory vitamin".[79-83]

Toxicity of retinol will occur after administrating doses bigger than the tolerable upper limit (TUL) that is reported 3000 mcg or >10,000 IU of retinol or retinol esters over the course of several months for individuals who do not have deficiencies. In comparison, perfect prevention of viral replication will be observed at doses ranging from 20,000 – 25,000 IU or 6,000 –7,500 mcg. To date, there is no reported toxic effect of remedy protocol for patients with virus infections, which is involved 20,000 – 25,000 IU for 7-14 days.[84-87]

Children and patients with renal dysfunction need much lower concentrations of vitamin A. Furthermore, the consumption of higher doses during pregnancy increases the risk of teratogenicity.[87] Owing to vitamin C and retinol synergistic immunological functions, their co-administration is recommended.[45]

Retinoic acid is considered as the most active retinoid, which adjusts the transcription of more than 500 genes by the following binding mechanism: The retinoic acid receptor (RAR) α/ß/γ to its retinoid X counterpart.[15,88] Many review articles discussed the role of vitamin A and its metabolites in immunity, which we have summarized in this section.[78,81,82,89-93]

Retinol indirectly affects the composition of the gut microbiome to prevent the transition of the virus into the bloodstream at the level of the gut due to enhancing the relative dominance of Lactobacillus spp. Prescribing vitamin A supplements could decrease the occurrence of some infections, such as Mycoplasma pneumonia infection that is regarded as a usual post-viral secondary bacterial infection in patients with COVID-19, HIV infection, measles, diarrhea, and malaria. Moreover, it has been shown that vitamin A supplementation could reduce the risk of morbidity and mortality from infectious diseases. However, there is conflicting data about pneumonia.[62,94-96]

Consequently, Vitamin A deficiency is considered an important risk factor for the augmented susceptibility to measles, diarrhea, and, more especially, infections, which are related to the virus-induced respiratory tract. So that sufficient protective immunologic responses to the nanoparticle bovine respiratory syncytial virus (BRSV-NP) vaccine were not obtained in young cows with the effects of vitamin A deficiency; therefore, they developed subsequent lung infections after being challenged by a virus. Moreover, chickens with the viral infection that showed lower levels of vitamin A experienced an improved rate of epithelial damage to tissues, while adequate concentrations of vitamin A enhances antibody titer responses after vaccination for influenza and measles.[44,62,82,97-100]

Siddiqui *et al.* carried out a study to investigate the effects of supplementation with vitamin A on the antibody titer after a course of antirabies vaccine (5 injections over 30 days). The age ranged from 10-35 years. Data analysis showed that individuals in the intervention group had significantly greater serum antibodies compared with the control group.[101]

The link between vitamin A and the incidence of respiratory diseases has been investigated even at subclinical levels.[102-104] Human respiratory syncytial virus (hRSV) is one of the most important respiratory pathogens in young children,[105,106] and causes up to 70% of hospitalized bronchiolitis cases in industrialized countries[107] is associated with endemic vitamin A deficiency.[108] It is important to mention that hRSV is closely related to BRSV, the cause of severe acute lower respiratory tract disease in young cattle[99] in terms of similarities in innate and adaptive immune responses, age dependence, and disease pathogenesis.[109-111] McGill *et al.*[99] showed the capacity of the host to respond to an intranasal, polyanhydride NP vaccine and to resist the subsequent viral challenge are severely affected by vitamin A deficiency. Inflammatory cytokine profiles have changed in the lungs of calves with vitamin A deficiency, and cellular immune responses or virus-specific immunoglobulin A (IgA) did not produce in lungs or peripheral blood.It seems that supplementation with vitamin A may be logical for faster recovery from COVID-19 in deficient and malnourished patients; however, the potential adverse effects of vitamin A should be considered.[66,112]

Water-soluble Vitamins

Vitamin B

Vitamin B complexes are commonly seen in prescriptions of orthopedic surgeons for a wide range of disorders, including chronic regional pain syndrome, stress fractures, peripheral neuropathy, and stress fractures.[113] There is a need to highlight the beneficial role of the vitamin B complex because of its pivotal effects on promoting timely activation of both innate and adaptive immune responses, energy metabolism, cell functioning, preserving endothelial integrity, enhancing respiratory function, reducing the length of hospitalization, preventing hypercoagulability, and reduction of pro-inflammatory cytokine levels so that it regulates the generation of cytokine/chemokine and interferes in the interaction with immune cells concerned in inflammation environment and pathophysiological pathways. Vitamin B2, B3, and B6 are documented to augment the immune response.[114-117]

Vitamin B complex deficiency leads to impaired immune function and inflammation because of hyperhomocysteinemia.[115,118-121] Some studies have evaluated the promising effects of B complex vitamins, which are categorized as water-soluble vitamins, in treating patients with COVID-19. It has already been used against Bovine Coronavirus, Avian Coronavirus, and Middle East respiratory syndrome (MERS).[115,122-124]

Dubeski *et al.*[144] investigated the effects of vitamin B supplementation on immunity and infection in 12 beef steer calves (153 ± 8 kg) which were limit-fed, weaned, and deprived of feed. In this study, a combination of

B vitamins and ascorbic acid was administrated every 48 hours to 6 calves prior to bovine herpesvirus type 1 (BHV1) inoculation (for 28 days). Notably, in all calves, a mild respiratory infection was observed with no difference. In other words, vitamins administration was not associated with a significant change in interferon titers in nasal secretions and lymphocyte blastogenesis; however, injection of B vitamins tended to increase serum IgG titers to BHV1 on both days 14 (P = 0.115) and 28 (P = 0.37) after infection.[124]

Aiming to the utilization of existing approved drugs in the treatment of COVID-19 patients, a recent study after examination of the crystal structure of SARS-CoV-2 protein, ranked vitamin B12 and B3 at the fourth and sixth place.[125,126] However, the SARS-CoV-2 can impair intestinal microbial proliferation via interfering with vitamin B12 metabolism.[120] A clinical study demonstrated that consumption of vitamin B12 supplements (500 µg), vitamin D (1000 IU), and magnesium has a potential role in decreasing the severity of COVID-19 symptoms as well as the intensive care support and need for oxygen.[127]

Vitamin B1 (Thiamine)

Vitamin B1 plays an important in the production of energy and protein, fat, and glucose metabolism due to its action as a coenzyme in phosphorylated forms and is considered as a precursor of coenzymes in amino acid and sugar catabolism. Impairment of synthesis of cholesterol and fatty acid in the nervous system, neuronal cell death as a result of induction of overexpression of pro-inflammatory mediators like cyclooxygenase-2, IL-6, IL-1, and TNF-α are results of vitamin B1 deficiency in the body.[15,128]

Generation of nicotinamide adenine dinucleotide phosphate (NADP) and glutathione cycling as a main antioxidant pathway requires thiamine and niacin.[129] In a trial of patients with septic shock, administration of vitamin B1 and its functional pathways have been studied and concluded that it could enhance mortality and reduce lactate concentration[130,131] and as a result of a number of studies, the combination of vitamin C (1500 mg every 6 hours), thiamine (200 mg every 12 hours), and hydrocortisone (50 mg every 6 hours) has beneficial effects in patients with sepsis by enhancement in time to shock reversal, organ injury, mortality and severe pneumonia.[123,132]

Protocol aiming at prophylactic and treatment for COVID-19 is a 1:1 combination of vitamin B1–vitamin B6, daily dose 250 mg and 250 mg, respectively for four weeks, and therapeutic treatment for mild and moderate symptomatic COVID-19 patients is a 1:1 combination of vitamin B1–vitamin B6 daily dose 750 mg and 750 mg, respectively divided into three daily doses for ten days.[133]

Vitamin B2 (Riboflavin)

Vitamin B2 acts as a precursor of coenzymes required for the flavoprotein enzyme reaction. Zhang and Liu[115] documented the effectiveness of vitamin B2 together with ultraviolet light in vitro studies to diminish the titers of the MERS-CoV to below the limit of detection after inoculating the virus into human plasma because of disturbance of replication of pathogen due to irreversible damage to nucleic acids, offering it could also be effective against SARS-CoV-2.[134,135] Furthermore, it has been shown that riboflavin could decrease the risk of infection with MERS-CoV in humans based on molecular and physiologic mechanisms.[115]

Vitamin B3 (Nicotinamide, Niacin)

Vitamin B3 has a considerable role in the creation of an intense anti-inflammatory effect owing to preventing infiltration of neutrophils into the lungs during induction of lung injury by the ventilator.[115,136,137] Briefly, niacin can reduce IL-1ß, IL-6, and TNF-α in stimulated alveolar macrophages and prevents nuclear factor kappa-light-chain-enhancer of activated B cells activation.[116,138-140] Notably, the importance of this issue is that targeting IL-6 with tocilizumab or sarilumab is a promising solution to control the inflammatory storm in COVID-19 patients.[141] It is considered as a precursor of coenzymes demanded in many metabolic processes.[15] As also, when chronic systemic inflammation occurs, niacin acts as a building block of NAD and NADP.[120,142]

One strategy for reducing the cellular inflammation in COVID-19 patients is increasing the expression of angiotensin-converting enzyme 2 (ACE2) receptors, the receptor with the important responsibility of binding the SAR-CoV2 viral spike and inducing COVID-19 infection.[143,144] The COVID-19 infection has an effective role in downregulating ACE-2 receptors by binding to infection-related transcription factors at the ACE2 regulatory regions.[143] Respiratory affliction in patients with COVID-19 and MERS is likely correlated with reduced expression of ACE2 receptor.[143-146]

A number of common compounds, including vitamin B3,[147] aspirin,[148] vitamin D,[149] nicotine,[150] vitamin C,[148,151] resveratrol,[152,153] and metformin[154] have the capability of enhancing the expression of ACE2.[155] Therefore, niacin may be beneficial as an adjunct treatment for COVID-19 patients due to its lung-protective property; however, future studies are warranted to identify the clinical importance of the observed effects.[115,156]

Vitamin B5 (Pantothenic acid)

There are finite investigations showing the effect of Vitamin B5 on immune responses, and it is under research scrutiny; nevertheless, it is regarded as a precursor of coenzyme A and has some roles, including improvement of mental health, including cholesterol and triglyceride-lowering properties, diminishing inflammation, and enhancing wound healing.[118]

Vitamin B6 (Pyridoxine, Pyridoxal, Pyridoxamine, Pyridoxal 5' -phosphate)

Vitamin B6 plays a critical role as a coenzyme in the

metabolism of cytokines and antibodies. Vitamin B6 deficiency leads to the impaired proliferation of lymphocytes, low blood T lymphocyte numbers, diminished IL-2 production in response to mitogens, and decreased antibody production as a result of a collision with an immunization,[157-159] thymus and spleen atrophy, impaired T lymphocyte-mediated immune responses[58] and reduced NK cell numbers.[160]

Taking vitamin B6 at levels below recommended over 21 days has not the ability to return the immune system function to the initial number, but repletion at recommended doses (22.5 µg/kg body weight per day) has.[58] In antiviral defense, the activity of NK cells and the positive cluster of differentiation (CD8+) cytotoxic T lymphocytes are so essential, and Vitamins B6, folate, and B12 all boost this acting.[58,160,161]

The European Union granted health claims to vitamin B6 and B12 for participating in the physiological function of the immune system.[45,162] Based on physiologic mechanistic pathways, vitamin B6 can present a novel insight for the treatment of patients with COVID-19.[9,163]

In a recent investigation, 96% of patients with COVID-19 were deficient in pyridoxal or 4-pyridoxic acid (4PA), and lonely 6% were deficient in pyridoxal-5-phosphate (PLP, the active form of vitamin B6).[164,165] A new preprint demonstrated that PLP reduced COVID-19 symptoms via mitigating pro-inflammatory cytokines, adjusting immune responses, hampering hypercoagulability, and maintaining endothelial integrity.[166] Besides, a reduction of abnormalities in blood clot formation phenomenon and platelet aggregation is observed due to the consumption of PLP.[167] Ataxia is sensory neuropathy are adverse effects that may be associated with vitamin B6 supplements.[168-170]

Vitamin B9 (folate, folic acid)

Folate is considered as a precursor demand for protein and DNA synthesis and repair, particularly during rapid cell division, and has a potential binding affinity to the SARS-CoV-2 protease.[15,171]

Folate deficiency leads to pan-hypogammaglobulinemia, megaloblastic anemia, decline cell-mediated immunity, altered pro-inflammatory cytokine profile, failure to thrive, and infections as a result of ruined T-cell proliferation response along with immunodeficiency.[15,172,173]

It was reported one decade ago that patients with chronic obstructive pulmonary disease have lower levels of folate and vitamin B12.[174] However, there is not much evidence of the importance of supplementation on enhancing pulmonary function, length of hospitalization, and promoting symptoms.[175]

Furin is introduced as an enzyme related to viral and bacterial infections and could be a promising target for the treatment of infections in pharmaceutical and biotechnological industries, and folic acid, as a furin inhibitor, hampers the binding of spike protein, cell entry, and turnover of SARS-CoV-2.[176] Kumar *et al.*[177] have been shown firm and powerful binding affinity against SARS-CoV-2 by folic acid and its derivatives (i.e., tetrahydrofolic acid, 5-methyl tetrahydrofolic acid) via structure-based molecular docking.

Vitamin B12 (cobalamins, cyanocobalamin, methylcobalamin)

Vitamin B12 acts as a coenzyme in metabolic reactions affecting fatty acids, DNA, and amino acid metabolism with potential binding affinity to the SARS-CoV-2 protease.[15,125] It is also responsible for inducing an imbalance in the cytokine and growth factor network in the central nervous system, enhancing the activity of NK cells as an essential factor in antiviral defense,[178,179] myelin synthesis, and modulating the gut microbiota.[116,120]

Cobalamin deficiency is commonly observed in elderly individuals owing to decreased absorption secondary to their clinical situations and medicines,[180] and is associated with the reduced phagocytic and bacterial killing capacity of neutrophils,[58] low NK cell activity, low CD8+ T lymphocyte count,[160] impaired antibody response to the synthesis of specific Ig and pneumococcal polysaccharide vaccine due to the unavailability of vitamin B12 for swiftly proliferating lymphocytes,[158,181] increased oxidative stress, inflammation, and ROS.[116]

There is little data about the effectiveness of vitamin B12 in the treatment of patients with COVID-19. One study has demonstrated that a combination of Vitamin B12, ribavirin, nicotinamide, and telbivudine can be administrated for the management of COVID-19. The clinical significance of the effects has not been adequately defined yet.[125,182]

Vitamin C (ascorbic acid)

Vitamin C, as a cofactor for some enzymatic reactions, is required in the biosynthesis of norepinephrine, collagen hydroxylation, regulation of hypoxia-inducible factor (HIF), amidation of peptide hormones, HIF hydroxylation, tyrosine metabolism, carnitine biosynthesis, and histone demethylation.[15,182]

Intake of this supplement, as an immunity-boosting nutrient is associated with enhancing the growth of lymphocytes and phagocytes, hampering and reducing inflammation due to its antioxidant properties through attenuation of nuclear factor- kappa B activation, reducing the risk of respiratory infections, augmenting immune responses, the help of repairing tissues,[1,183-185] promotion of maturation and development of T-lymphocytes and enhancement of lung epithelial barrier function.[15] It may also be involved in mediating the adrenocortical stress response, especially in sepsis.[186-188] Severe respiratory infections, in particular, are regarded as common complications of severe vitamin C deficiency.[189] Results of placebo-controlled trials testing 200 micrograms per day and even higher doses of oral ascorbic acid for treatment and preventing the common cold, reduction of incidence did not observe in the general population,[15,190] but it can be helpful for patients who experienced short periods of intense physical exercise and in high concentrations for

patients with active cold symptoms and as a candidate for the treatment of individuals with sepsis and acute respiratory distress syndrome (ARDS).[191-195]

Vasopressor sparing effects, a decreased need for mechanical ventilation, and reduced time of ICU stay without much impact on overall mortality have been observed in a meta-analysis of intravenous vitamin C in patients with sepsis, burns, and septic shock.[196,197] A clinical study in Switzerland showed that the best-desired effects of vitamin C were obtained in conjunction with zinc,[198] and in association with vitamin A. It has the capability of generating firm antigen-specific regulatory T cells in animal models of autoimmune or acute graft versus host diseases.[199-201]

Considering the anti-inflammatory properties of vitamin C and consequential effects on cellular immunity and vascular integrity, the potential role of high doses of vitamin C in SARS-CoV-2 induced ARDS and sepsis has been evaluated.[15,202,203] Results of these studies have indicated that high doses of vitamin C (10 g to 20 g) improved the oxygenation index in 50 patients with moderate and severe COVID-19. Importantly, all of the patients were cured and discharged. Based on the National Institutes of Health (NIH) expert panel document, vitamin C (1.5 g/kg body weight) is safe and has no major adverse events. Despite all mentioned immune-boosting properties of folic acid and beneficial effects of vitamin C against SARS coronavirus and even 82% comparability between SARS-CoV-2 and SARS, we have to wait for the elucidation of ongoing investigations.[115,204-211]

Cai *et al.* conducted a study to investigate the effects of vitamin C on influenza virus infection and pneumonia in a restraint-stressed mouse model. Fulminant viral pneumonia, severe inflammation, and considerable damage were detected in the restraint stress-loaded infected mouse model. Data analysis showed that administration of vitamin C (125 and 250 mg/kg) in mice is associated with increased survival rates and prolonging survival time. In addition, vitamin C could decrease the levels of inflammatory cytokines four days after infection. They concluded that vitamin C could prevent influenza virus infection and subsequent pneumonia in the restraint-stressed mouse model.[212] Furthermore, according to the limited data, vitamin C administration could lead to the reduction of cytokine storm during the late stage of COVID-19. Following the observed effects of vitamin C in preclinical studies, promising results have also shown the effectiveness of intravenous vitamin C administration for the treatment of COVID-19. It has been shown that vitamin C could reduce the risk of the development of cytokine storm during the late stage of COVID-19.[213-215] Also, high doses of intravenous vitamin C could improve the clinical outcome in patients with moderate (10 g daily) and severe (20 g daily) COVID-19. Moreover, vitamin C supplementation could reduce the duration of hospital stay (3–5 days).[213,216,217]

Furthermore, the combination of vitamin C with other medications also has shown favorable results. For example, it has been shown that the administration of vitamin C, curcumin, and glycyrrhizic acid could prevent excessive inflammatory response and improve innate antiviral immunological response.[213,218] Moreover, the administration of vitamin C in combination with diammonium glycyrrhizinate and quercetin resulted in significant relief of symptoms of non-hospitalized patients with COVID-19[213,219] and a synergistic antiviral effect, respectively.[211, 213]

The studies that have been conducted to determine the efficacy of vitamins in the prevention and treatment of respiratory tract infections are summarized in Table 1.

Ongoing Clinical Trials on Vitamins in COVID-19

Numerous studies are underway to evaluate the effectiveness of vitamins in the prevention and treatment of patients with COVID-19, which are listed in Table 2. A total of 30 studies are conducting in several countries, including Turkey, Egypt, Canada, Argentina, the United Kingdom, the United States of America, Mexico, Australia, Spain, France, Iran, Denmark, Saudi Arabia, New Zealand, and Brazil with sample size ranges from 20 to 27000, with a cumulative sample size of 45593 and an age range of 1 to 100 years in diverse population including healthcare workers, pregnant women, pediatric patients and people in a nursing home and various issues such as its effects on prevention and reducing the risk, severity, mortality, morbidity, improvement of outcome after infection, its role as a prognostic marker in COVID-19, its relationship with inflammatory immune status, etc. have been studied. Type of studies are interventional and, in limited cases are observational. In some studies, the effectiveness of vitamin D with other minerals and vitamins such as zinc and vitamin B12 and some medications like aspirin and famotidine has also been evaluated. The efficacy of vitamin C in lessening organ dysfunction and clinical outcome of patients infected with COVID-19 are being investigated in eight studies alone or in combination with minerals, zinc citrate, vitamin D3, vitamin B12 azithromycin, hydroxychloroquine, famotidine, quercetin, and bromelain. Several outcomes like days of stay at the hospital after treatment and discharge, day of negative conversion for nasopharyngeal swab for reverse transcription-polymerase chain reaction (RT-PCR), mechanical ventilation requirement, mortality rate, and duration of hospital and ICU stay, WBC count, days free of dialysis, and serum levels of inflammatory biomarkers such as C-reactive proteins, ferritin, and D-dimer are being evaluated. Furthermore, one ongoing study is being carried out in the USA with a sample size of 800 and the age range of 55-120 to evaluate the efficacy and safety of B complex (alongside Nitazoxanide) for the prophylaxis of COVID-19 and other respiratory illnesses in the elderly individuals. Another trial evaluates the effects of B3 on the clinical outcome of COVID-19 in the elderly over 70 years with a sample size of 100 in Denmark.

Table 1. Studies that have examined the immunological effects of vitamins and multi-nutrients.[28]

Author; Published Year	Nutrient	Purpose	Intervention; Control; Dose/Frequency	Study population; Sample size (I/C); Male/Female; Age (years)	Study design; Duration; Jadad score	Significant anti-viral outcome
Ginde *et al*.[24]; 2017	Vitamin D	Evaluation effects of high dose vitamin D in acute respiratory infection among elderly care residents.	IG: Vitamin D_3 100,000 IU/month CG: Placebo, for participants receiving 400–1000 IU/day; 12000 IU of vitamin D3/month for those receiving <400 IU/day	Elderly cases; 55/52; 45/62; ≥60	R, DB, PC; 12 months; 5 points	Incidence of acute respiratory infections was lower in cases in IG group compared with CG.
Abu-Mouch *et al*.[25]; 2011	Vitamin D	Assessment of Vitamin D effects on HCV response to antiviral therapy.	IG: Vitamin D_3 (2000 IU/day) with antiviral treatment CG: Antiviral treatment	Chronic HCV patients; 36/36; 39/33; 18–65	R, C; 48 weeks; 1 point	Number of patients with negative HCV-RNA was significantly more in those received vitamin D compared with CG. Supplementation with vitamin D led to sustained virologic response.
Aglipay *et al*.[26]; 2017	Vitamin D	Comparing effects of standard dose of vitamin D compared with high-dose in viral respiratory tract infections.	IG: Vitamin D_3 high dose (2000 IU/day) CG: Vitamin D_3 standard dose (400 IU/day)	Healthy children; 349/354; 404/296;1–5	R, DB, C; 4–8 months; 5 points	Incidence of respiratory tract infections was lower in IG group compared with CG
Meydani *et al*.[66]; 2004	Vitamin E	Evaluation efficacy of vitamin E on respiratory infections in elderly nursing home residents.	IG: Vitamin E (α-tocopherol, 200 IU) in soybean oil, one capsule/day CG: Placebo (4 IU of vitamin E) in soybean oil, one capsule/day	Elderly participants; 231/220; 113/338; ≥65	R, DB, PC; 12 months; 5 points	Vitamin E had no statistically significant effect on incidence of lower respiratory tract infections, while it could have a protective effect on common cold.
Andreone *et al*.[77]; 2001	Vitamin E	Evaluation effects vitamin E supplement in the treatment of Chronic HBV.	IG: Vitamin E (300 mg twice daily) CG: No treatment	Chronic HBV patients; 15/17; NM; I: 37 C: 42	R, C; 3 months; 2 points	Patients in IG experienced significantly higher rate of complete response, alanine aminotransferase normalization, and HBV-DNA negativization compared with CG.
Siddiqui *et al*.[101]; 2001	Vitamin A	Evaluation effects of Vitamin A on humoral immunity after anti-rabies vaccine.	IG: Vitamin A (100000 IU on 1st vaccine day and 100000 IU on the following day) and anti-rabies vaccine CG: Anti-rabies vaccine	Healthy participants; 20/20; 30/10; 10–35	C; 30 days; 0 points	NAIG group had significantly higher serum anti-rabies titer compared with CG.
Patel *et al*.[220]; 2019	Vitamin A and Vitamin D	Evaluation effects of vitamins A and D on humoral immune responses after pediatric influenza vaccination.	IG: Oral gummy (Vitamin A 20,000 IU and Vitamin D 2000 IU), on days 0 and 28 CG: Placebo	Healthy children; 39/40;33/46; 2–8	R, DB, PC; 28 days; 2 points	Supplementation with vitamins A and D could improve immune responses to vaccines among those with insufficient baseline levels of vitamin A and D.
Goncalves-Mendes *et al*.[221]; 2019	Vitamin D	Evaluation effects of Vitamin D in elderly individuals on influenza infection and immune response.	IG: Vitamin D (6 doses 100,000 IU, 1 vial/15 days) and influenza vaccine CG: Placebo (6 doses, 1 vial/15 days) and influenza vaccine	Elderly participants (Vitamin D deficient); 19/19; Both genders >65	R, DB, PC; 3 months; 5 points	Individuals in IG had a higher TGFβ plasma level after influenza vaccination with no improvement in antibody response.

Table 1. Continued

Author; Published Year	Nutrient	Purpose	Intervention; Control; Dose/Frequency	Study population; Sample size (I/C); Male/Female; Age (years)	Study design; Duration; Jadad score	Significant anti-viral outcome
Nimer & Mouch[222]; 2012	Vitamin D	Assessment of effects of vitamin D on viral response therapeutic outcomes of patients with HCV genotype 2–3.	IG: Vitamin D3 (2000 IU/day) with antiviral therapy CG: Antiviral therapy	Chronic HCV patients; 20/30; 31/19; 18–65	R, C; 24 weeks; 1 point	After 24 weeks, individual in IG group experienced sustained virological response compared with CG. Supplementation with vitamin D is a predictor of viral response.
Fiorino *et al*.[223]; 2017	Vitamin E	Assessment the efficacy and safety of vitamin E for the treatment of individuals with HBe-antigen positive chronic HBV.	IG: Vitamin E (15 mg/kg/day) CG: No treatment	Children with chronic HBV; 23/23; 34/12; 2–17	R, C; 12 months; 3 points	Supplementation with vitamin E could lead to significantly higher virologic response and anti-HBe seroconversion.
Hemilä & Kaprio[224]; 2008	Vitamin E and β-carotene	Evaluation effects of vitamin E on pneumonia risk in individuals who started smoking at early ages.	IG: Vitamin E (α-tocopheryl acetate, 50 mg/day), or β-carotene (20 mg/day), or Both vitamin E and β-ca CG: Placebo	Cases who smoked at least 5 cigarettes/day and initiated smoking at ≤ 20 years; 10,784/10,873; Males only; 50–69	R, DB, PC; 5–8 years; 3 points	Vitamin E had no significant effect on the risk of pneumonia in cases with body weight of 70 to 89 kg; however, it could increase the risk of pneumonia in those with body weight of less than 60 kg and more than 100 kg.
Girodon *et al*.[225]; 1999	Multi-nutrient	Investigation efficacy of long-term vitamin and trace elements on incidence of infections and immunity in institutionalized elderlies.	IG: Trace element (Zinc 20 mg plus Selenium 100 µg), or ascorbic acid (120 mg) plus beta carotene (6 mg) plus αtocopherol (15 mg), or trace elements and vitamins CG: Placebo group	Elderly participants; 182:180:181/182; 185/540; 5–103	4 points	Zinc and selenium supplementation could lead to significant improvement in these individuals through increasing the humoral response following vaccination. It could reduce morbidity from respiratory tract infections.
Graat *et al*.[226]; 2002	Multi-nutrient	Evaluation effects of supplementation with vitamin E and multivitamin-mineral on acute respiratory tract infections in elderly.	IG: Multivitamin-mineral, or Vitamin E (200 mg), or multivitamin-mineral Plus vitamin E CG: Placebo	Elderly individuals; 163:164:172/153 Both genders ≥60	R, DB, PC; 15 months; 5 points	Multivitamin mineral supplementation at physiological dose and vitamin E had no significant beneficial effects on acute respiratory tract infections in well-nourished non- institutionalized elderly case.

Conclusion

The SARS-CoV-2 is not the first pathogen to pose a global challenge, and it will not be the last. It has drawn the world's attention to our immune system. Diet plays a critical role in regulating overall homeostasis by modifying/manipulating master nutrient-sensing pathways. Therefore, it is of particular importance not only in patients but also in healthcare workers. Besides, malnutrition leads to impaired immunity and severe complications for human health. Therefore, the need to understand the importance of proper nutrition, especially during this pandemic, needs special attention. Although according to the NIH guidelines, there are not sufficient data to recommend for or against the administration of vitamins in the management of patients with COVID-19 and, owing to the vital role of vitamins in the normal function immune system as well as controversial evidence regarding the inverse association between the severity of the disease and plasma levels of

Table 2. Ongoing clinical trials on vitamins in COVID-19.

ID	Status	Study Design	Country	Number Enrolled	Intervention group(s)	Comparison group(s)	Age	Outcome measure
NCT04370288	Recruiting	Phase 1, Randomized clinical trial	Iran	20	Drug: MCN (Methylene blue, vitamin C, N-acetyl cysteine)	None	18 Years to 90 Years (Adult, Older Adult)	-Percentage of individuals remaining free of need for mechanical ventilation -Mortality rate -Pao2/Fio2 ratio improvement
NCT04386850	Recruiting	Phase 2, Randomized double blinded placebo-controlled clinical trial	Iran	1500	Drug: Oral 25-Hydroxyvitamin D3	None	18 Years to 75 Years (Adult, Older Adult)	-COVID-19 infection -Severity of COVID-19 infection -Hospitalization
NCT04360980	Recruiting	Phase 2, Randomized Double Blind Clinical Trial	Iran	80	Drug: Colchicine Standard care including vitamins C 3 gram and D (dose is not defined)	Standard care including vitamins C 3 gram and D	18 Years and older (Adult, Older Adult)	-CRP change -Clinical deterioration by the WHO definition -PCR viral load
NCT04394390	Enrolling by invitation	Case-Control	Turkey	100	Dietary Supplement: vitamin d (dose is not defined)	None	Child, Adult, Older Adult	-Laboratory measured vitamin D levels
NCT04487951	Recruiting	Case-Control	Egypt	100	Vitamin D (dose is not defined)	Pro BNP	18 Years and older	-Evaluation of correlations between vitamin D and NT-pro-BNP and mechanical ventilation requirement or death in patients with COVID-19
NCT04385940	Not yet recruiting	Phase 3, Randomized double blinded clinical trial	None	64	Dietary Supplement: Ddrops® products, 50,000 IU, Oral Dietary Supplement: Vitamin D3 (dose is not defined)	None	17 Years and older	-Symptoms recovery -Hospitalization -Blood white blood cell count
NCT04483635	Not yet recruiting	Phase 3, Randomized clinical trial	Canada	2414	Dietary Supplement: Vitamin D (dose is not defined)	Dietary Supplement: Placebo	18 Years to 69 Years	-Laboratory-confirmed COVID-19 incidence -COVID-19 positivity length -Disease severity distribution
NCT04411446	Recruiting	Phase 4, Randomized, controlled, double-blind, clinical trial	Argentina	1265	Vitamin D (dose is not defined)	Placebo	18 Years and older	-Respiratory SOFA -Oxygen or mechanical ventilation requirement -Oxygen saturation variations
NCT04519034	Not yet recruiting	Retrospective	United Kingdom	27000	None	None	1 Year to 100 Years	-COVID-19 screening results collecting together with laboratory results.
NCT04535791	Recruiting	Phase 3, Blinded randomized clinical trial	Mexico	400	Cholecalciferol(dose is not defined)	None	18 Years to 70 Years	-Number of individuals and hospitalization cases with COVID-19 -Vitamin D serum concentration
NCT04536298	Not yet recruiting	Phase 3, Cluster-Randomized, Double-Blind, Placebo-Controlled clinical trial	United States	2700	vitamin D (dose is not defined)	Placebo	30 Years and older	-Mortality or hospitalization -Severity of disease -Time to mortality or hospitalization

Table 2. Continued.

ID	Status	Study Design	Country	Number Enrolled	Intervention group(s)	Comparison group(s)	Age	Outcome measure
NCT04401150	Recruiting	Phase 3, Multicentre concealed-allocation parallel-group blinded randomized controlled trial	Canada	800	Vitamin C (dose is not defined)	Control	18 Years and older	-Mortality or persistent organ dysfunction -ICU-free days -Persistent organ dysfunction-free days in ICU
NCT04407572	Completed	Case-Control	Turkey	44	Zinc, vitamin D, vitamin B12	None	18 Years to 45 Years	-Serum vitamins D, B12 and Zinc levels
NCT04395768	Recruiting	Phase 2, Randomized investigator-blinded controlled trial	Australia	200	Vitamin C (dose is not defined), Hydroxychloroquine, Azithromycin	None	18 Years and older	-Symptoms -Hospital stay length -Invasive mechanical ventilation or death
NCT04482673	Recruiting	Phase 4, Randomized clinical trial	United States	140	Daily Vitamin D3(bolus)	Placebo(Bolus)	50 Years and older	-Change serum levels of vitamin D and SARS-CoV-2 antibody titers in patients with COVID-19
NCT04579640	Not yet recruiting	Phase 3, Randomized clinical trial	United Kingdom	5440	Vitamin D (dose is not defined)	None	16 Years and older	-Percentage of individuals developing COVID-19 according to a symptom score.
NCT04552951	Recruiting	Phase 4,, Randomized clinical trial	Spain	80	Cholecalciferol (dose is not defined)	None	Child, Adult, Older Adult	-Mortality -Admission to ICU -Time of hospitalization
NCT04502667	Recruiting	Phase 3, Open controlled clinical trial (Open Label)	Mexico	40	Cholecalciferol (dose is not defined)	None	1 Month to 17 Years	-Interleukins (IL-2,6,7,10) (pg/ml) -Ferritin (ng/ml), D-dimer ,Vitamin D (ng/ml)
NCT04468139	Recruiting	Phase 4, Single Group Assignment (open label)	Saudi Arabia	60	Quercetin, bromelain, Zinc, Vitamin C (dose is not defined)	None	18 Years and older	-Hospitalization -Serum zinc before and after treatment
NCT04363840	Not yet recruiting	Phase 2, Multi-center, prospective, randomized controlled trial (open label)	None	1080	Aspirin 81 mg, Vitamin D (dose is not defined)	None	18 Years and older	-Hospitalization
NCT04400890	Recruiting	Phase 2, Randomized Double-Blind Placebo-Controlled clinical trial	United States	200	Plant Polyphenol, Vitamin D3(dose is not defined)	None	45 Years and older	-Hospitalization due to COVID-19 -ICU admission -Invasive ventilation
NCT04435119	Completed	Cohort	France	96	vitamin D3 (bolus)	None	70 Years and olde	-Mortality among nursing-home residents with COVID-19 (any cause)
NCT04344041	Recruiting	Phase 3, Multicenter Randomized Controlled Trial (open label)	France	260	cholecalciferol 200,000 IU cholecalciferol 50,000 IU	None	65 Years and older	-Mortality (any cause) during 14 and 28 days after the inclusion and intervention.
NCT04279197	Recruiting	Phase 2, Multicenter Randomized Controlled Trial, Masking: Triple (Participant, Care Provider, Investigator)	China	160	Fuzheng Huayu Tablet Vitamin C(dose is not defined)	Placebo	18 Years to 70 Years	-Pulmonary fibrosis improvement -Blood oxygen saturation -Clinical symptom score

Table 2. Continued.

ID	Status	Study Design	Country	Number Enrolled	Intervention group(s)	Comparison group(s)	Age	Outcome measure
NCT04343248	Recruiting	Phase 3, Randomized, Double-Blind, Placebo Controlled Trial	United States	800	Nitazoxanide, Vitamin Super B-Complex	Placebo	55 Years to 120 Years	-Symptomatic laboratory-confirmed COVID-19 and other viral infections
NCT04407390	Recruiting	Phase 2, Randomized Double-blind, Placebo-controlled Trial	Denmark	100	Nicotinamide riboside	Placebo	70 Years and older	-Hypoxic respiratory failure, Mortality, -Sepsis
NCT04407286	Recruiting	Phase 1, open label treatment study	United States	100	Vitamin D3 (dose is not defined)	None	18 Years and older	-None
NCT03333278	Completed	Multi-centre, Randomised, Open-label controlled Trial (open label)	Multi-country	216	Vitamin C (1.5 g every 6 hours), thiamine (200 mg every 12 hours), and hydrocortisone (50 mg every 6 hours)	Hydrocortisone (50 mg every 6 hours)	mean age, 61.7 years	-Time alive and vasopressor free -Mortality (hospital, ICU) -Alive and ICU-free days -SOFA score -Hospitalized and RRT length
CVIT-3334	Completed	Cohort	China	78	Vitamin C 12 gram every 12 h for 7 days	Placebo	≥18 and < 80 years	-Mortality -ICU Stay length -PaO2/FiO2 ratio -Inflammatory markers levels -Vasopressor or invasive mechanical ventilation requirement
NCT04264533	Completed	Phase 2, Randomized Clinical Trial, Masking: Triple (Participant, Care Provider, Outcomes Assessor)	China	56	Vitamin C (dose was not defined)	Placebo (Sterile Water for Injection)	≥18	-Ventilation-free days - 28 days mortality -ICU length of stay

vitamins, screening and treating patients with insufficient vitamins should be considered in the pandemic mode. Data regarding their higher doses of beneficial effects in the acute treatment of COVID-19 is not adequate to draw a conclusion. According to the limited available data, vitamin C could reduce the development of hyperinflammatory responses and improve antiviral immunological responses as well as vitamin D may lower mortality rate, probably through effects against acute respiratory infections. Finally, the results of ongoing studies are desired to determine the exact effects of vitamins in the pathogenesis, prevention, and treatment of COVID-19.

Author Contributions

TEM, HR[1], HR[2] and SK: Acquisition and drafting the work, HR[3], SK and MP: Drafting the work and revision, HR[1], SK, HBB and MP and TEM: Analysis, interpretation of data and revision. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors have no the conflict of interest.

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