Review

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Vitamin supplementation as a potential adjunctive therapeutic approach for COVID-19: biological and clinical plausibility

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Abstract: The recent pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19) has introduced itself into the human population in the 21st century after the coronavirus diseases SARS-CoV and Middle East respiratory syndrome (MERS-CoV). Major investigations are underway worldwide in the search for pharmaceutical interventions for COVID-19 and many agents are administered in off-label routes. Several cases are under study to check or restrict clinical manifestations of COVID-19. According to the fact that the efficacy of some micro-nutrients like vitamins is proven to treat or prevent infectious diseases because of their antimicrobial and immunomodulatory activity, the

potential role of vitamins in the COVID-19 treatment or prevention must be considered.

Keywords: COVID-19; immunomodulatory functions; prophylaxis; treatment; vitamins.

Introduction

COVID-19 is associated with a wide spectrum of clinical manifestations ranging from asymptomatic to multi organ damage. This variability in clinical manifestations and severity of the disease is related to different factors including age, sex, nutritional status, habits, and comorbidities which can affect innate and adaptive immune response. Considering these factors can help to explore the most effective preventative and therapeutic options for COVID-19 [1, 2]. Although vaccination is the best option for countering the pandemic, since the time required immunizing 7.8 million people is lengthy, evidence-based effective treatment is urgent. Suboptimal immune responses to SARS-CoV-2 and severe complications in some population groups may be due to a variety of factors, the most prominent of which is micronutrient deficiency [3]. Malnutrition raises the risk of morbidity and mortality by increasing the rate of infections and extending recovery time since the immune system necessitates a variety of nutrients to function optimally. The general associations and extrapolations analysis signify the value of micronutrients and clinical practitioners are strongly advised to carry out a further search into treatment options [4]. Vitamins are the micronutrients with the most evidence for immune support and have been proposed to reduce the duration and severity of complications in viral infections because of their anti-inflammatory and antioxidant properties. These dietary supplements can attenuate vascular complications and overexpression of proinflammatory cytokines associated with infectious disease. Whether these agents could benefit COVID-19 patients is a research question worth investigating [5].

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A wealth of clinical and preclinical observations suggested that insufficient vitamin levels were observed in hospitalized COVID-19 patients compared to the control group, which may explain the importance of vitamin supplementation in COVID-19 patients [6, 7]. Evidence supports the notion that, in addition to their specific and non-specific functions in immune system support, vitamins have a promising role in scavenging reactive oxygen species (ROS) and protecting cells from COVID-19-induced oxidative damage [8]. They also participate in the modulation of the renin–angiotensin system (RAS), which in turn regulates the normal expression of the angiotensin-converting enzyme 2 (ACE2) receptor, a common binding site for SARS-CoV-2. Other COVID-19-induced complications, such as acute lung damage, endothelial dysfunction, and immune thrombosis, can be mitigated by these supplements [9, 10]. Furthermore, evidence suggests that some vitamins, particularly vitamin D, have antiviral effects and contribute to maintain respiratory homeostasis by either stimulating the exhibition of antimicrobial peptides or directly interfering with the replication of respiratory viruses. They may also exert activity in lung tissue and influence experimental interstitial pneumonitis. The objective of this review is to present the detailed therapeutic potential and physiological functions of vitamins in the management and treatment of COVID-19.

Vitamin A

Vitamin A is a multifunctional vitamin that is engaged in a wide range of biological processes. Retinol, retinal, and retinoic acid (RA) are the three main forms of vitamin A, with RA being the most physiologically active and all-trans retinoic acid (ATRA) being its main metabolite [11, 12]. Due to the different functions of vitamin A such as immunomodulatory and antimicrobial activity, it can be proposed as a beneficial approach to fight against viral infections such as COVID-19 [13]. Its immunomodulatory effects are perhaps the most pleiotropic, impacting not just development but also the functional fate of almost every cell involved in adaptive or innate immunity, whether protective or regulatory. This is especially important near the intestinal barrier, which is where dietary vitamin A is absorbed [14]. Vitamin A keeps the immune system in check by regulating the activity of a number of innate and adaptive immune cells [12, 14]. RA promotes the maturation of T helper 2 (Th2) cells and regulatory T cells (Tregs) while inhibiting Th1 and Th17 differentiation. It also stimulates B cell differentiation and contributes to the maintenance of antibody production. Low levels of RA may result in an

inadequate level of antibodies, notably immunoglobulin (Ig) A [15, 16]. Retinoid induces monocyte differentiation toward macrophages and suppresses macrophage production of proinflammatory cytokines, contributing to the temporary transformation of M1 macrophages into M2 macrophages in the bone marrow, resulting in immunomodulation [12]. Individuals with vitamin A deficiency encounter problems with lymphocyte development and function that are linked to C–C motif chemokine receptor 9 (CCR9) and 4-7-integrin. Vitamin A deficiency limits the number of T and B cells in the lamina propria of the small intestine, rendering it susceptible to pathogens received through the diet [9]. RA is linked to the balance of Th1 and Th2 cells, implying that in individuals with vitamin A deficiency, Th2 differentiation, and Th1-Th2 balance are disrupted [17, 18]. Vitamin A has been demonstrated in several studies to be able to regulate the production of interleukin-10 (IL-10) by Th2 cells. It inhibits the synthesis of proinflammatory Th1-type cytokines including interferon (IFN) and IL-2 in both T and natural killer (NK) cells, making it anti-inflammatory [19]. Thus, this process is linked to the lack of some infections to elicit inflammatory responses [20, 21].

Coronaviruses can suppress type-I interferon (IFN-I)-mediated antiviral responses, limiting therapeutic approaches [22]. According to recent research by di Bari et al., SARS-CoV-2 may exploit a host TF implicated in IFN, RA signaling, and ribonucleic acid (RNA) polymerase II transcription regulation to facilitate its replication cycle. Through this mechanism, it may be able to compete to steal the human TF that is engaged in these processes. It has prompted scientists to compile a compelling body of data indicating that SARS-CoV-2 can impair IFN-I signaling in host cells as well as explaining the mechanism of SARS retinoic acid depletion syndrome, which culminates in a cytokine storm [23]. Since the host's IFN-I response to SARS-CoV-2 is linked to retinol storage and endogenous RA serum concentrations, sufficient amounts of vitamin A can contribute to enhanced outcomes [24]. Since retinoids can potentiate the function of IFN-I consumption of retinoids in combination with IFN-I against COVID-19 may have beneficial effects. Thus, vitamin A supplementation in COVID-19 patients may yield encouraging outcomes, suggesting it as an adjunctive treatment for COVID-19; nevertheless, further research is required. Regarding evidence, COVID-19 patients have a substantial decrease in RA storage which can be also manifested as conjunctivitis or pink eye [24, 25]. Three mechanisms are underlying low RA levels in these patients, which are as follows: First, the change of lipofibroblasts to active myofibroblasts, which deposit extracellular matrix proteins abundantly and lose their retinoid reserves, is a

hallmark of SARS-CoV-2-induced pulmonary fibrosis. Second, since lipofibroblasts rely on retinoids to initiate, coordinate, and regulate alveolar septal eruption and alveologenesis, inflammation-induced reductions in RA uptake and metabolism to polar metabolites may impair the lung's capacity to regenerate from pulmonary fibrosis. Third, the capacity to transport retinoid to the lung is impaired during severe infection due to a decline in circulating vitamin A levels [26]. Retinoid signaling may be the main pathogenetic disorder in COVID-19 which can be used to influence the development of adjuvants, therapeutic targets, and potential medicines [24, 27]. Likewise, a recent retrospective cohort study of individuals with post infectious olfactory impairment, a long-term consequence in COVID-19 patients, discovered that topically administering vitamin A at a dose of 10,000 IU/day for eight weeks improved clinical outcome [28, 29].

In COVID-19, the development of acute respiratory distress syndrome (ARDS) is primarily linked to inflammatory cytokine release and the subsequent exudative liquid buildup. The impact of retinol derivatives lecithin, colin, and inositol deficiency in the medium on ARDS pathogenesis and the probable reduction of surfactant synthesis due to RA deficiency in the body owing to a severe catabolic state and severe infection should not be neglected. These retinol compounds play a significant role in surfactant structure and are essential issues that must be researched concerning the development and severity of the ARDS presentation [30]. In this way, Yang et al. discovered that RA-SS therapy significantly decreased inflammatory infiltration and proliferative alterations in the pulmonary stroma [31].

The evidence suggests that the impact of vitamin A is dose-dependent [32]. Accordingly, low-dose RA stimulates the release of inflammatory mediators at physiological doses (1 nM). According to a case-control study, the length of symptom and mean SPO₂ variations in patients receiving vitamin A after 24 and 48 h revealed a marginally nonsignificant improvement over placebo. To avoid a respiratory viral infection, the recommended dose for elderly individuals, adults, and adolescents is to supplement 2,000–4,000 IU vitamin A per day, and the optimal vitamin A dose as supportive therapy after hospitalization for severe COVID-19 is as follows: Based on current evidence, all COVID-19 patients should receive an initial bolus dosage of vitamin A ranging from 50,000 to 200,000 IUs. Following that, 10,000 IU vitamin A should be administered for a month, continued by 5,000 IU orally [33].

Furthermore, research suggests that calves given dietary vitamin A (3,300 U/kg dry matter diet) exhibited

higher serum retinol levels and a stronger IgG1 response to bovine coronavirus intramuscular inoculations. Surprisingly, these immunized vitamin A supplemented calves had a greater IgG1 to IgG2 ratio. Immune response to mucosal bovine respiratory syncytial virus (BRSV) vaccine was impaired in vitamin A deficient individuals owing to this adjuvant-like ability; hence vitamin A may be worth considering for coadministration alongside vaccine trials in the future [33].

B vitamins

B vitamins are a vitamin family with at least eight members that contribute to cell metabolic pathways while also having a remarkable association with immune responses [34]. Studies on the correlation of B vitamins with immune responses and prevailing viral infections, such as SARS-CoV-2 infection, suggest that B vitamins play a key role in innate and adaptive immune responses. The involvement of vitamins B6 and B9 in nucleic acid and amino acid synthesis supports an undeniable link between B vitamins and immune responses [35]. B vitamins have been shown to modulate proinflammatory immune responses as well as their significant association with alleviating multi organ clinical manifestations in COVID-19 patients by affecting cytokines levels, enhancing pulmonary function, and endothelial integrity, in addition to its specific role in preventing coagulopathies [36]. The significance of vitamin B in the prognosis and treatment of COVID-19 patients has compelled clinicians to consider vitamin B as a nonpharmaceutical adjunct to current treatments and to assess vitamin B status in COVID-19 patients, which has been suggested to have an inverse correlation with the length of hospitalization in these patients [37]. Furthermore, studies suggest that vitamin B has a complicated dominance in controlling immune responses via mucosa-associated invariant T (MAIT) cells, which are primarily found in the intestine, liver, and lung and express a semi invariant T cell receptor restricted by the major histocompatibility complex (MHC) class 1-related molecule [38, 39].

Vitamin B1

Vitamin B1 (thiamine) has been linked to the adequacy of humoral immune responses in COVID-19 patients, with a lack of B1 resulting in an abnormal antibody response, which can lead to serious consequences such as neuroinflammation and cardiovascular complications [36].

Thiamine has a significant anti inflammatory effect and can diminish cytokine storms in individuals who have a proinflammatory reaction [40]. Thiamine deficiency has been believed to trigger a proinflammatory response in Th1 and Th17 cells, since these cells play an important role in the management of COVID-19, appropriate amounts of this vitamin should be considered in COVID-19 cases [40]. In COVID-19 patients with severe symptoms, daily 500 mg thiamine is recommended [41, 42]. Furthermore, vitamin B1 deficiency has been shown to alter the tricarboxylic acid cycle, resulting in fewer naive B cells in Peyer's patches; as a result, individuals with vitamin B1 deficiency are more susceptible to infections obtained from the diet [38]. Encephalopathy is a neurological complication of COVID-19, and according to a case series research, thiamine replacement may be beneficial for COVID-19-associated encephalopathy by improving functional outcomes and lowering mortality [41]. According to the findings of Al Sulaiman et al., administering thiamine to COVID-19 patients admitted to the intensive care unit (ICU) reduced the risk of thrombosis by 81% as compared to the control group showing the potential of thiamine in enhancing the prognosis of COVID-19 patients [43].

Vitamin B2

Vitamin B2 (riboflavin) has been shown to be capable of altering the nucleic acids of microbial pathogens in the presence of ultraviolet (UV) radiation, causing detrimental effects on these microorganisms and inhibiting their replication in in vitro experiments [35]. Although the risk of SARS-CoV-2 infection by transfusion is believed to be minimal, utilizing a PI technology such as riboflavin and UV light may be a vital first line of defense against a threat [44]. The use of convalescent plasma (CP) is a suggested therapeutic method for COVID-19 in which riboflavin plays a key role [44]. CP is a therapy in which putatively antibody-rich plasma is extracted and transfused from patients who have recovered from the disease to provide passive immunity to the disease [35]. It is the most widely available source of anti-SARS-CoV-2 antibodies, and its use is universally accepted. Pathogen reduction utilizing riboflavin and UV light dramatically lower SARS-CoV-2 infectivity in inoculated plasma and whole blood. Previous research on the relationship between vitamin B2 and MERS-CoV infection revealed the positive efficacy of vitamin B2 in patients with MERS-CoV infection, proposing

a powerful beneficial contribution of vitamin B2 to SARS-CoV-2 infection [35].

Vitamin B3

Vitamin B3 (niacin) contributes to producing nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP), which play an initial role in chronic systemic inflammation by functioning as a co-enzyme in various metabolic pathways that must be regulated to overcome various pathophysiological conditions [36]. Almost all processes in the COVID-19 molecular disease pathway are either triggered by or arose from NAD⁺ depletion [45]. It is mediated by NAD and adenosine triphosphate (ATP), and excessive NAD intake lowers ATP levels, resulting in cognitive impairment. Besides that, despite RAS activation, COVID-19 patients' aldosterone levels drop and they become hypovolemic. It appears that aldosterone synthesis is turned off somewhere in the CNS or the adrenal gland [46]. The inevitable fact serotonin deficiency is a key molecule that serves a number of activities, including stimulating aldosterone release. The tryptophan resources, which serve as the raw material for the production of serotonin and NAD, are depleted in COVID-19 patients [47]. Also, concerning ARDS, serotonin levels drop, resulting in hypoaldosteronism. Hyponatremia and hypovolemia are two conditions that can occur. Fatigue and varying degrees of mood problems are the most common symptoms. NAD, ATP, and serotonin decline all have effects that may be handled by NAD, niacin, and other supplements taken concurrently [48].

NAD⁺, which is increased by vitamin B3 revealed to be associated with immunomodulation by inhibiting the release of proinflammatory cytokines like IL-1 β , IL-6, and tumor necrosis factor α (TNF- α) [49]. Moreover, studies have demonstrated that vitamin B3 contributes to managing cytokine release status in COVID-19 patients by affecting IL-6 [27]. It is also capable of exerting anti inflammatory and immunomodulatory effects through hindering neutrophil infiltration, especially in patients with ventilator-induced lung injury [50]. Recent investigations have shown that niacin may efficiently bind to certain proteins in the novel coronavirus; it is hypothesized that niacin may be able to bring the IL-1B to target the SARS-CoV-2 as a result of these bindings. Overall, it is anticipated that niacin adjuvant supplementation may improve the therapeutic effectiveness of current clinical

antiviral medications and immunotherapy in the treatment of the fatal COVID-19 [40].

Vitamin B6

Vitamin B6 (pyridoxine) is required as a coenzyme in many inflammatory pathways, antibody, cytokine, sphingosine, and tryptophan metabolism, as in the regulation of endothelial integrity, platelet aggregation, maintaining cytotoxic activity of NK cells, B-cell antibody production, the clotting cascade, and blood pressure regulation via renin-angiotensin secretion [51]. Its deficiency impairs lymphocyte prefiltration and IL-2 production in response to mitogens and immunization-induced antibody synthesis. Pyridoxal phosphate (PLP), also known as an active form of vitamin B6 has been shown to play a role in alleviating COVID-19 manifestation by regulating proinflammatory cytokines, while also affecting endothelial integrity and avoiding coagulopathies [52, 53]. The precise mechanism of PLP's immune-modulatory function has not been elucidated; however, it is conceivable that the interaction of proxy radicals with PLP scavenges free radicals owing to the pyridine's amino group [54, 55]. Vitamin B6 has been identified to have an essential role in the maintenance and function of lymphoid tissues. Immune deficiencies such as lymphoid atrophy, lymphopenia, and disturbed primary and secondary antibody response develop in individuals with vitamin B6 deficiency [39].

The administration of an adequate dose of vitamin B6 to COVID-19 patients has been proposed as an adjunctive treatment, even via supplementing formulas, to better stabilize the disruption of cellular metabolism of the homocysteine pathway induced by the SARS-CoV-2 infection [56]. Vitamin B6 defined requirements are 1.6 mg/day for females and 1.7 mg/day for males, with a UL of 25 mg/day for both. In the case of being pregnant or lactating (1.8 and 1.7 mg/day, respectively), requirement values are raised, while PRI and UL are decreased for children and infants [57].

Vitamin B6 is thought to regulate hyperinflammation by blocking the NLRP3 inflammasome, therefore decreasing viral spread and cytokine storm, at least in part. Its anti inflammasome action implies that it may have a therapeutic effect in reducing the severity of COVID-19 and its implications, which is in accordance with the notion that the NLRP3 inflammasome plays a key role in chronic diseases including CVD, diabetes, and acute viral pneumonia [58]. Altogether, it may be effective in preventing the severity of COVID-19 and its complications [59].

Vitamin B9

Vitamin B9 (folate) is a vital component of DNA synthesis, and its deficiency reduces the formation of proteins, nucleic acids, and immune cells. It plays a crucial role in the adaptive immune response by inhibiting furin, an enzyme involved in bacterial and viral infections that have been identified as a promising therapeutic target [60]. It disrupts SARS-CoV-2 binding and cell entry by blocking furin, which is an early phase in the virus's pathogenesis. Thus, vitamin B9 contributes to the management of COVID-19 in the early stages of the disease [60]. Moreover, Tregs must be differentiated from naive T cells, which necessitates the need for vitamin B9 [61]. The function of CD8⁺ T cells and NK cells are disrupted in individuals with vitamin B9 deficiency, resulting in significant unfavorable outcomes in prevailing a variety of infections [39].

Another potential benefit of supplementing vitamin B9 is its advantageous impact on minimizing oxidative damage following COVID-19 via increasing the activity of antioxidant enzymes. The SARS-CoV-2 infection causes one of the most striking alterations in intracellular metabolomics, resulting in depleted levels of intracellular glucose and folate, supporting the hypothesis that host glucose and folate metabolism were hijacked to fulfill the demand for viral subgenomic RNA replication [62]. Simultaneously, there is a significant drop in host mRNA abundance, which is presumed to have been destabilized by SARS-CoV-2's host "shut-off" activity to salvage host nucleotide supply for viral biosynthesis [62]. Furthermore, evidence highlighted that 5–10 mg per day orally (or 50–100 mcg intravenously of the active form 5-methyltetrahydrofolate may have a favorable impact on pulmonary perfusion or the treatment of pulmonary hypertension, both directly and indirectly, by improving the efficacy of inhaled nitric oxide (iNO) or avoiding tachyphylaxis to iNO, at least in some individuals, with minimal risk of adverse effects [63, 64]. Levomefolic acid has the capacity to inhibit SARS-CoV-2 Spike protein from binding to the human ACE2 receptor. As a result, this medication should be considered for further *in vitro* studies as an ACE2 and spike protein inhibitor candidate [65].

Vitamin B12

Vitamin B12 (cobalamin) contributes to the healthy balance of the immune system. So inadequate levels of this vitamin can significantly alter immune responses by affecting the production of nucleic acid, protein synthesis, inhibiting

the activity of immune cells, and interfering with metabolic processes, including methylation and serine, glycine, and purine cycles [66].

SARS-CoV-2 could interfere with vitamin B12 metabolism, culminating in vitamin B12 depletion, which may manifest as increased oxidative stress and lactate dehydrogenase, hyperhomocysteinemia, activation of the coagulation cascade, vasoconstriction, and renal and pulmonary vasculopathy [36]. Vitamin B12 deficiency can also cause respiratory, gastrointestinal, and neurological complications in COVID-19 patients [67, 68]. Oxidative stress and homocysteine levels rise in COVID-19 patients, along with an elevated lactate dehydrogenase (LDH) level, thrombocytopenia, low reticulocyte count, intravascular coagulation thrombosis, and renal and pulmonary vasculopathy, all of which occur in both B12 deficiency and COVID-19, resulting in respiratory, gastrointestinal, and central nervous system (CNS) impairments [34].

Low levels of B12 in critically ill patients lead to an increase in methylmalonic acid and homocysteine, which causes inflammation and intensifies disease severity, implying a link between vitamin B12 deficiency and the development of inflammation [69]. According to the fact that cobalamin acts as an antioxidant and an anti-inflammatory agent, it can protect against multiple organ dysfunction by modulating the activity of certain cytokines, growth factors, and other substrates. As a result, high-dose intravenous or intramuscular injections could be used as part of a novel strategy to treat COVID-19 patients with ARDS. To consider vitamin B12 as a pharmaconutrient, however, higher doses than those currently recommended for routine parental nutrition (PN) or enteral nutrition (EN) therapy will be required [70]. Furthermore, vitamin B12 role in enhancing cellular immunity through an interaction with CD8⁺ and NK cells suggests the efficacious role of vitamin B12 in COVID-19 prevention, prognosis, and treatment [71]. Since folate affects various conditions in which pulmonary hypertension occurs, it is hypothesized that it may have a specific benefit for patients with hypoxemia associated with severe pneumonia in which iNO therapy is conducted. In a study by Esko Wiltshire et al., it was hypothesized that daily oral administration of 5–10 mg folic acid or the equivalent intravenous dose of 50–100 mcg of the active form 5-methyltetrahydrofolate might rapidly improve hypoxemia due to pulmonary hypertension and prevent tachyphylaxis to iNO therapy [64].

Anemia is a common and persistent finding in COVID-19 patients during hospitalization, and vitamin B12 supplementation is appropriate. The British National Formulary currently recommends 1,000 µg of OH-B12 intramuscularly three times per week for two weeks, then once

every three months for pernicious anemia and other macrocytic anemias in the individuals without neurological dysfunction [72]. A clinical trial found that giving COVID-19 patients with 500 mg of vitamin B12 along with 1,000 IU vitamin D and magnesium reduces the severity of symptoms as well as the need for oxygen and intensive care support [73]. Overall, cobalamin has been shown to be efficacious in alleviating COVID-19 manifestations [74, 75].

Vitamin C

Vitamin C is widely acknowledged as a helpful therapeutic agent for respiratory infections owing to its antioxidative, anti-inflammatory, and immune-supportive properties [76]. Vitamin C is a water-soluble vitamin that reduces numerous free radicals and oxidants by one or two electrons. According to the research, vitamin C has antiviral properties; a study performed by Nina A. Mikirova et al. established that vitamin C can diminish Epstein-Barr virus (EBV) early antigen activity and viral load [77]. Furthermore, studies have shown that administering vitamin C in combination with antiviral medicines like ganciclovir and foscarnet for pretreatment of human foreskin fibroblast and endothelial cells infected with cytomegalovirus (CMV) leads to lower viral load and replication; meanwhile, the administration of antiviral drugs in the absence of vitamin C had no noticeable impact on viral replication. Also, vitamin C has been shown to suppress viral replication in individuals infected with herpes simplex virus-1 (HSV-1), influenza type A virus, poliovirus type 1, and rhinovirus [78]. Vitamin C is essential for immune defense as it regulates multiple cellular processes in both the innate and adaptive immune systems. It has been shown to contribute to the differentiation and maturation of T and NK cells, as well as their resistance to certain cell death stimuli, resulting in improved cellular immune responses and antibody production [79]. Also, it has been found to interact with pathogen-induced lipopolysaccharide (LPS), which is associated with the production of proinflammatory cytokines such as TNF- α and IFN- γ , while also increasing anti-inflammatory IL-10, which serves as an immunomodulatory agent [79]. Lymphocytes and neutrophils receive support from vitamin C's antioxidant protection. Neutrophils accumulate large amounts of vitamin C via the sodium-dependent vitamin C transporter 2 (SVCT2), and they may also accumulate vitamin C in the oxidized form, dehydroascorbate (DHA), via glucose transporters (GLUTs) [79]. It typically occurs after the oxidative burst is triggered; showing that vitamin C protects these cells from oxidative damage. Furthermore, investigations have

shown that vitamin C has the capacity to inhibit the formation of extracellular neutrophil traps, which are linked to death and multi organ damage in COVID-19 patients [80, 81]. It restricts monocytes via altering intracytoplasmic cytokine synthesis, resulting in decreased release of pro inflammatory cytokines such as IL-1, IL-2, IL-6, and TNF- α , as well as its propensity to inhibit nuclear factor-B (NF-B). This characteristic of vitamin C protects against cytokine-induced damage associated with a number of infectious diseases [79]. It also stimulates lymphocyte proliferation, which optimizes antibody response, in addition to its efficiency in reinforcing the oxidant-sensitive caspase-dependent apoptotic pathway that occurs following neutrophil immune responses against pathogens. It plays an early role in apoptosis and the clearance of neutrophils from inflammatory sites via macrophages, therefore protecting the body from severe tissue damage [82, 83]. It is supported by research on peritoneal isolated neutrophils from Gulo mice with vitamin C deficiency, which illustrates that apoptosis impairment of neutrophils ensued by vitamin C deficiency leads to long stability of these immune cells in sites of inflammation and the occurrence of necrotic cell death in neutrophils [80].

Even though the vitamin C levels of patients with COVID-19 have not ever been stated in the literature, it is speculated that the vitamin C status of patients with community-acquired pneumonia is evacuated and is linked to increased oxidative stress. However, it is not well understood whether vitamin C deficiency is a cause or a consequence of severe infection since requirements for vitamin C increase [84]. Previous research has shown that vitamin C status in individuals with respiratory infections, particularly those with severe vitamin C deficiency, has a striking association with the severity of outcomes [85].

Vitamin C supplementation has been proven effective for prophylaxis and treatment of the COVID-19 due to its various impacts on immune responses and other specific implications [86, 87] (Table 1). The infection raises oxidant levels and activates the nuclear factor kappa-B (NF- κ B) pathway. NF- κ B initiates a signaling cascade that culminates in an increase in reactive oxygen species (ROS) and other inflammatory mediators which ultimately leads to inflammation [38]. Previous SARS-CoV pandemic experience suggests that vitamin C plays an important role in prevailing free oxidative radicals and viral infections, proposing it as a generic therapy for severe viral respiratory infections [102]. Upon SARS-CoV-2 infection, the first line of innate immunity is displayed by neutrophil recruitment into infected tissues and the response against host-derived inflammatory signals (tissue damage signals) and pathogens. The migration of large numbers of neutrophils to the

infection site is ensued by the expression of more than 30 chemokines [8, 42, 103].

Several studies have been conducted to explore vitamin C's potent anti inflammatory properties. This vitamin has been demonstrated to suppress the NF- κ B pathway as well as hinder cytokine production in septic Gulo knockout mice [103]. Moreover, animal studies have shown that leukocytes derived from vitamin C-treated pigs as compared to a control group, full chemotactic functions enhanced neutrophil phagocytosis, which corresponds to infection cure [104]. In this way, Johnston et al. discovered that vitamin C had an antihistamine impact with increased chemotaxis, which is another attribute in the battle against inflammation [105]. Vitamin C has been shown to reduce IFN γ , proinflammatory cytokines TNF- α and IL-6 production, while enhancing anti inflammatory IL-10 production which are crucial in battling against COVID-19. As a result of its anti inflammatory characteristics, vitamin C may have a role to play in reducing the pathogenesis induced by SARS-CoV-2 infection, hence enhancing the patient's recovery [106, 107]. Indeed, in a preliminary pilot study of COVID-19 patients requiring intensive care, high-dose intravenous vitamin C significantly improved oxygenation, diminished organ-damaging cytokine storm (IL-6), and showed a tendency toward lower mortality in critically ill patients [108, 109]. Another pilot study discovered inadequate vitamin C and vitamin D serum levels in the majority of critically ill COVID-19 patients. Older age and a deficit in vitamin C were revealed to be codependent risk factors for mortality [110].

Clinical trials have shown that administering high-dose intravenous vitamin C (24 g/day) for seven days to individuals with severe COVID-19 leads to considerable positive outcomes [111]. Additionally, clinical trials on severely ill COVID-19 patients show that extra bolus doses of vitamin C result in a promising outcome. Even a 50,000 mg vitamin C infusion over 4 h in severely ill patients led to major remission with no complaints of adverse side effects [98].

Though the pilot trial found that adding high-dose (24 g per day for seven days) intravenous vitamin C to the standard-of-care treatment for severe COVID-19 seemed not to affect ventilation-free days, it might indicate a possible benefit in oxygenation and IL-6 release [100]. High levels of IL-6 were found in COVID-19 patients, indicating that it might be used as a biomarker for disease severity. COVID-19 induces a wide range of biological consequences, including pulmonary infiltration and organ damage [112]. Furthermore, a recent meta-analysis based on data from eight vitamin C trials involving a total of 685 patients found that vitamin C shortened the time spent on mechanical ventilation in critically ill patients [113]. Zhang

Table 1: The table summarizes recent clinical trials concerning the administration of various micronutrients to COVID-19 patients of various clinical classifications.

Study	Design	Sample size	Clinical classification	Intervention	Comparator	Outcomes
Abulmeaty et al. [3]	Placebo-controlled, double-blind randomized trial	Intervention: 18 Comparator: 16	Non-critical COVID-19 patients	1,500 ug vitamin A, 250 mg vitamin C, 90 mg vitamin E, 15 µg selenium, and 7.5 mg zinc	Placebo	The lower cytokine storm and improved clinical parameters in the intervention group compared to the comparator group
Alcala-Diaz et al. [88]	Retrospective, observational, cohort study	Intervention: 79 Comparator: 458	Not reported	0.532 mg oral calcifediol and 0.266 mg on days 3 and 7 then weekly until discharge or ICU admission	No adjunctive intervention	The lower mortality rate in the intervention group (5%) compared to the comparator group (20%)
Annweiler et al. [89]	Quasi experimental	Intervention: 57 Comparator: 9	Not reported	80,000 IU oral cholecalciferol either within a week following the suspicion, diagnosis or during the prior month	No adjunctive intervention	The lower mortality rate in the intervention group (17.5%) compared to the comparator group (55.6%)
Annweiler et al. [90]	Quasi experimental	Intervention: 16 Comparator: 32	Not reported	80,000 IU oral cholecalciferol within a few hours of diagnosis	No adjunctive intervention	The lower 14-day mortality rate in the intervention group (18.8%) compared to the comparator group (31.3%)
Castillo et al. [86]	Open-label, randomized, and controlled trial	Intervention: 50 Comparator: 26	Not reported	0.532 mg oral calcifediol and 0.266 mg on days 3 and 7 then weekly until discharge or ICU admission	No adjunctive intervention	The lower need for ICU admission the intervention group (2%) compared to the comparator group (50%)
Gao et al. [91]	Retrospective, observational, and cohort study	Intervention: 46 Comparator: 30	Moderate to critically ill COVID-19 patients	6 g intravenous vitamin C per 12 h on the first day, and 6 g once for the following four days	Standard care	The lower mortality in the intervention group (2.2%) compared to the comparator group (16.7%)
Giannini et al. [92]	Retrospective, observational, and cohort study	Intervention: 36 Comparator: 55	Comorbid COVID-19 patients	400,000 IU oral cholecalciferol (200,000 IU administered in two consecutive days)	No adjunctive intervention	The lower need for ICU support or mortality rate in the intervention group (38.9%) compared to the comparator group (52.7%)
Hakamifard et al. [93]	Open-label, randomized, and controlled trial	Intervention: 38 Comparator: 34	Not reported	1,000 mg daily oral vitamin C and 400 IU daily vitamin E	No adjunctive intervention	The outcomes didn't differ in the intervention group compared to the comparator group
Hiedra et al. [94]	Retrospective, observational, Case series study	Intervention: 17	Moderate to severe COVID-19 patients	1 g intravenous vitamin C every 8 h for three days	Not applicable	The significant decrease in inflammatory markers and lower FiO2 requirements in the intervention group
Lakkireddy et al. [95]	Open-label, randomized, and controlled trial	Intervention: 65 Comparator: 65	Mild to moderate COVID-19 patients with hypovitaminosis D	60,000 IU vitamin D per day for eight days for subjects with $18 \leq \text{BMI} \leq 25$ and 10 days for subjects with $\text{BMI} > 25$	No adjunctive intervention	Improvement in vitamin D level to 80–100 ng/mL significantly mitigated inflammatory markers associated with COVID-19 with no adverse effects.

Table 1: (continued)

Study	Design	Sample size	Clinical classification	Intervention	Comparator	Outcomes
Murai et al. [96]	Placebo-controlled, double-blind randomized trial	Intervention: 120 Comparator: 120	Moderate to severe COVID-19 patients	Single dose of 200,000 IU oral cholecalciferol	Placebo	The hospitalization length, ICU support, need for a mechanical ventilator, and mortality didn't differ significantly in the intervention group compared to the comparator group
Oliveira et al. [41]	Retrospective, observational, Case series study	Intervention: 15	COVID-19 patients with encephalopathy	500 mg intravenous thiamine three times a day for five days	Not applicable	Improved neurological outcomes in the intervention group (73%)
Rastogi et al. [6]	Placebo-controlled, randomized trial	Intervention: 16 Comparator: 24	Asymptomatic or mildly symptomatic COVID-19 patients with hypovitaminosis D	60,000 IU oral cholecalciferol for seven days with therapeutic target of 25(OH) D>50 ng/mL	Placebo	There was a significant decrease in fibrinogen level in the intervention group compared to the comparator group
Sabico et al. [97]	Open-label, randomized, and controlled trial	Intervention: 36 Comparator: 33	Mild to moderate COVID-19 patients with sub-optimal vitamin D level	5,000 IU oral vitamin D ₃ daily for two weeks	1,000 IU oral vitamin D ₃ daily for two weeks	Reduced recovery time in the intervention group (six days) compared to the comparator group (seven days)
Siahkali et al. [98]	Open-label, randomized, and controlled trial	Intervention: 30 Comparator: 30	Severe COVID-19 patients	6 g daily high-dose intravenous vitamin C	No adjunctive intervention	The outcomes didn't differ in the intervention group compared to the comparator group.
Sulaiman et al. [43]	Retrospective, observational, and cohort study	Intervention: 88 Comparator: 650	Critically ill COVID-19 patients	The median 100 mg (50–200 mg) thiamine for a median duration of seven days (5–12 days)	No adjunctive intervention	The lower in-hospital mortality rate in the intervention group (18.4%) compared to the comparator group (38.7%) and lower incidence of thrombosis during ICU stay in the intervention group (2.4%) compared to the comparator group (11.1%)
Tan et al. [73]	Retrospective, observational, and cohort study	Intervention: 17 Comparator: 26	Not reported	Combination of 1,000 IU oral vitamin D ₃ , 150 mg oral magnesium, and 500 mcg oral vitamin B12 daily upon admission	No adjunctive intervention	The lower need for ICU support in the intervention group (5.9%) compared to the comparator group (30.8%) and lower need for oxygen therapy in the intervention group (17.6%) compared to the comparator group (61.5%)
Thomas et al. [99]	Open-label, randomized, and controlled trial	Intervention: 164 Comparator: 50	Ambulatory COVID-19 patients	Either 50 mg zinc gluconate, 8,000 mg ascorbic acid, or their combination for 10 days	Standard care	The duration of symptoms didn't differ in the intervention group compared to the comparator group

Table 1: (continued)

Study	Design	Sample size	Clinical classification	Intervention	Comparator	Outcomes
Zhang et al. [100]	Placebo-controlled, double-blind randomized trial	Intervention: 27 Comparator: 29	Critically ill COVID-19 patients	12 g intravenous vitamin C/50 mL every 12 h for seven days at a rate of 12 mL/h	Placebo	The invasive mechanical ventilation-free days in 28 days in the intervention group didn't differ compared to the comparator group, but the oxygenation (PaO ₂ /FiO ₂) was improved, and the IL-6 level was reduced in the intervention group.
Zhao et al. [101]	Retrospective before-after case-matched study	Intervention: 55 Comparator: 55	Moderate COVID-19 patients	100 mg/kg daily intravenous vitamin C for seven days at a rate of 1 g/h since admission	No adjunctive intervention	The lower incidence and duration of SIRS in the intervention group (9.5%-2days) compared to the comparator group (45.4%-6days) on day 7. The intervention group had lower CRP levels, improved coagulation factors, and more CD4 ⁺ T cells compared to the comparator group.

et al. administered 24 g per day in the form of 12 g of vitamin C/50 mL every 12 h for seven days at a rate of 12 mL/h, which was consistent with these findings. Although they did not find noteworthy results in terms of extending invasive mechanical ventilation-free days in 28 days, they did uncover better PaO₂/FiO₂ and, as a consequence, improved oxygenation for critically ill patients [100].

Aside from a poor diet, several factors are associated with depleted vitamin C levels, which enhance susceptibility to COVID-19 owing to insufficient micronutrient levels for appropriate immunological and organ function. These factors consist of gender, comorbidities, and obesity. According to the research, vitamin C serum/plasma concentrations are greater in women than in men (24–26), and males have considerably higher rates of deficiency, which is adversely related to C serum level the lower serum level of vitamin C might be other reason for worse outcome in males than females with COVID-19 [57]. Furthermore, there is a well-documented negative connection between serum C level and obesity. Considering these criteria while administering adequate doses of the vitamin may contribute to improved outcomes for patients [114].

Vitamin D

The significance of vitamin D in cases of respiratory infection is demonstrated by the fact that low vitamin D levels are

widespread throughout the world population and have been linked to an increased risk of pneumonia [115]. Evidence suggests that low serum vitamin D levels are associated with an increased risk of high burdens of viral infections [116]. Regarding vitamin D's immune-modulatory effects, the efficacy of its supplementation in patients with infectious disease, particularly vitamin D-deficient individuals, cannot be overlooked [115]. Several studies have been conducted (Table 1) to validate vitamin D's prophylactic and therapeutic relevance in COVID-19 patients. According to Luo et al., serum 25(OH)D concentrations are substantially lower in severe COVID-19 patients than in nonsevere patients. It was observed that vitamin D deficiency was associated with COVID-19 severity, after adjusting for several potential confounders, such as age, sex, comorbidities, body mass index (BMI), and smoking status. Interestingly, it was shown in the same study that 25(OH)D concentrations in the death group were lower than those in the discharged group (18.7 vs. 23.2 nmol/L) [117]. Regarding a recent clinic-based cohort study of 185 COVID-19 patients, regardless of age, gender, and comorbidities, the risk of invasive mechanical ventilation or death (primary endpoint) among patients with adequate vitamin D levels was nearly 80% lower. Likewise, over 90% of mortality in this group was statistically linked to vitamin D deficiency [118]. Several studies on the impact of vitamin D deficiency on COVID-19 incidence and poor outcomes found an inverse relationship between vitamin D

levels and susceptibility to COVID-19 and its severe implications. As a result, individuals with vitamin D deficiency are considered a high-risk category for disease incidence and must be supplemented with vitamin D to meet current requirements, given that current standards have been defined addressing the requirements of bone [119]. Given the complex correlation between vitamin D and viral infections rather than immune function, elucidating how vitamin D imposes its impacts on COVID-19 patients is crucial; it is suggested that vitamin D supplementation in the COVID-19 pandemic, even in vitamin D-replete individuals, is worth consideration [120]. Taken together, evidence supports the notion that there is a strong relationship between low vitamin D and COVID-19 severity. Since vitamin D is important for immune system regulation and antiviral activities [121]. Cell junctions are the body's initial line of defense against infections, and they can be disrupted by several viruses, namely SARS-CoV-2 [122]. Vitamin D and its receptor can preserve tissue barrier integrity since there is a connection between vitamin D/vitamin D receptors (VDR) signaling and tissue barrier integrity. VDRs are expressed in nearly all tissues, including endothelial cells, vascular smooth muscles, and cardiomyocytes [123]. The ligand-bound VDR is a transcriptional factor that binds to the promoter region of target genes and modulates the expression of the specific genes, which has been found to be associated with persuading NO synthesis through endothelial nitric acid synthase (eNOS) bioactivity. It is essential in mediating angiogenesis by enhancing endothelial cell migration [124]. Moreover, it can maintain the formation of capillary-like structures in human umbilical endothelial cells (HUVEC) and the human coronary artery [125]. It has been reported in the literature that it can persuade cell migration and proliferation by upregulating gene expression of matrix metalloproteinase 2 (MMP-2) and an extracellular matrix dissolving factor. The rigidity of tight junctions, particularly in the pulmonary tissue, has been shown to be an effective preventative factor against immune cell infiltration, which contributes to the development of severe pneumonia and ARDS in COVID-19 patients [124] (Figure 1).

It is well understood that virus clearance by the host at the onset of infection is critical; otherwise, the virus will infiltrate tissues with high ACE2 receptor expression, such as the lungs and kidneys, causing inflammation mediated by the innate immune system, specifically through the release of pro-inflammatory cytokines by macrophages and Th1 cells [126]. As angiotensin (Ang) II levels in individuals with adequate 25(OH)D levels (30 ng/mL), insufficiency (15–29.9 ng/mL), and the deficiency (15 ng/mL) were compared, it was suggested that vitamin D sufficient individuals had greater circulating Ang II levels. Conversely, individuals with vitamin D deficiency exhibited significantly slower renal plasma flow responses to Ang II infusion

[127]. In this way, its interaction with ACE2 in COVID-19 patients is an issue worth considering. Inadequate vitamin D levels may activate the RAS, which can lead to chronic cardiovascular disease and reduced lung function by triggering lung fibrosis [127]. SARS-CoV-2 activates A disintegrin and metalloproteinase 17 (ADAM17), which suppresses not only ACE2 expression but also the ACE2/Ang 1–7/Mas axis, enabling the virus to enter the cell more readily. This leads to an increase in Ang II, which in turn upregulates ADAM17. This leads to the rise in Ang II, which upregulates ADAM17. Lung damage, myocardial injury (heart failure), and vascular damage (fatal thrombosis) are all possible outcomes of this procedure. Active vitamin D can interfere with ACE2-angiotensin 1-7-ADAM17, which promotes ACE2 synthesis meanwhile restricting Ang II synthesis [128, 129]. Vitamin D's renoprotective function is largely attributed to its inhibition of ACE2 expression in the kidney, according to studies on patients with kidney disease [130, 131]. 1,25(OH)₂D can alleviate LPS-induced acute lung injury; therefore, through this mechanism, vitamin D supplementation can be accompanied by patients' survival [132]. The evidence shows that vitamin D analog calcitriol enhances ACE2 expression in the lungs, which can facilitate viral binding to the pulmonary epithelium. According to research, 1,25(OH)₂D₃ can decrease renin gene expression by binding to the transcription factor cyclic adenosine monophosphate (cAMP) response element-binding (CREB) protein, leading to reduced cAMP response element activity in the renin gene promoter [133]. It may be followed by a decrease in Ang II production, resulting in less pulmonary vasoconstriction [133]. Although vitamin D increases the expression of ACE2, it limits the pulmonary vasoconstriction response in COVID-19 patients, which is a paradoxical impact of vitamin D [131]. As in COVID-19 patients ACE2 is disturbed during infection and Ang II is supposed to be converted by ACE2, it starts to accumulate leading to severe outcomes of disease related to over-activated pro-inflammatory responses including ARDS, myocarditis, or cardiac injury [131]. So, in COVID-19 patients, vitamin D supplementation reduces pro-inflammatory cytokine production by hindering renin release [131]. However, since both vitamin D and ACE2 are considered to be negative RAS mediators, evidence suggests that ACE2 may have distinct effects on COVID-19 patients at the same time. ACE2 expression is linked with the development of severe COVID-19, even though it regulates the RAS. These findings raise the challenge of whether antiviral medications that impact ACE2 are effective for these patients or if they might aggravate their condition. The optimal time and dosage of vitamin D for therapeutic approaches are prominent once evaluating SARS-CoV-2 infection as three stages [134, 135].

Figure 1: Vitamin D has a twofold effect on the immune system and inflammation.

Vitamin D appears to boost the immune responses in the battle between host and virus by regulating some key elements in infected cells such as ER stress. This vitamin regulates immune responses by suppressing proinflammatory environment and increasing secretion of anti inflammatory cytokines. It additionally suppresses T cell proliferation which results in a shift from a Th1 to a Th2 phenotype, meanwhile it provokes macrophage differentiation, inhibit DCs maturation, and promotes immuno-regulatory functions of Tregs. Vitamin D has antifibrotic effect and can increase vasodilation via increasing ACE2 expression, and decreasing ACE1 expression. Furthermore, 1,25(OH)₂D₃ is known to suppress the NF-κB pathway, resulting in the prevention of oxidative stress, which ultimately inhibits formation of blood clots and endothelial dysfunction. ER, Endoplasmic reticulum; ACE, angiotensin-converting enzyme; VDR-RXR, Vitamin D receptor/retinoic acid X receptor; NF-κB, Nuclear factor kappa-B; Ang-2, Angiotensin-2; IL, Interleukin; AT1R, Angiotensin receptor type 1; DC, Dendritic cell; Th, T helper; IFN γ , Interferon gamma; eNOS, Endothelial nitric acid synthase; JNK, C-jun kinase; TNF-R, Tumor necrosis factor-receptor; NET, Neutrophil extracellular trap.

Serum 25(OH)D levels are positively correlated with serum C-reactive protein (CRP) levels whereas neutrophil and lymphocyte counts are negatively correlated. Therefore, increased inflammation underlies the fact that low serum vitamin D levels increase the severity of the disease and mortality. Vitamin D, like tocilizumab, appears to regulate the activity of an IL-6, lowering the acute-phase response linked to increased lung injury and complications such as ARDS or sepsis [136].

Since VDRs are expressed on B cells, T cells, and antigen-presenting cells (APCs) of the immune system,

these cells produce the active vitamin D metabolite, which has a remarkable connection with autocrine activities of the local immunologic milieu [16]. Studies demonstrate that 1,25(OH)₂VD₃ inhibits over-activated immune responses through a variety of mechanisms, which are mainly mediated via the memory T cell compartment due to the greater expression of VDR on these cells compared to naive T cells [9]. The attachment of the vitamin D receptor/retinoic acid X receptor (VDR-RXR) complex to the VDR in the promoter of genes encoding IL-2 and IFN γ by 1,25(OH)₂VD₃ inhibits the production of IL-2 and IFN γ [137].

Vitamin D controls immune responses and the COVID-19-induced cytokine storm, which is linked to various clinical multi organ complications of COVID-19, by modulating T cell proliferation via T cell VDR. $1,25(\text{OH})_2\text{VD}_3$ suppresses T cell proliferation by reducing IL-2 production, which plays an important role in cell proliferation [138]. T cell proliferation inhibition causes a shift from a Th1 to a Th2 phenotype, in which decreased Th1 immune responses and increased Th2 immune responses stimulate anti-inflammatory responses and avoid their deleterious effects by inhibiting them [16]. Since Th1 produces proinflammatory cytokines while Th2 produces anti-inflammatory cytokines, vitamin D inhibits Th1 proliferation besides promoting Th2 and Treg production, resulting in reduced and regulated proinflammatory responses, primarily by reducing IL-6 and increasing production of anti inflammatory cytokines such as IL-10. It is a major target for cytokine storm management, particularly in COVID-19 [16, 139]. $1,25(\text{OH})_2\text{VD}_3$ inhibits the production of inflammatory cytokines including IL-1, IL-6, IL-8, IL-12, and TNF α by suppressing monocytes and it affects dendritic cell (DC) differentiation and maturation by reducing the major histocompatibility complex (MHC) MHC class II molecules, costimulatory molecules, and IL-12 [9]. As a result, improved vitamin D status in COVID-19 patients is directly connected to COVID-19-induced manifestations, particularly in severely infected individuals [140]. $1,25(\text{OH})_2\text{VD}_3$, on the other hand, has the ability to suppress T cell function by increasing nonspecific T cell suppressor activity, resulting in decreased lymphocyte reactivity and cytotoxic T cell responses [9, 141]. Furthermore, $1,25(\text{OH})_2\text{VD}_3$ suppresses B cell proliferation while disrupting differentiation and function, resulting in Ig suppression and modulation [16]. In addition, $1,25(\text{OH})_2\text{VD}_3$ contributes to inhibit and modulate the immune responses of DCs and monocytes [9]. As a result, $1,25(\text{OH})_2\text{VD}_3$ and its analogs have been demonstrated to be effective in the treatment of inflammatory and autoimmune diseases [142, 143]

Moreover, it is well known that ROS are formed in a variety of inflammatory diseases, and that increased ROS release causes damage to various organs and tissues, which may be mitigated owing to vitamin D's anti oxidant properties [144]. According to the evidence, paricalcitol serves as a ligand for VDR and is analogous to vitamin D. It protects the kidneys in spontaneously hypertensive rats by limiting NOX activity and avoiding mitochondrial injury (pro oxidative enzyme). In renal cortex cells from these animals, these alterations were mediated by an increase in intracellular levels of heat shock protein 70 and a decrease in Ang II type 1 receptors [144].

In acute viral respiratory infections, vitamin D acts as an immunomodulatory component of the innate immune

system by upregulating cytochrome P450 family 27 sub-family B member 1 (CYP27B1) in respiratory epithelial cells altering gene expression in innate immune cells such as macrophages, monocytes, and DCs, which contain all the necessary characteristics such as CYP27B1 enzyme and VDR resulting in the formation of $1,25(\text{OH})_2\text{D}_3$ from an inactive form of locally stored vitamin D and subsequent regulated immune responses to limit further damage caused by over-activated immune responses while retaining antiviral activities against pathogens [145]. According to a study by Zhang and colleagues, vitamin D can protect against endothelial dysfunction (ED) by reducing oxidative stress and NF- κ B activation [146]. It has been demonstrated in research by Liu et al. that vitamin D effectiveness in *Mycobacterium tuberculosis* is mediated by both VDR and CYP27B1 of activated macrophages, leading to the synthesis of antimicrobial peptides (AMPs), including molecules known as cathelicidins and defensins [147]. These are antimicrobial peptides that have been linked to the direct pathogen killing or endotoxin binding via activating ion channels and permeable membranes [148]. Cathelicidin has also been shown to be generated in lung injuries by respiratory epithelial cells expressing CYP27B1 converting the inactive form of vitamin D to the active form [145]. Despite the lack of data on the effects of vitamin D on NK cells in COVID-19 patients, it has been illustrated that low levels of vitamin D in serum correlate with reduced NK activity in patients with chronic disease. It posits a link between vitamin D and enhanced cytotoxicity and exocytosis of NK cells [145, 149].

Additionally, in diseases with neurological complications as COVID-19, vitamin D potency in neuroprotective functions is considerable. Vitamin D interacts with neurotrophin, which is linked to ischemic brain injuries and neurodegenerative diseases, to alter nerve cell differentiation and preservation in the peripheral nervous system (PNS) and CNS [150, 151].

Clinicians might consider vitamin D administration because of its effective prophylactic and restorative action against COVID-19 [145, 152]. According to COVID-19 medical data, these patients' nutrition levels have been alleviated to some extent. Vitamin D deficiency is the most frequent, with 76% of patients having a deficit (≤ 20 ng/dL) and 24% having a severe deficiency (≤ 10 ng/dL) [120, 153]. Regarding the other nutrients, it is yet unknown if individual nutrient deficiencies influence immunity or whether nutrient deficiency worsens a patient's overall condition; hence, vitamin D deficiency is regarded as both a possible risk factor and underlying condition in COVID-19 patients [154, 155]. Some randomized trials are evaluating the role of vitamin D in COVID-19 infections and severities that have

yet to be disclosed. In a study by Karahan Adata et al., the relationship between vitamin D deficiency and the prognosis of COVID-19 has been suggested [156]. In hospitalized moderate-to-severely ill COVID-19 patients, vitamin D deficiency/insufficiency was particularly abundant. The mean level of 25(OH)D was 15.2 ± 10.3 ng/mL. As COVID-19 severity increased, the level of 25(OH)D was further reduced [157]. It is demonstrated that there is a negative correlation between serum 25(OH) vitamin D level and age ($r = -0.3$, $p < 0.001$). Thus, it can be speculated that disproportionately severe clinical outcomes seen in the elderly may be partly due to age-related vitamin D deficiency [157].

There is a lot of debate over what is deemed “normal” or “optimal” serum 25(OH)D levels. However, many scientists and doctors prefer to adopt the lower bound of acceptable vitamin D status of 30 ng/mL (75 nmol/L), as proposed by the Endocrine Society, and some have also advised, in light of the COVID-19 pandemic, to reach and maintain 30 ng/mL levels at least in the elderly or in Citizens of nations with a high incidence of vitamin D insufficiency, notably COVID-19 patients at high risk of intensive care unit hospitalization. Others, on the other hand, recommended a range of 40–60 ng/mL as an optimal range for human health, claiming that such levels might lower the risk of certain infections (influenza, various coronavirus infections, etc.) as well as cancer, diabetes, rheumatic diseases, and pregnancy complications [158].

Vitamin D levels greater than 30 ng/mL have been attributed to a substantial reduction in SARS-CoV-2 infection severity and mortality [157]. As shown in a prior meta-analysis, in comparison to individuals with serum 25(OH)D concentrations >25 nmol/L, the protective impact of vitamin D was higher in subjects with baseline serum 25(OH)D levels 25 nmol/L [159]. Vitamin D supplementation of 20–50 µg/day (800–1,000 IU) had formerly been regarded to be safe. Adults who take up to 100 µg of vitamin D per day (4,000 IU) have been revealed to have no adverse effects [120]. Some researchers have discovered that taking a vitamin D supplement at a dosage of 100–250 µg/day (4,000–10,000) for six weeks raises the baseline serum concentration of 25(OH)D by two–three folds, with no side effects. According to the research, taking up to 250 µg/day for a month can raise serum 25(OH)D levels to the optimal range of 75–125 nmol/L. After a month, the dosage can be lowered to 100 µg/day to maintain circulating 25(OH)D concentrations [160]. According to the findings of a study, a single dosage of 600,000 IU vitamin D can raise D3 serum to 25(OH)D to >30 ng/mL in elderly individuals for at least four weeks without triggering any side effects [161]. However, a systematic review found that supplementing with a high dose of vitamin D, about 100,000 IU, failed to raise

25(OH)D levels over 30 ng/mL. Ashu Rastogi’s study recommended a daily cholecalciferol dosage of 60,000 IU (420,000 IU for the first week) [6]. It’s greater than current standards, but it’s been shown to be safe, with no indications of hypercalcemia. This study endorses the safety of taking large dosages of vitamin D for a short period. The literature review shows that vitamin D supplementation appears to lower the risk of SARS-CoV-2 infection and may result in early viral clearance [153]. Furthermore, research shows that supplementing with 300,000 IU vitamin D for COVID-19 patients who are not in the ICU can reduce symptoms; nevertheless, the majority of studies imply that vitamin D supplementation does not affect the length of hospitalization [6, 162, 163].

In terms of vitamin D’s initial role in regulating inflammation, it increases the asymptomatic carriage state while decreasing symptomatic implications in these patients [119]. Vitamin D may be an effective therapy for anticoagulant individuals who are experiencing bleeding issues. Hejazi et al. demonstrated that vitamin D supplementation allowed for a reduced warfarin dosage regimen and was linked with fewer adverse reactions in those with thromboembolism [164]. Vitamin D or its analogs have been shown in previous researches to reduce the expression of tissue factors such as prothrombotic plasminogen activator inhibitor1 and thrombospondin1, while increasing the expression of thrombomodulin. Thus, it appears that a sufficient dose of vitamin D may help to minimize the risk of thrombosis. Even though larger studies haven’t ever identified significant variations in COVID-19 patients’ coagulopathy between vitamin D treatment and the control group, further research is required to determine a definitive link between vitamin D supplementation and COVID-19-induced coagulopathies [165].

Notably, Lemke et al. claimed that irregular coagulation in individuals with severe COVID-19 is “consumptive.” The authors further proposed that, in addition to depleting key coagulation factors, clinical manifestations of improper clotting in many serious COVID-19 patients consume a vital anticoagulant, protein S [166]. Protein S levels were found to be low in a cohort study performed at Colentina University Hospital in Romania. As a result, any increase in vitamin D’s anticoagulant activity will be advantageous to those individuals [167].

It is proposed to conduct magnesium supplementation coupled with vitamin D supplements. Magnesium facilitates vitamin D-related processes. All the enzymes that metabolize vitamin D seem to require magnesium, which is an essential cofactor for vitamin D synthesis and leads to increased intestinal absorption of vitamin D. The proper dose of magnesium for maintaining hemostasis like the stability of cell function, RNA and DNA synthesis, and cell

repair, as well as maintaining the cell's antioxidant status, should be in the range of 250–500 mg/day [168, 169]. Even though in this large-scale MR study, no evidence was found to support increasing 25(OH)D levels.

Vitamin E

Vitamin E is a dietary lipophilic antioxidant that preserves polyunsaturated fatty acids (PUFAs) in the membrane from oxidation while also regulating the production of ROS, reactive nitrogen species (RNS), and signal transduction [170]. Vitamin E (alpha-tocopherol) has been demonstrated to be an effective antiferroptosis agent that compensates for a lack of various antioxidants, namely glutathione peroxidase 4, through inhibiting 15-lipoxygenase owing to its antioxidant characteristic. It inhibits 15-lipoxygenase by reduction of the non-heme iron of the enzyme from its active Fe^{3+} form to the Fe^{2+} form [171, 172]. Ferroptosis is a kind of programmed cell death that is linked to inflammation, neurodegeneration, or, more generally, multi organ failure. Ferroptosis has been attributed to multi-organ damage in COVID-19 patients, indicating that vitamin E supplementation in these patients might provide positive benefits. As a result, supplementation with a high dose of 500 mg/kg vitamin E might serve a protective role against multi organ complications in these patients [173]. Likewise, vitamin E depletion has been found to trigger lipid peroxidation, which has been substantiated an inverse correlation between vitamin E and plasma lipoperoxidase levels [174]. Its deficiency also has been suggested to contribute to gene mutations that enhance virulence in various viruses, including influenza and SARS-CoV-2 [175].

Vitamin E is an immunomodulator agent that has been widely known to be involved in various aspects of the immune system which exert its effects via multiple pathways that have been found to be well-associated with the immune response to different pathogens including SARS-CoV-2. It downregulates prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) through attenuating nitrogen oxides formation to modulate inflammatory responses. It also regulates Th1/Th2 ratio while also initiating naive T-lymphocyte synapse formation and activation signals [176, 177]. Furthermore, vitamin E boosts humoral immune responses. According to Broome et al., individuals over the age of 65 who were administered 60 or 200 mg daily vitamin E had a higher humoral immune response to poliovirus and fewer mutant viral strains as compared to those in the placebo group [178, 179]. It underpins the debate about whether vitamin

E supplementation can improve the efficacy of the COVID-19 vaccination.

Vitamin K

Although little is known regarding the possible benefits of taking vitamin K to improve COVID-19 outcomes, it is widely known that individuals with severe COVID-19 experience prominent symptoms of coagulopathy and thrombosis [180]. Elastic fibers are key components of the extracellular matrix of the lungs, where matrix Gla protein (MGP) is abundantly expressed [181]. As a result, MGP appears to have a similar role in the pulmonary compartment as it does in the vasculature, and it is critical for the preservation of elastic fibers against calcification. Complications with MGP activation may be linked to the degradation of elastic fibers. Mineralization occurs more frequently in elastic fibers that have been partially degraded. Additionally, the release of matrix metalloproteinases (MMPs) may accelerate the calcification of elastic fibers, leading to lung fibrosis [182].

COVID-19 patients demonstrated a substantial increase in extrahepatic inactive MGP, indicating a menaquinone-7 (MK-7) deficit. Furthermore, a subset of pulmonary macrophages that synthesize MMPs seems to be augmented during severe SARS-CoV-2 pneumonia, leading to elastic fiber degradation [181, 183]. Accelerated elastic fiber breakdown and insufficient active MGP in COVID-19 patients indicate a correlation between MK-7 deficiency and COVID-19. As a result, COVID-19 may hypothetically be related to MK-7 deficiency [181]. In line with these findings, it is reported that plasma dephosphorylated-uncarboxylated matrix Gla-protein (dp-ucMGP) has a significant cross-sectional correlation with kidney function, with circulating dp-ucMGP rising with decreasing renal function, which is a complication of 32–46% of COVID-19 patients [184].

It is hypothesized that the vitamin K deficiency during the early stages of COVID-19 infection may contribute to the activation of the Th2 storm, resulting in higher output in the presence of CRP and IL-6 vitamin K deficiency is frequently observed in COVID-19 patients and that the deficit is greater in males than in females [185]. Furthermore, in male patients, vitamin K deficiency is coupled with a greater IL-6 level in the general circulation [186]. It is also speculated that vitamin K deficiency has a contribution to other COVID-19-specific clinical manifestations. Although dp-ucMGP is raised in COVID-19, hepatic procoagulant and vitamin K status, assessed by protein induced by vitamin K absence-II (PIVKA-II) did not differ [182]. Endothelial cells are responsible for approximately 50% of protein S synthesis. The preferential activation of

hepatic proteins over extrahepatic proteins suggests that the uncarboxylated protein S fraction will rise, increasing the risk of thrombosis [182].

Concerning vitamin K deficit in COVID-19 patients, caution is advised while using vitamin D in a state of vitamin K deficiency, because vitamin D intake in these instances may jeopardize pulmonary and vascular health. Several studies have raised concerns that vitamin D administration is linked to premature death among vitamin K-deficient stable kidney transplant recipients [187]. It may thus be appropriate to initially supply vitamin K is always vitamin K-deficient COVID-19 hospitalized patients and to begin vitamin D administration only after extrahepatic vitamin K status has been restored in those who are vitamin D-deficient coagulation is a common complication of COVID-19 which is ensued by the direct function of endothelial cells [181]. Indeed, they secrete coagulation inhibitors such as protein S and serve as receptors for anticoagulant proteins found in the blood that interfere with clot formation (like protein C). Thus, the imbalance of the coagulation system by lysing endothelial cells following infection might make a significant contribution to thrombosis [188].

Vitamin K antagonists (VKAs), such as warfarin, are still extensively employed as anticoagulant medications [189] (Figure 2). VKAs disrupt the vitamin K cycle by blocking vitamin K 2,3-epoxide reductase, resulting in vitamin K deficiency. As mentioned earlier, vitamin K has anticoagulant properties via activating proteins C, S, and Z. Contrary to proteins C and Z, which are mostly synthesized in the liver, half of protein S is produced in endothelial cells and so plays a vital role in the prevention of local thrombosis [190]. Interestingly, vitamin K1 administration had no influence on VKA anticoagulant efficacy; nevertheless, high doses of vitamin K2 (MK-7, MK-8, MK-9, and larger isoforms) indicated that patients receiving VKA should avoid eating foods or taking supplements containing large amounts of K2 analogs. Furthermore, vitamin K has the ability to suppress the development of arterial calcification via triggering MGP. In pulmonary disease, low vitamin K levels have been attributed to greater elastin degradation. Vitamin K-dependent MGP hinders the mineralization of elastic fibers, which are important components of the extracellular matrix (ECM) and play a role in lung fibrosis [191].

Vitamin K is an immunomodulatory agent that inhibits the production of pro-inflammatory cytokines such as IFN-,

Figure 2: Warfarin-vitamin K2 interaction in the prevention of SARS-CoV-2-induced immune thrombosis.

Blood clotting complications are frequent in COVID-19, and proinflammatory cytokines and NETosis following SARS-CoV-2 infection play an important role in clot formation. Vitamin K2 contributes to the production of many proteins, most particularly prothrombin, which is a vitamin K2-dependent protein that is directly involved in blood clotting. Warfarin inhibits the function of vitamin K2, which tends to increase the time it takes for a clot to form. This is the intended outcome of the therapy. Increasing the vitamin K2 supplementation while taking warfarin will provoke the drug to operate against the body. ACE2, Angiotensin-converting enzyme 2; DC, Dendritic cell; NK, Natural killer; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; NET, Neutrophil extracellular trap.

IL-6, IL-2, and others, which are among the cytokines that contribute to the severity of COVID-19 and the onset of ARDS [192, 193]. Additionally, further research revealed that vitamin K2, particularly menaquinone-4, was a more potent anti-inflammatory agent than vitamin K1 [194]. Furthermore, vitamin K can activate proteins C and S, which downregulate natural anticoagulant pathways and initiate an increase in procoagulant activity, compromising the force balance in the alveolar epithelium and, collectively, play a protective role in maintaining the alveolar membrane's integrity [195–197].

Activated protein C (APC) is an anticoagulant protein that is formed after the activation of protein C by the thrombin–thrombomodulin complex on the surface of cells, including alveolar epithelial cells. The endothelial protein C receptor (EPCR) accelerates protein C activation in a concentration-dependent manner [198]. Thus, vitamin K supplementation may assist to reduce cytokine levels while also protecting the integrity of the alveolar-capillary membrane, lowering the risk of ARDS development in COVID-19 patients [199].

Conclusion

The recent COVID-19 pandemic has widely enlightened us that, despite scientific advances, the emergence of a novel infectious disease can put humans in jeopardy, and that introducing an effective approach and immunization can be time-consuming and fraught with high mortality. So, elucidating the precise pathogenesis and determinants factor associated with disease severity is the primary concern of researchers in order to design a definite approach. It is noticeable that novel approaches will have unequal distributions throughout the world, and in pandemics, the main issue of concern is time. As a result, the most challenging research consideration is designating some more accessible approaches applicable to these emerging diseases. In this context, vitamin supplementation is the most accessible and feasible approach that can even be obtained through diet, so study on these micronutrients and their efficacy is critical. Recent clinical studies have revealed that COVID-19 patients have some micronutrients deficiency, which is associated with severe outcomes, recommending vitamin supplementation as an adjunctive treatment option in these patients. However, research has yet to determine optimal dosage and the most effective micronutrient combination in these interventions. It has been established that these micronutrients are immunoregulatory agents that modulate and enhance

immune cell functionality, which is an appropriate priority in infectious disease; they also serve some antiviral activities that are synergistic with current antiviral pharmaceutical approaches. These supplements have been shown to attenuate the severity of COVID-19 complications such as RAS dysfunction, coagulopathies, and so on. As a result, suboptimal micronutrient levels in these patients can facilitate SARS-CoV-2 pathogenesis, which suggests that habitual vitamin supplementation, even in vitamin-replete individuals, will lead to improved prophylaxis and prognosis. Furthermore, prior research has shown that these supplements improve the humoral immune response induced by vaccination, underpinning the question of how to integrate these micronutrients with vaccination strategies to terminate pandemics.

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