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Review

Potential roles of micronutrient deficiency and immune system dysfunction in the coronavirus disease 2019 (COVID-19) pandemic



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ABSTRACT

Preliminary studies indicate that a robust immune response across different cell types is crucial in recovery from coronavirus disease 2019 (COVID-19). An enormous number of investigations point to the vital importance of various micronutrients in the interactions between the host immune system and viruses, including COVID-19. There are complex and multifaceted links among micronutrient status, the host immune response, and the virulence of pathogenic viruses. Micronutrients play a critical role in the coordinated recruitment of innate and adaptive immune responses to viral infections, particularly in the regulation of pro- and anti-inflammatory host responses. Furthermore, inadequate amounts of micronutrients not only weaken the immune system in combating viral infections, but also contribute to the emergence of more virulent strains via alterations of the genetic makeup of the viral genome. The aim of this study was to evaluate the evidence that suggests the contribution of micronutrients in the spread as well as the morbidity and mortality of COVID-19. Both the presence of micronutrient deficiencies among infected individuals and the effect of micronutrient supplementation on the immune responses and overall outcome of the disease could be of great interest when weighing the use of micronutrients in the prevention and treatment of COVID-19 infection. These investigations could be of great value in dealing with future viral epidemics.

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Introduction

Coronaviruses (CoV) are a large group of RNA viruses that primarily target the human respiratory system and can lead to a wide range of illnesses from the common cold to severe respiratory syndromes. In the past 2 decades, outbreaks of CoV-related infections, including the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, led to great public health problems and concerns [1]. A new coronavirus termed COVID-19 (coronavirus disease 2019) is currently associated with an increasing number and rate of morbidities and fatalities. The genetic analysis of the COVID-19 exhibited >50% sequence identity to MERS-CoV and 80% to SARS-CoV [2].

The innate immune system represents the first line of defense against viruses, which can inhibit virus replication, improve virus clearance, promote tissue repair, and activate a prolonged adaptive immune response against the viruses [3]. Viruses, such as CoV, could affect the function of the immune system in different ways, such as dysregulation of the macrophage antiviral response, induction of excessive cytokine-mediated immune system responses, and the activation of complement and coagulation cascades, which may result in enhanced infectivity and worse outcomes [4].

Because there currently is no effective drug or vaccine, boosting the immune system could be a reasonable option to combat COVID-19. A functional immune system is a prerequisite for the host's ability to prevent or limit viral infections. It is well known that the nutrition of the host may influence the immune system and its susceptibility to viral infection. Numerous studies pointed to the increase in either susceptibility to or severity of various viral infections in nutritionally deficient individuals [5]. In addition to the host's response, various micronutrients can have a significant influence on disease severity via the modulation of viral pathogenesis, such as mutations in the viral genome [6]. On the contrary, a

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viral pathogen in the micronutrient-deficient population could replicate to a new, more pathogenic strain [7]. The objective of this review was to provide a collection of evidence that points to the key role of various micronutrients on the interactions between the host immune system and viruses, particularly CoVs. Furthermore, we describe the evidence that may support the contribution of micronutrient deficiency and immune system dysfunction to the viral outbreaks, including COVID-19.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January 1961 to April 2020, by use of the terms “coronavirus,” “immune system,” “micronutrients,” “vitamin,” and “COVID-19.” Relevant articles were identified through searches in Google Scholar and Springer Online Archives Collection. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles indicate a strong link between viral infections; particularly CoV infection, with micronutrients and the immune system were selected. Articles published in English and Spanish were included.

Immune response to COVID-19

The recruitment of various immune cells, including antibody-secreting cells and follicular helper T cells as well as activated CD4⁺ and CD8⁺ T cells, along with immunoglobulin (Ig)M and IgG COVID-19-binding antibodies have been reported in a patient with non-severe COVID-19 [8]. In the initiation stage of severe COVID-19, increased amounts of proinflammatory cytokines and chemokines, like interleukin (IL)-2, IL-6, granulocyte-colony stimulating factor, interferon (IFN) γ -induced protein 10, monocyte chemoattractant protein-1, vascular endothelial growth factor, macrophage inflammatory protein-1 α , and tumor necrosis factor (TNF)- α , as well as lymphopenia have been detected in the serum of some patients. However, infection with COVID-19 in its critical stage exacerbates the secretion of T-helper 2 (Th2) cytokines, such as IL-4, IL-1RA, and IL-10, which suppress the inflammatory response [9,10]. The preliminary data indicate the ability of the immune system to recognize COVID-19 and initiate an effective immune response across different cell types leading to successful recovery from the infection in cases with mild to moderate symptoms.

The majority of patients with COVID-19 only have mild to moderate symptoms. However, the cytokine storm aggravates the severity of the infection and worsens the prognosis [9,10]. Poor outcomes with enormously high values of proinflammatory cytokines have been reported in patients infected with MERS-CoV and SARS-CoV [11]. Additionally, it has been suggested that a significantly elevated amount of platelets in patients with COVID-19, which is associated with a longer average hospitalization and poor prognosis, may be stimulated by the higher inflammatory cytokine levels [12]. Baseline total lymphocytes were significantly higher in survivors than in non-survivors. In survivors, lymphopenia improved during hospitalization, whereas severe reduction of lymphocytes continued to decrease until death in non-survivors. The values of serum ferritin and IL-6 were markedly greater in non-survivors than in survivors [13].

Role of micronutrients in the interaction between immune response and viruses

Owing to the supporting role of micronutrients on the host immune responses to viral infections (Table 1), it is not surprising

that micronutrient deficiency would be associated with a weakened immune system and a higher risk for the occurrence and severity of viral infections.

Zinc

Zinc homeostasis is essential for sustaining proper immune function [14]. Zinc plays an important role in host–virus interactions owing to its effect on nucleic acid synthesis and repair, apoptosis, inflammation, and redox homeostasis [15]. Zinc baseline level is a crucial factor that can affect antiviral immunity, especially in zinc-deficient populations [16]. Zinc deficiency is associated with impaired immune responses and leads to a higher risk for respiratory viral infections, particularly in elderly individuals [17]. Zinc is involved in the modulation of the proinflammatory response by targeting nuclear factor (NF)- κ B. Zinc deficiency enhances the production of proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , and reduces the lytic activity of natural killer (NK) cells. Furthermore, zinc deficiency leads to a decrease in antibody production via the alteration of the function and number of various immune cells [14].

The zinc-finger domain is found in various proteins encoded by the genome of different CoVs, such as SARS-CoV [18], and plays a key role in viral replication and transcription [19]. A specific mutation within the zinc-finger domain of CoV caused reduced antiviral response [20]. Disruption of the zinc-binding function of CoV-229E nonstructural protein-13 (nsp13) or deletion of the entire zinc-binding domain affects both transcription and replication of CoV [21]. Furthermore, it has been shown that the zinc-binding domain may start to unfold during the first transition of SARS-CoV and lead to a reduction in pathogen virulence [22]. Enhancement of the intracellular zinc level can efficiently impair CoV replication. The application of zinc with pyrithione inhibits the replication of SARS-CoV, possibly via the inhibition of RNA polymerase activity [23]. Moreover, zinc potentially inhibits the protease activity of SARS-CoV and exerts an antiviral effect on human CoV-229E [24]. The prophylactic administration of zinc was significantly inhibitory to avian influenza H5N1/H1N1 virus infection in mice [25]. Several clinical trials have suggested that zinc supplementation may decrease the duration of symptoms, reduce the number of patients, enhance lymphocyte transformation and phagocytosis, and improve the response to immunotherapy in various viral infections [14].

Selenium

Selenium deficiency not only weakens the host immune system against viral infections but also leads to viral genome mutations from benign variants to highly pathogenic viruses [4]. Inadequate antioxidant protection against various mutating RNA viruses, including SARS-CoV, has been observed in individuals with blood selenium concentrations <1 μ M/L [26]. Human selenium deficiency decreases the production of free radicals and impairs the functions of neutrophils, T cells, lymphocytes, NK cells, and thymocytes [27]. Selenium enhances the polarization of M1 macrophages (proinflammatory) to M2 (anti-inflammatory) macrophages [28]. Selenium may exert its anti-inflammatory effect through epigenetic modulation of inflammatory gene expression, such as NF- κ B, and subsequently, reduce the synthesis of proinflammatory cytokines [29]. Several clinical studies revealed the beneficial effects of selenium supplementation on the increasing lymphocyte proliferation, improving NK cell activity, and enhancing IL-2 receptor expression [30].

Table 1
Impact of COVID-19 and various micronutrients on the innate and adaptive immune systems.

		Innate immunity	Adaptive immunity
COVID-19	Non-severe	Cytokines and chemokines ↑ or →	Antibody-secreting cells ↑ Activated CD4 ⁺ and CD8 ⁺ T cells ↑ IgM and IgG antibodies ↑ Follicular helper T cells ↑ Cytokine storm ↑↑
	Severe	Cytokine storm ↑↑ Serum lymphocyte ↓	Th2 immune response ↑ Th2 cytokines ↑ Proliferation of CD8 ⁺ T cells ↑ Th1 response ↑ Cytokines (IL-1β, IL-6, and TNF-α) ↑ M1 macrophages ↑ T lymphocyte proliferation ↑ Ig production ↑ T-cell activity ↑
Zinc		Antioxidant activity ↑ Cytokine release ↑ Premature/Immature B cells ↓	T-cell proliferation ↑ Antibody production ↑ Self-protection of immune cells ↑ Differentiation and proliferation of T lymphocyte antioxidant activity ↑
Selenium		Antioxidant activity ↑ Leukocyte and NK cell function ↑	
Iodide		Cytokine and chemokine secretion ↑ B-cell and NK-cell activities ↑	
Copper		Antioxidant activity ↑ IL-2 production and response ↑	
Iron		Cytokine production/action ↑ Neutrophil function ↑ Antioxidant activity ↑	
Vitamin A		Function of NK cells, macrophages, and neutrophils ↑	Function of T and B lymphocytes ↑ Th2 anti-inflammatory response ↑
Vitamin B ₁		Function of B cells ↑	
Vitamin B ₂		Proinflammatory cytokines ↓	Anti-inflammatory cytokine ↑
Vitamin B ₃		Production of proinflammatory cytokines ↓	T cells ↓ Modulate cytokine release NF-κB activity ↓
Vitamin B ₆		Anti-inflammatory cytokines ↑ Cytokine production ↑ NK-cell activity ↑ Lymphocyte production ↑	Lymphocyte proliferation, differentiation, and maturation ↑ Th1 immune response ↓ Antibody production ↑ Proinflammatory cytokines ↓
Vitamin B ₉		NK-cell function ↑	Th1-mediated immune response ↓ NF-κB production ↓
Vitamin B ₁₂		NK-cell function ↑	CD8 ⁺ T cells ↑ Production of T lymphocytes ↑ Serum levels of antibodies ↑ Lymphocyte differentiation ↑
Vitamin C		Antioxidant activity ↑ Proinflammatory cytokines ↓ Leukocytes ↑ NK-cell activity ↑	
Vitamin D		Monocyte differentiation to macrophages ↑ Cytokine production ↑ B-cell antibody production ↓	Antibody production by B cells ↓ T-cell proliferation ↓
Vitamin E		Antioxidant activity ↑ IL-2 production ↑ NK-cell activity ↑	T-cell function ↑ Lymphocyte proliferation ↑ Th1 response ↑ Th2 response ↓

Ig, immunoglobulin; IL, interleukin; NF, nuclear factor; NK, natural killer cell; Th, T helper; TNF, tumor necrosis factor

Most of the beneficial effects of selenium in reducing the risk for viral infections are due to its incorporation in the form of selenocysteine into a group of proteins that are named selenoproteins; many of which are potent antioxidant enzymes, like glutathione peroxidases and thioredoxin reductases [31]. Selenium exerts an antiviral effect via its modulatory role in antioxidant defense, redox signaling, and redox homeostasis [32]. Selenium alone or in combination with other nutrients exerts an accelerated cellular antiviral immune response and mediates resistance to different viruses, such as influenza A [27]. Selenium supplementation enhanced plasma selenium levels and increased the cellular immune response in individuals with low plasma selenium challenged with an oral live attenuated poliomyelitis vaccine, presumably via a greater production of IFN-γ and other cytokines [33]. Furthermore, selenium exerts a potent control over virus pathogenicity, and a direct link between selenium deficiency and increased risk for the occurrence and progression of some viral infections has been reported [34]. Administration of sodium selenite effectively prevented Keshan disease, congestive cardiomyopathy caused by a

combination of selenium deficiency and a mutated strain of Coxsackievirus [35].

Iodide

Iodide modulates the transcriptional immune signature of human peripheral blood immune cells and induces greater cytokine and chemokine secretion, such as IL-6, IL-8, and IL-10 [36]. Iodide is found in the salivary glands, nasal mucosa, and lung secretions [37]. The sodium-iodine symporter, a plasma membrane glycoprotein that mediates active iodide transport in different tissues, contributes to the oxidation of iodide in the lungs, which improves the antiviral respiratory defense system [38]. The oral intake of potassium iodide increased serum iodide concentrations and led to the accumulation of iodide in the surface liquid of the upper airway at concentrations that can support antiviral activities [39]. The airway epithelial cells generated sufficient hydrogen peroxide to inactivate respiratory syncytial virus after the application of iodide, possibly via oxidization of thiol groups in surface

proteins [39]. Gargle/mouthwash of povidone-iodine inactivated SARS-CoV and MERS-CoV within 15s of exposure, presumably through the impairment of protein synthesis and changes of cell membrane properties [40].

Copper

Copper is an essential nutrient for the development and maintenance of the human immune system. Copper is crucial for the generation and response of IL-2 to adaptive immune cells, the production of antibodies, maintaining intracellular antioxidant balance, and self-protection of immune cells [41,42]. Copper deficiency can lead to increased viral virulence, decreased IL-2 levels and T-cell proliferation, and reduced phagocytic ability [43]. Copper exhibits a potent antiviral property, possibly via binding electron donor groups on viral proteins or nucleic acids [44]. Copper antiviral effects may also be due to the regulatory roles of copper on certain enzymes, which are critical for the function of various types of immune cells [42,43]. Additionally, activated macrophages accumulate copper within the phagosome to inactivate the pathogens. This event plays an important role in the control of pulmonary infections [45]. Intravenous copper administration results in a greater copper concentration in the lung [46], suggesting a possible direct effect on boosting immune cells against respiratory tract infections (RTIs). It has been suggested that the accessibility of copper in infected cells could be a potentially disrupting factor in the virus life cycle through the distortion of the protein structures on the viral surface [47]. Copper demolishes human CoV-229E genomes and irreversibly alters virus morphology, including the disintegration of its envelope [24].

Iron

Investigations of the antiviral role of iron have shown conflicting results. Viruses require iron, transferrin, and ferritin for replication, survival, growth, and entry into host cells [48]. As both hosts and viruses require iron, the innate immune response controls iron metabolism to limit its availability during infection [48]. To achieve an optimal immune response, an appropriate level of iron should be accurately maintained. Indeed, iron deficiency decreases the ability of the immune system to limit viral infection, especially when the virus attacks immune cells [49]. On the other hand, iron overload may weaken the host immune response to the virus [50]. Heparin, a key modulator of the entry of iron into the circulation, could help to select infected individuals who will benefit most from iron therapy [51].

Iron is a key element in T-cell differentiation and proliferation and plays an important role in the regulation of the ratio between helper and cytotoxic T cells. Furthermore, iron is a key prerequisite for the generation of reactive oxygen species (ROS) and myeloperoxidase activity of neutrophils in defense against viruses [41]. Elevated iron levels promote macrophage M2 phenotype and decrease the M1 proinflammatory response. Furthermore, iron overload in macrophages inhibits the proinflammatory response through the reduction of NF- κ B nuclear translocation [52]. Iron modulates the production and activity of various cytokines, either directly or via hepcidin [53]. A higher iron deficiency anemia has been observed when the viral infection severely implicated the immune system [54].

Iron inhibited various viral infections, such as infections with influenza A virus and HIV [55]. Iron oxide nanoparticles exert a potent antiviral activity against influenza virus strain A/H1N1 via the alteration of RNA transcription [56]. Iron oxide enzymes

inactivate influenza A viruses and promote protection efficacy, possibly through peroxidation of viral lipid envelope [57].

Vitamin A

Vitamin A plays an immunoregulatory role in both cellular and humoral immune responses. Vitamin A maintains the function of NK cells, macrophages, and neutrophils, promotes CD8⁺ T-cell migration, supports the Th2 anti-inflammatory response, improves B-cell activities, and upregulates the secretion of cytokines, such as IL-2 [41]. Increased levels of IL-17 in the serum and bronchoalveolar secretion were associated with poor outcome in MERS-CoV, SARS-CoV, and other respiratory viral infections [58]. Activation of the retinoic acid receptor inhibits the generation of Th17 cells as well as the production of the key inflammatory cytokine IL-17 and promotes the anti-inflammatory forkhead box P3-positive T cells [59]. Vitamin A deficiency leads to the reduced weight of the thymus, decreased lymphocyte proliferation, impaired T cell-mediated response, and enhanced pathogen binding to respiratory epithelial tissues [60]. Vitamin A inhibits viral replication, promotes immune response, and decreases morbidity and mortality of some viral infections [61]. The beneficial effects of vitamin A on morbidity and mortality of some viral infections, such as measles and HIV, could be due to increased antibody production and lymphocyte proliferation as well as enhanced T-cell lymphopoiesis [62].

Clinical investigations and in vitro studies have indicated that vitamin A is the main regulator of mucosal immunity and could affect immune responses to mucosal infections [63]. Retinoic acid increased gastrointestinal mucosal immunity and systemic immunity during immunization of piglets with transmissible gastroenteritis coronavirus [64]. A diet deficient in vitamin A lessens the efficacy of bovine coronavirus vaccines and places calves at greater risk for coronavirus infection [65]. Infectious bronchitis virus, a widespread avian coronavirus, significantly reduced plasma retinol values. The severity of this infection was markedly increased in chicken fed with a diet deficient in vitamin A [66].

B vitamins

There is a strong link between B vitamins and host immune response to infections. Vitamins B₁, B₂, and B₅ control the host immune response through the regulation of energy generation in various immune cells [67]. Vitamin B₁ deficiency impairs the maintenance of B cells, whereas vitamin B₃ regulates the differentiation of T cells, decreases the production of several proinflammatory cytokines, and downregulates transforming growth factor- β gene expression and NF- κ B activity [68]. Vitamin B₅ deficiency causes inflammation through the higher production of proinflammatory mediators [67]. Furthermore, vitamin B₅ activates the phagocytic activity of macrophages, enhances the production of IL-6 and TNF- α , and modulates Th1 and Th17 responses [69]. Vitamin B₆ deficiency leads to lymphocytopenia and excessive Th2 responses and lowers lymphoid tissue weight and antibody responses [70]. Vitamin B₆ mobilizes to the sites of inflammation where it may serve as a cofactor in pathways producing mediators with anti-inflammatory effects [71]. The plasma level of vitamin B6 is inversely associated with several inflammatory biomarkers in population-based investigations [71]. Vitamin B₉ deficiency causes an impaired immune response and the reduced blastogenic response of T lymphocytes [68]. Vitamin B₁₂ maintains the function and proliferation of NK cell and CD8⁺ T cells. Deficiency in vitamin B₁₂ leads to a reduction in the number of NK cells and IL-6 levels as well as an enhancement of CD4⁺/CD8⁺ ratio and TNF- α value [41].

There are several experimental and clinical studies indicating the antiviral effects of B vitamins. Patients with HIV had a high prevalence of vitamin B₁ deficiency. Vitamin B₁ affects HIV infection via non-genomic mechanisms, which may lead to beneficial effects in patients with HIV [72]. Vitamin B₂ alone or in combination with ultraviolet light has a potent antiviral effect on a wide range of viruses, such as MERS-CoV [73]. Deficiencies in vitamins B₆, B₉, and B₁₂ render people more susceptible to viral respiratory infections, such as influenza [74]. It has been suggested that a vitamin A–vitamin B₆ conjugate analog can exert an antiviral effect by regulating transcription and/or replication of various RNA viruses, including *coronavirus* [75].

Vitamin C

A wide range of studies point to the importance of vitamin C in immune host responses to viral infections. Vitamin C promotes the production, function, and migration of immune cells, and enhances serum values of antibodies and complement proteins [76]. Vitamin C also supports the differentiation and proliferation of lymphocyte and enhances apoptosis, chemotaxis, and IFN production [77]. Clinical trials and experimental studies suggest that vitamin C inhibits the proinflammatory cytokines, like TNF and IL-6, and increases the proinflammatory cytokines, such as TNF, IL-6, and IL-1 β [78]. Vitamin C exerts an antiviral immune response against the influenza virus via the enhancement of IFN-IL-1 α/β production [79].

Vitamin C enhances the resistance of broiler chicks [80] and chick embryo tracheal organ cultures [81] to infections induced by an avian *coronavirus*. Vitamin C reduced the cytokine levels (TNF- α and IL-1 β) in an animal model of acute respiratory distress syndrome (ARDS); suggesting its beneficial effect for the treatment of similar inflammatory disorders [82]. Indeed, the intravenous administration of vitamin C in patients with sepsis and ARDS significantly reduced the mortality rate [83]. Several investigations have suggested that vitamin C in high dosages has direct virucidal effects [84]. Several clinical trials have shown a significantly lower incidence of RTIs in vitamin C-treated patients [85]. On the contrary, vitamin C deficiency enhances the risk for respiratory infections, particularly in the elderly [74]. Vitamin C has been suggested to provide effective containment for the viral pandemic as it exerts a beneficial antioxidant effect in patients suffering from severe avian influenza [86].

Vitamin D

Vitamin D is actively involved in the regulation of both innate and adaptive immune responses against viral infections [87]. Vitamin D promotes the differentiation of monocytic precursors to mature macrophages, downregulates toll-like receptors (TLR)-2 and TLR-4 in monocytes; decreases inflammatory responses, and prevents tissue damage associated with excessive inflammation [88]. Furthermore, vitamin D limits the potential damages associated with Th1 immune responses by the inhibition of INF- γ and IL-4 release [89]. Vitamin D also modulates the generation of regulatory T cell, reduces IFN- γ and IL-17 values, stimulates the secretion of IL-4 and IL-10, and suppresses B-cell antibody production [87].

Acute viral infection of calves with bovine *coronavirus* caused an increase in haptoglobin, IFN- γ , IL-2, and IL-6 serum levels, which was associated with a rapid decrease in vitamin D and E values [90]. Exogenous application of vitamin D inhibits rhinovirus replication in bronchial epithelial cells, most likely via the activation of the innate IFN pathway [91]. The SARS-CoV accessory protein ORF6 interrupts the activity of several karyopherin-dependent host transcription factors, including vitamin D receptors, which are

crucial for the regulation of host immune responses and initiation of antiviral responses [92].

Vitamin D deficiency was associated with greater illness severity, multiple organ dysfunctions, and mortality in critically ill patients, particularly those with sepsis and pneumonia [93]. Intake of supplementary doses of vitamin D decreases overall mortality risk and improves the general health of patients [94]. High-dose vitamin D₃ may improve clinical outcomes in critically ill ventilated adults via the promotion of oxidative stress [95]. Low vitamin D and A values were significantly associated with more intensive care unit (ICU) admissions and mechanical ventilation [96]. Coapplication of vitamin D with an inactivated influenza virus has been shown to increase both the antibody response against the viral hemagglutinin and mucosal immunity [97].

Individual vitamin D values reach their lowest levels at the end of winter and the maximum after summer. Interestingly, this seasonal variation mirrors the defined seasonal variations of respiratory viral infections and sepsis [98]. It has been suggested that seasonal variation in human immune response and vitamin D levels may contribute to the seasonal patterns of respiratory infections [99]. Substantial negative correlations were reported between solar ultraviolet-B doses and population mean vitamin D status with case fatality and pneumonia rates during the 1918–1919 influenza pandemic [99]. Vitamin D supplementation was associated with a decreased risk for lower RTI and hospitalization in infants born in Wuhan, China from 2013 to 2016 [100].

Vitamin E

Vitamin E supports the integrity of epithelial membranes and increases IL-2 production, NK cell activity, T cell-mediated functions, and lymphocyte proliferation. Furthermore, vitamin E initiates T-cell activation, promotes Th1 proliferation, and inhibits Th2 response [101]. Vitamin E supplementation causes more IL-2 and IFN- γ production with a lower lung virus titer in animals with the influenza virus [102]. Vitamin E deficiency markedly increases the viral pathogenicity and heart damage in mice infected with Coxsackieviruses-B3 [103]. Administration of vitamin E increased lymphocyte proliferation as well as IL-2 and IFN- γ production in healthy individuals and aged mice after influenza infections [102]. A modest level of vitamin E supplementation regulates the cellular free radical-antioxidant balance, enhances the antibody response, and activates the immune cells of broilers vaccinated with the infectious bronchitis virus [104]. H1N1-infected mice have shown positive associations between anti-inflammatory cytokine IL-10 levels and vitamin E metabolism [105].

Vitamin E and selenium exhibit strong control over viral replication and mutation. In a nutritional deficiency condition of these micronutrients, RNA viruses are able to convert to more virulent strains [106]. Vitamin E-deficient mice failed to exhibit an appropriate immune response to HSV-1 infection [107]. A significant increase in lung and serum vitamin E levels has been observed a few days after infection with the influenza virus in mice [108]. Critically ill patients who were admitted to an ICU with ARDS have shown a significant reduction of vitamin E plasma level [109]. The use of vitamins E and C in critically ill patients reduced the incidence of ARDS and pneumonia and shortened ICU length of stay [110].

Micronutrient, immune system, and COVID-19

The most vulnerable groups to the severe-critical complications of COVID-19 are individuals >60 y of age and those with chronic diseases, including hypertension, diabetes, and cardiovascular or respiratory diseases [111,112]. Although only 36% of patients

infected with COVID-19 in Italy were >70 y of age, >80% of deaths occurred in this group of patients [113]. Furthermore, elderly adults are more susceptible to severe COVID-19 at admission [114].

Immune function in elderly adults can be modified by nutritional and pharmacologic interventions [115]. Aging causes alterations in every component of the immune system, which leads to increased morbidity and mortality following infectious diseases [116,117]. The altered function of the immune system in the elderly can be promoted via the manipulation of cytokine production, changes of metabolic pathways in immune cells, and immune system rejuvenation aimed at reactivating the generation of new lymphocytes [118]. Micronutrient interventions have shown a promising effect in targeting the immune system impairments observed in the elderly and improve the infection-related morbidity and mortality [119,120].

Micronutrient deficiencies affect ~2 billion people worldwide and contribute essentially to the global burden of several diseases [121]. For instance, zinc deficiency affects ~30% of the world population ranging from 4% to 73% across different countries and implicated in about 16% of lower RTIs [122]. Micronutrient deficiencies decrease the ability to resist infections and are common causes of immunodeficiency in developing countries [123]. Although micronutrient deficiencies are a major public health challenge in developing countries, about 30% of the population in industrialized societies are also affected [124]. Silent epidemics of micronutrient deficiencies could be due to insufficient intake and/or sufficient intakes in association with impaired absorption owing to infection, inflammation, or chronic diseases [123,125]. Approximately 35% of populations >50 y of age in Europe, the United States, and Canada have an obvious deficiency of one or more essential micronutrients [126]. In addition to an insufficient intake of micronutrients, elderly individuals lose their ability to produce endogenous antioxidants [127]. Italy, Spain, and France have experienced the highest COVID-19 death toll in Europe and the elderly in these countries have shown the highest prevalence of vitamin D deficiency compared with many other European countries [128,129]. Approximately 60% of people who died from COVID-19 in Italy were living in the Lombardy region. During the cold seasons, up to 90% of the population in this region shows deficient/insufficient values of vitamin D [130]. The Lombardy region, the most air-polluted area of Italy, has a high rate of hospitalizations and respiratory illnesses [131]. Air pollution associated with increased ozone values absorbs ultraviolet B radiation and leads to vitamin D deficiency [132]. The overall prevalence of low vitamin D status is >40% in the U.S. population [133]. Several clinical studies indicate the vital role of micronutrients in the prevention and treatment of viral infections [134,135]. Micronutrient deficiencies, including zinc and vitamins B₂, B₆, B₁₂, C, and D, were reported to be common in the Ecuadorian elderly, which weakened their immune system and placed them at greater risk for viral RTIs [74]. Administration of zinc and vitamin A significantly decreased the incidence of pneumonia in children [136], and oral zinc supplementation could shorten the duration of symptoms of respiratory infection [137]. The Food and Agriculture Organization of the United Nations has reported that nutrition and antiviral drugs are equal in the treatment of HIV infection and regular intake of micronutrients is crucial for promoting the immune response and maintaining good health for both infected and uninfected individuals [138]. Early administration of vitamin A reduced the mortality rate of patients with Ebola virus disease during the western African outbreak [139].

Supplementation of micronutrients in elderly individuals enhanced the number of T cells and lymphocytes, improved lymphocyte response to mitogen, increased IL-2 levels and NK cell activity, promoted the response to the influenza virus vaccine, and

reduced the duration of viral diseases [41,140]. Some commonly used drugs, such as antibiotics, can lead to various micronutrient depletions, such as iron and vitamins A, B, and D [141]. A combination of micronutrient supplementation in elderly adults may decrease antibiotic usage and causes a higher post-vaccination immune response [126]. Interestingly, some countries with higher morbidity and mortality of COVID-19, such as Italy and Spain, have a greater consumption of antibiotics compared with other European countries [142,143]. Mice treated with antibiotics are unable to stimulate cytokine release in the lung and augment protective T-cell responses after influenza infection [144].

Infectious disease outbreaks could indeed be the result of infection by a virus whose virulence has altered as a result of replicating in a nutritionally deficient host so that a non-virulent virus becomes a pathogen due to changes in its genome [5]. The steady emergence of new strains of pathogen RNA viruses with new pathogenic properties, such as CoV, could be facilitated via increased mutation rates in micronutrient-deprived populations [106]. Micronutrient deficiency could lead to increased opportunities for viral mutations through the host cell permissiveness for viral replication as well as the enhancement of oxidative damages to the RNA genome [33]. The epidemic of peripheral neuropathy in Cuba and the facilitated crossing over of HIV in Africa could be explained by the emergence of virulent mutated RNA viruses in the population with micronutrient deficiency [33,145,146].

Conclusion

There are few clinical investigations concerning the role of micronutrients on host immune responses in pandemic viral infections. Both the presence of micronutrient deficiencies among infected individuals and the effect of micronutrient supplementation on the overall outcome of the disease could be of great interest when weighing the use of micronutrients in the prevention and/or treatment of infectious illnesses, such as COVID-19. Additionally, available data strongly suggest that the association of unpredictable occurrence of novel viral pathogens combined with decreased host immunity and micronutrient deficiency poses a twofold threat to human health in the near future. Further investigating the role of micronutrients and their substitution on immune system activity, therefore, may present a highly cost-efficient and uncomplicated measure with promising long-term benefits on future viral outbreaks. The development of novel vaccinations and drugs targeting pathogens that cause currently relevant diseases is often an expensive and risky process associated with a narrow spectrum efficacy due to their selective applications. Furthermore, the use of novel vaccines and drugs is usually restricted due to their high costs. A decade ago, the Copenhagen Consensus: Hunger and Malnutrition Assessment concluded that efforts to provide micronutrients for the global population generate higher returns than any other public health measure [147].

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