THE EFFECT OF NUTRITIONAL MICRONUTRIENTS IN IMMUNE SYSTEM AGAINST CORONAVIRUS DISEASE (COVID-19)

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Abstract
According to preliminary research, recovery from coronavirus disease needs a strong immune response across multiple cell types (COVID-19). The latest coronavirus pandemic is affecting people all over the world. The virus is known to infect several tissues and, in extreme cases, can lead to respiratory failure. The immune system must be healthy to prevent the disease from progressing to this stage and to limit the damage caused by the Coronavirus (SARS-CoV-2). Nutritional health is important for effective immunological defence and, as a result, a good response to SARS-CoV-2. Micronutrients help immune cells conduct functions that are critical for stopping SARS-CoV-2. Their regular intake is part of a non-pharmacological strategy to maintain the immune system in good shape. Various micronutrients play a critical role in the interactions between the host immune system and viruses, like COVID-19, according to a large number of studies. The relationship between micronutrient status, the host immune response, and pathogenic virus virulence is complex and multifaceted. Micronutrients are essential for the coordinated recruitment of innate and adaptive immune responses to viral infections, as well as the regulation of pro- and anti-inflammatory host responses. Furthermore, insufficient micronutrients not only impair the immune system's ability to fight viral infections, but also lead to the development of more virulent strains by altering the viral genome's genetic makeup. The aim of this study was to assess the evidence that indicates micronutrients play a role in COVID-19 transmission, morbidity, and mortality. When considering the use of micronutrients in the prevention and treatment of COVID-19 infection, both the prevalence of micronutrient deficiencies among infected individuals and the impact of micronutrient supplementation on immune responses and overall disease outcome may be of great interest. These studies may be extremely useful in dealing with potential viral outbreaks.

Keywords: COVID-19; pandemic; minerals; virus infection; vitamin A; vitamin C

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1. INTRODUCTION

Coronaviruses (CoV) are a broad group of RNA viruses that mainly attack the human respiratory system and cause a variety of illnesses ranging from the common cold to extreme respiratory syndromes. Outbreaks of CoV-related infections, such as the extreme acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, have caused significant public health issues and concerns over the last two decades (Arnold, 2013). COVID-19 (coronavirus disease 2019) is a new coronavirus that has been linked to an increase in the number and incidence of morbidities and deaths. COVID-19 showed >50% sequence similarity to MERS-CoV and 80% similarity to SARS-CoV in genetic research (Peng et al. 2020). The innate immune system, which can prevent virus replication, increase virus clearance, promote tissue repair, and trigger a long-term adaptive immune response to viruses, is the first line of defense against viruses (Li et al. 2020).

Viruses like CoV can disrupt immune system function in a variety of ways, including dysregulation of the macrophage antiviral response, induction of excessive cytokine-mediated immune system responses, and activation of complement and coagulation cascades, all of which can lead to increased infectivity and worse outcomes (Gralinski and Baric, 2015). Since there is currently no effective drug or vaccine to fight COVID-19, improving the immune system may be a viable alternative. The capacity of the host to prevent

or restrict viral infections requires a functioning immune system. It is well understood that the host's diet will affect the immune system and susceptibility to viral infection. Numerous studies have linked nutritional deficiency to an increase in either susceptibility to or severity of various viral infections (Beck and Matthews, 2000). Various micronutrients, in addition to the host's reaction, may have a major impact on disease severity by modulating viral pathogenesis, such as viral genome mutations (Beck, 1997). A viral pathogen in a micronutrient-deficient population, on the other hand, could replicate into a new, more pathogenic strain (Beck and Levander, 2000). The aim of this review was to compile evidence that various micronutrients play a critical role in the interactions between the host immune system and viruses, especially CoVs. We also go through the evidence that suggests micronutrient deficiency and immune system dysfunction can play a role in viral outbreaks, including COVID-19.

COVID-19 Immune response

Immune cells such as antibody-secreting cells and follicular helper T cells, as well as activated $CD4^+$ and $CD8^+$ T cells, as well as immunoglobulin (Ig)M and IgG, are recruited. A patient with non-severe COVID-19-binding antibodies has been identified. COVID-19 is a virus that infects people (Thevarajan et al. 2020). In the onset stage of severe COVID-19 infection, the amounts of proinflammatory cytokines and chemokines increased, such as interleukin (IL)-2, IL-6, agranulocyte colony stimulating factor (IFN) γ-induced by g10, monocyte chemoattractant protein. Detection of vascular endothelial growth factor, macrophage inflammatory protein-1α, and tumor necrosis factor (TNF)-α, in addition to serum lymphopenia in 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 (Huang et al. 2020; Wang et al. 2020). Preliminary data indicates the ability of the immune system to recognize COVID-19 and initiate an effective immune response across different types of cells leading to successful recovery from infection in mild to moderate symptomatic cases.

The majority of COVID-19 patients have only mild to moderate symptoms. The cytokine wind, on the other hand, worsens the seriousness of the infection and the prognosis (Huang et al. 2020; Wang et al. 2020). Patients infected with MERS-CoV and SARS-CoV has documented poor results and extremely high levels of proinflammatory cytokines (He et al. 2016). Furthermore, it has been suggested that the higher inflammatory cytokine levels may stimulate a significantly increased amount of platelets in COVID-19 patients, which is linked to a longer average hospitalisation and poor prognosis (Qu et al. 2020). Total lymphocytes were substantially higher in survivors than in non-survivors at the start of the study. Survivors' lymphopenia improved during hospitalisation, while non-survivors' extreme loss in lymphocytes continued until death. Nonsurvivors had significantly higher serum ferritin and IL-6 levels than survivors (Zhou et al. 2020).

Micronutrients' role in the immune responses interaction with viruses

Given the importance of micronutrients in promoting host immune responses to viral infections, it is unsurprising that micronutrient deficiency is linked to a weakened immune system and a higher risk of viral infection occurrence and severity.

Minerals and the Immune System

The Effect of Zinc in the Immune System

Zinc homeostasis is needed for proper immune function to be maintained (Gammoh and Rink, 2017). Because of its effects on nucleic acid synthesis and repair, apoptosis, inflammation, and redox homeostasis, zinc plays a significant role in host-virus interactions (Jarosz et al. 2017).

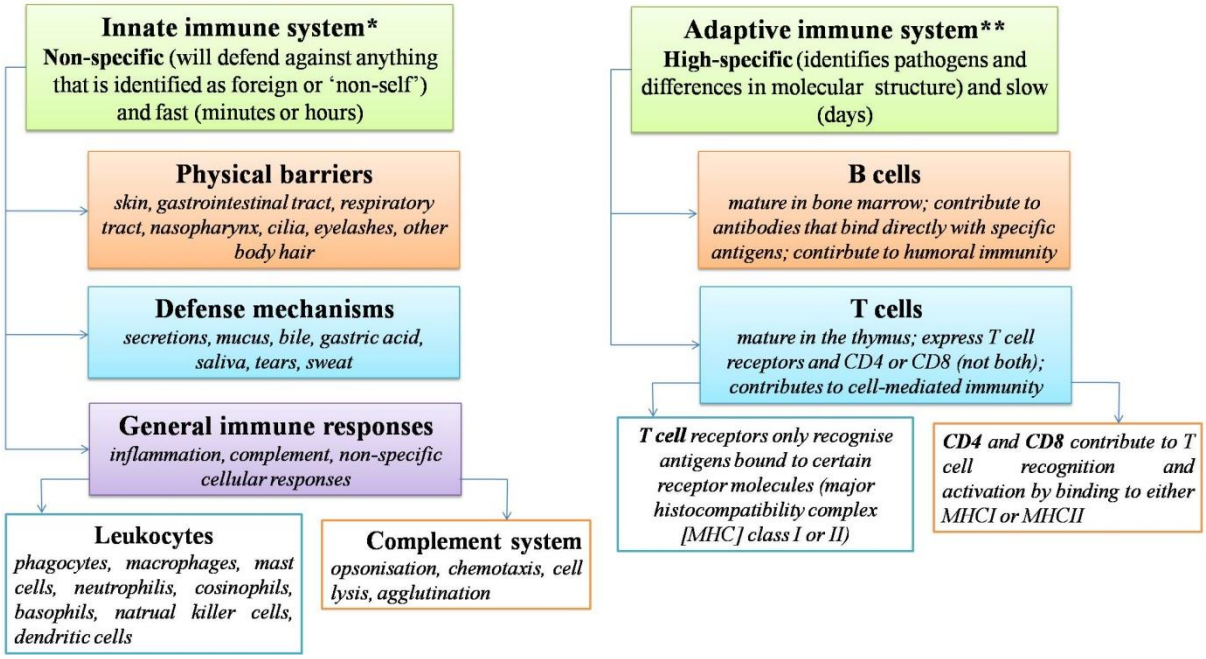

Figure1. The immune system in a nutshell. The immune system's three layers (physical and biochemical barriers; cells such as monocytes; granulocytes, lymphocytes, and B and T cells; and antibodies or immunoglabulins) function together to protect the body from infections by combining innate and adaptive defense mechanisms.

The baseline level of zinc, particularly in zinc-deficient populations, is a critical factor that can affect antiviral immunity (Read et al. 2019). Zinc deficiency is linked to weakened immune responses and an increased risk of respiratory viral infections, particularly in the elderly (Meydani et al. 2007). Zinc targets nuclear factor (NF)-kB, which is involved in the modulation of the proinflammatory response. Zinc deficiency increases the development of proinflammatory cytokines including IL-1b, IL-6, and TNF-α while decreasing natural killer (NK) cell lytic activity. Furthermore, zinc deficiency reduces antibody development by affecting the function and number of different immune cells (Gammoh and Rink, 2017).

The zinc-finger domain is present in a variety of proteins encoded by the genomes of various CoVs, including SARS-CoV (Lei et al. 2018), and is essential for viral replication and transcription (Ma et al. 2015). CoV's antiviral response was decreased due to a mutation in the zinc-finger domain (Becares et al. 2016). Both transcription and replication of CoV are affected when the zinc-binding mechanism of CoV-229E nonstructural protein-13 (nsp13) is disrupted or the entire zinc-binding domain is deleted (Hao et al. 2017). Furthermore, it has been demonstrated that the zinc-binding domain of SARS-CoV could begin to unfold during the first transition, resulting in a decrease in pathogen virulence (Chou et al. 2012). CoV replication can be effectively slowed by increasing intracellular zinc levels. Zinc in combination with pyrithione inhibits SARS-CoV replication, likely by inhibiting RNA polymerase activity (te Velthuis et al. 2012). Furthermore, zinc inhibits the protease function of SARS-CoV and has antiviral properties against human CoV-229E (Warnes et al. 2015). In mice, prophylactic zinc administration significantly reduced avian influenza H5N1/H1N1 virus infection (Barnard et al. 2007).

Zinc supplementation has been shown in many clinical trials to reduce the duration of symptoms, reduce the number of patients, improve lymphocyte transformation and phagocytosis, and improve immunotherapy response in a variety of viral infections (Gammoh and Rink, 2017).

The Effect of Selenium in the Immune System

Selenium deficiency not only impairs the host immune system's ability to fight viral infections, but it also causes viral genome mutations that range from benign to highly pathogenic (Gralinski and Baric, 2015). Individuals with blood selenium concentrations below 1 mM/L have been shown to have insufficient antioxidant defenses against various mutating RNA viruses, including SARS-CoV (Harthill, 2011). Human selenium deficiency reduces free radical activity and impairs neutrophil, T cell, lymphocyte, NK cell, and thymocyte functions (Gill and Walker, 2008). Selenium promotes the transition of proinflammatory M1 macrophages to anti-inflammatory M2 macrophages (Kudva et al. 2015). Selenium's anti-inflammatory effect may be mediated by epigenetic regulation of inflammatory gene expression, such as NF-kB, which reduces the output of proinflammatory cytokines (Narayan et al. 2015). Selenium supplementation has been shown to increase lymphocyte proliferation, improve NK cell function, and enhance IL-2 receptor expression in several clinical studies (Beck et al. 1998).

The absorption of selenium in the form of selenocysteine into a group of proteins known as selenoproteins, many of which are potent antioxidant enzymes including glutathione peroxidases and thioredoxin reductases, is responsible for the majority of selenium's beneficial effects in reducing the risk of viral infections (Guillin et al. 2019). Selenium inhibits the spread of viruses by modulating antioxidant defense, redox signalling, and redox homeostasis (Rayman, 2012). Selenium, alone or in conjunction with other nutrients, promotes cellular antiviral immunity and mediates resistance to various viruses, including influenza A (Gill and Walker, 2008). Individuals with low plasma selenium were given an oral live attenuated poliomyelitis vaccine, and selenium supplementation improved plasma selenium levels as well as the cellular immune response, most likely through increased IFN-g and other cytokines output (Broome et al. 2004). Furthermore, selenium regulates virus pathogenicity, and a direct correlation has been established between selenium deficiency and an increased risk of the incidence and development of certain viral infections (Beck and Levander, 1998). Sodium selenite treatment successfully avoided Keshan disease, a congestive cardiomyopathy caused by a combination of selenium deficiency and a mutated Coxsackievirus strain (Beck et al. 2004).

The Effect of Iodide in the Immune System

Iodide alters the transcriptional immune signature of human peripheral blood immune cells, resulting in increased production of cytokines and chemokines including IL-6, IL-8, and IL-10 (Bilal et al. 2017). Salivary glands, nasal mucosa, and lung secretions all contain iodide. (Brown-Grant, 1961). The sodium-iodine symporter, a plasma membrane glycoprotein that mediates active iodide transport in various tissues, aids in iodide oxidation in the lungs, enhancing the antiviral respiratory defense system (Portulano et al. 2014). Oral potassium iodide administration increased serum iodide concentrations and resulted in iodide accumulation in the upper airway surface liquid at levels that promote antiviral activity (Fischer et al. 2011). After the application of iodide, the airway epithelial cells produced enough hydrogen peroxide to inactivate respiratory syncytial virus, likely through oxidation of thiol groups in surface proteins (Fischer et al. 2011). Within 15 seconds of exposure, povidone-iodine gargle/mouthwash inactivated SARS-CoV and MERS-CoV, possibly due to protein synthesis deficiency and changes in cell membrane properties (Eggers et al. 2018).

The Effect of Copper in the Immune System

Copper is needed for the production and maintenance of the immune system in humans. Copper is needed for the development of antibodies, the maintenance of intracellular antioxidant balance, and immune cell self-

protection, as well as the generation and response of IL-2 to adaptive immune cells (Maggini et al. 2018; Gombart et al. 2020). Increased viral virulence, decreased IL-2 levels and T-cell proliferation, and reduced phagocytic capacity have all been linked to copper deficiency (Percival, 1998). Copper has antiviral properties, presumably due to its ability to bind electron donor groups on viral proteins or nucleic acids (Borkow et al. 2008). Copper's antiviral effects may also be attributed to copper's regulatory roles on certain enzymes, which are important for immune cell function (Gombart et al. 2020; Percival, 1998). Activated macrophages also absorb copper within the phagosome to render pathogens inactive. This occurrence is critical in the management of pulmonary infections (Besold et al. 2016). Intravenous copper administration raises copper concentrations in the lungs (Thanawongnuwech et al. 2000), implying a potential direct impact on immune cells fighting respiratory infections (RTIs). Copper accessibility in infected cells has been suggested as a possible disrupting factor in the virus life cycle by causing protein structures on the viral surface to be distorted (Ishida, 2018). Human CoV-229E genomes are demolished by copper, and the virus's anatomy is irreversibly altered, including the disintegration of its envelope (Warnes et al. 2015).

The Effect of Iron in the Immune Systems

Investigations into the antiviral properties of iron have shown mixed results. For replication, survival, development, and entry into host cells, viruses require iron, transferrin, and ferritin (Wessling-Resnick, 2018). Since both hosts and viruses require iron, the innate immune response regulates iron metabolism during infection to reduce its availability (Wessling-Resnick, 2018). An accurate level of iron should be preserved in order to achieve an optimum immune response. Indeed, iron deficiency impairs the immune system's ability to fight viral infection, especially when the virus targets immune cells (Ekiz et al. 2005). Iron overload, on the other hand, can compromise the host's immune response to the virus (Deugnier et al. 1991). Hepcidin, a central regulator of iron absorption into the bloodstream, could aid in the identification of infected people who would benefit the most from iron therapy (de Mast et al. 2010).

Iron is an essential component of T-cell differentiation and proliferation, as well as the regulation of the ratio of helper to cytotoxic T cells. Furthermore, iron is required for the production of reactive oxygen species (ROS) and neutrophil myeloperoxidase activity in virus protection (Maggini et al. 2018). Increased iron levels promote the M2 phenotype of macrophages while suppressing the M1 proinflammatory response. Furthermore, iron overload in macrophages reduces NF-kB nuclear translocation, which inhibits the proinflammatory response (Agoro et al. 2018). Iron affects cytokine development and function, either directly or by hepcidin (Maggini et al. 2007). When the immune system was seriously harmed by the viral infection, a higher rate of iron deficiency anemia was found (Tolentino and Friedman, 2007). Various viral infections, such as influenza A virus infections and HIV infections, were inhibited by iron (Wang et al. 2018). By altering RNA transcription, iron oxide nanoparticles have a potent antiviral effect against influenza virus strain A/H1N1 (Kumar et al. 2019). Iron oxide enzymes inactivate influenza A viruses and increase defense effectiveness, likely by oxidizing the viral lipid envelope (Qin et al. 2019).

Vitamins and the Immune System

The Effect of Vitamin A in the Immune System

In both cellular and humoral immune responses, vitamin A acts as an immunoregulator. Vitamin A helps NK cells, macrophages, and neutrophils work properly, promotes $CD8^+$ T-cell migration, supports the Th2 anti-inflammatory response, enhances B-cell activities, and increases the secretion of cytokines including IL-2 (Maggini et al. 2018).

MERS-CoV, SARSCoV, and other respiratory viral infections have been linked to increased levels of IL-17 in the serum and bronchoalveolar secretion (Chan et al. 2015). The anti-inflammatory forkhead box P3 positive T cells are promoted when the retinoic acid receptor is activated, which inhibits the generation of Th17 cells as well as the development of the primary inflammatory cytokine IL-17 (Elias et al. 2008). Reduced thymus weight, decreased lymphocyte proliferation, impaired T cell-mediated response, and increased pathogen binding to respiratory epithelial tissues are all symptoms of vitamin A deficiency (Huang et al. 2018). Vitamin A prevents viral replication, boosts the immune system, and reduces the morbidity and mortality associated with some viral infections (Mawson, 2013). The beneficial effects of vitamin A on morbidity and mortality from some viral infections, such as measles and HIV, may be due to increased antibody production and lymphocyte proliferation as well as improved lymphogenesis in T cells (Villamor and Fawzi, 2005).

Vitamin A is the key regulator of mucosal immunity, according to clinical and in vitro studies, and it can influence immune responses to mucosal infections (Kunisawa and Kiyono, 2013). During the immunisation of piglets with the transmissible gastroenteritis coronavirus, retinoic acid improved gastrointestinal mucosal immunity as well as systemic immunity (Chai et al. 2014). Vitamin A deficiency reduces the effectiveness of bovine coronavirus vaccines and increases the risk of coronavirus infection in calves (Jee et al. 2013). The avian coronavirus infectious bronchitis virus dramatically decreased plasma retinol levels. The incidence of this infection was significantly increased in chicken fed a vitamin A-deficient diet (West et al. 1992).

The Effect of B vitamins in the Immune System

The immune response of the host to infections is strongly linked to B vitamins. Vitamins B1, B2, and B5 regulate energy generation in immune cells and thus influence the host immune response (Yoshii et al. 2019). Vitamin B1 deficiency impairs B cell maintenance, while vitamin B3 controls T cell differentiation, lowers proinflammatory cytokine output, and inhibits transforming growth factor-b gene expression and NF-kB function (Mikkelsen et al. 2017). Inflammation is caused by a lack of vitamin B5 due to increased development of proinflammatory mediators (Yoshii et al. 2019). Vitamin B5 also stimulates macrophage phagocytic activity, increases IL-6 and TNFa development, and modulates Th1 and Th17 responses (He et al. 2018). Vitamin B6 deficiency causes lymphocytopenia and increased Th2 responses, as well as reduced lymphoid tissue weight and antibody responses (Qian et al. 2017). Vitamin B6 is transported to the sites of inflammation, where it can function as a cofactor in the production of anti-inflammatory mediators (Ueland et al. 2017). In population-based studies, vitamin B6 plasma levels are inversely related to many inflammatory biomarkers (Ueland et al. 2017). Vitamin B9 deficiency impairs immune function and decreases T lymphocyte blastogenic response (Mikkelsen et al. 2017). The activity and proliferation of NK cells and CD8+ T cells are both maintained by vitamin B12. Vitamin B12 deficiency causes a decrease in the number of NK cells and IL-6 levels, as well as an increase in the CD4+/CD8+ ratio and TNF-a value (Maggini et al. 2018).

The B vitamins have been shown to have antiviral properties in many laboratory and clinical trials. Vitamin B1 deficiency was very common among HIV patients. Vitamin B1 causes HIV infection by non-genomic pathways, which may have a positive impact on HIV patients (Ng and Nguyen, 2013). Vitamin B2 has a potent antiviral effect on a wide variety of viruses, including MERS-CoV (Keil et al. 2016), whether taken alone or in combination with ultraviolet light. Vitamin B6, B9, and B12 deficiency makes people more vulnerable to viral respiratory infections

including influenza (Hamer et al. 2009). A vitamin A-vitamin B6 conjugate analogue has been proposed to have antiviral properties by controlling the transcription and/or replication of various RNA viruses, including coronavirus (Kesel, 2003).

The Effect of Vitamin C in the Immune System

According to a number of studies, Vitamin C plays an important role in the immune host's response to viral infections. Vitamin C boosts antibody and complement protein levels in the blood, promoting immune cell development, function, and migration (Ang et al. 2018). Vitamin C also promotes lymphocyte differentiation and proliferation, as well as apoptosis, chemotaxis, and the development of interferon (Marik, 2020). Vitamin C appears to suppress proinflammatory cytokines like TNF and IL-6 thus increasing proinflammatory cytokines like TNF, IL-6, and IL-1β in clinical trials and laboratory studies (Carr and Maggini, 2017).

Vitamin C boosts the synthesis of IFN-IL-1α/β, which has an antiviral effect against the influenza virus (Kim et al. 2013). Broiler chicks (Davelaar and Bos, 1992) and chick embryo tracheal organ cultures (Atherton et al. 1978) are more resistant to infections caused by an avian coronavirus when given vitamin C. In an animal model of acute respiratory distress syndrome (ARDS), vitamin C decreased cytokine levels (TNF-α and IL-1β), implying that it could be useful in the treatment of related inflammatory disorders (Erol et al. 2019). Vitamin C was given intravenously to patients with sepsis and ARDS, and it greatly decreased mortality (Fowler et al. 2019). Several studies have suggested that high doses of vitamin C have direct virucidal effects (Colunga Biancatelli et al. 2020). RTIs were found to be substantially less common in vitamin C-treated patients in several clinical trials (Hemila, 2003). Vitamin C deficiency, on the other hand, increases the risk of respiratory infections, particularly in the elderly (Hamer et al. 2009). Vitamin C has been proposed as a possible means of containing the virus pandemic because it has an antioxidant role in patients with extreme avian influenza (Ely, 2007).

The Effect of Vitamin D in the Immune System

Vitamin D plays an important role in both the innate and adaptive immune responses to viral infections (Medrano et al. 2018). Vitamin D promotes the maturation of monocytic precursors into mature macrophages, inhibits the expression of toll-like receptors (TLR)-2 and TLR-4 in monocytes, reduces inflammatory responses, and protects tissue from tissue damage caused by excessive inflammation (Sadeghi et al. 2006). Furthermore, vitamin D inhibits the release of INF-γ and IL-4, limiting the possible harm associated with Th1 immune responses (Boonstra et al. 2001). Vitamin D also suppresses B-cell antibody formation, reduces IFN-γ and IL-17 levels, stimulates the secretion of IL-4 and IL-10, and modulates the generation of regulatory T cells (Medrano et al. 2018).

Acute viral infection of calves with bovine coronavirus resulted in a rise in serum levels of haptoglobin, IFN-γ, IL-2, and IL-6, as well as a rapid decrease in vitamin D and E levels (Nonnecke et al. 2014). Vitamin D prevents rhinovirus replication in bronchial epithelial cells by activating the innate IFN pathway, which is thought to be the case (Telcian et al. 2017). The ORF6 is a SARS-CoV accessory protein that inhibits the function of several karyopherin-dependent host transcription factors, including vitamin D receptors, which are essential for the regulation of host immune responses and the initiation of antiviral responses (Sims et al. 2013).

In critically ill patients, especially those with sepsis and pneumonia, vitamin D deficiency has been linked to increased illness severity, multiple organ dysfunctions, and mortality

(Schöttker et al. 2014). Supplemental vitamin D consumption lowers overall mortality risk and increases patients' overall health (Mata-Granados et al. 2010). The promotion of oxidative stress by high-dose vitamin D_3 can improve clinical outcomes in critically ill ventilated adults (Han et al. 2018). Low vitamin D and A levels were found to be linked to more ICU admissions and the use of mechanical ventilation (Hurwitz et al. 2017). Vitamin D combined with an inactivated influenza virus has been shown to boost both antibody and mucosal immunity against the viral hemagglutinin (Daynes et al. 1995).

Individual vitamin D levels are at their lowest in the winter and at their highest in the summer. This seasonal variation is strikingly similar to the well-known seasonal fluctuations in respiratory viral infections and sepsis (Prietl et al. 2013). Seasonal variations in human immune response and vitamin D levels have been proposed as possible contributors to respiratory infection seasonal trends (Grant and Giovannucci, 2009). During the 1918-1919 influenza pandemic, there were significant negative associations between solar ultraviolet-B doses and population mean vitamin D status and case fatality and pneumonia rates (Grant and Giovannucci, 2009). From 2013 to 2016, vitamin D supplementation was linked to a lower risk of RTI and hospitalisation in infants born in Wuhan, China (Hong et al. 2020).

The Effect of Vitamin E in the Immune System

Vitamin E increases IL-2 content, NK cell activity, T cell-mediated functions, and lymphocyte proliferation while maintaining epithelial membrane integrity. Vitamin E also activates T cells, encourages Th1 proliferation, and inhibits the Th2 response (Lee and Han, 2018). In animals infected with the influenza virus, vitamin E supplementation induces increased IL-2 and IFN-γ development as well as a lower lung virus titer (Han et al. 2000). In mice infected with Coxsackieviruses-B3, vitamin E deficiency significantly increases viral pathogenicity and heart damage (Beck et al. 1994). After influenza infections, vitamin E administration increased lymphocyte proliferation as well as IL-2 and IFN-γ development in healthy people and elderly mice (Han et al. 2000). In broilers vaccinated with the contagious bronchitis virus, a small amount of vitamin E supplementation controls the cellular free radical-antioxidant balance, improves antibody response, and stimulates immune cells (Leshchinsky and Klasing, 2001). The anti-inflammatory cytokine IL-10 levels and vitamin E metabolism have been linked in H1N1-infected mice (Chandler et al. 2016).

Vitamin E and selenium have a powerful inhibitory effect on viral replication and mutation. RNA viruses will transform into more virulent strains when these micronutrients are deficient in the diet (Beck et al. 1995). Mice lacking vitamin E did not have an adequate immune response to HSV-1 infection (Sheridan and Beck, 2008). A few days after infection with the influenza virus, mice showed a substantial rise in lung and serum vitamin E levels (Mileva et al. 2002). Vitamin E plasma levels were found to be significantly lower in critically ill patients admitted to an ICU with ARDS (Richard et al. 1990). Vitamin E and C supplementation in critically ill patients decreased the incidence of ARDS and pneumonia, as well as the amount of time spent in the ICU (Nathens et al. 2002).

COVID-19, micronutrients, and the immune system

Individuals over 60 years of age, as well as those with chronic diseases such as hypertension, diabetes, and cardiovascular or respiratory diseases, are the most susceptible classes to COVID-19's severe-critical complications (World Health Organization, 2020; Yang et al. 2020). Despite the fact that only 36% of COVID-19 patients in Italy were over 70 years old, this category of patients accounted for over 80% of deaths (Statista, 2020). Furthermore, at the time of entry,

elderly adults are more vulnerable to extreme COVID-1 (Shi et al. 2020).

Nutritional and pharmacologic therapies may improve immune function in the elderly (Custodero et al. 2018). Every part of the immune system changes with age, resulting in increased morbidity and mortality from infectious diseases (Albright and Albright, 2003; De Martinis et al. 2005). Manipulation of cytokine synthesis, improvements in immune cell metabolic pathways, and immune system rejuvenation aimed at reactivating the generation of new lymphocytes may all help the immune system function better in the elderly (Nikolich-Zugich, 2018). Micronutrient therapies have shown promise in improving infection-related morbidity and mortality in the elderly, as well as targeting immune system impairments (Maijó et al. 2014; Bendich, 1993).

Micronutrient shortages affect approximately 2 billion people worldwide and play a significant role in the global burden of disease (Allen et al. 2006). Zinc deficiency, for example, affects about 30% of the world's population, ranging from 4% to 73 percent in different countries, and is linked to about 16% of lower RTIs (World Health Organization, 2013). Micronutrient deficiencies weaken the immune system and are a frequent cause of immunodeficiency in developing countries (Katona and Matone-Apte, 2008). While micronutrient deficiencies are a major public health concern in developing countries, they also affect about 30% of the population in developed countries (Samaras et al. 2013). Insufficient and/or adequate intakes in combination with impaired absorption due to infection, inflammation, or chronic diseases may cause silent epidemics of micronutrient deficiencies (Katona and Katona-Apte, 2008; Bordoni et al. 2017). In Europe, the United States, and Canada, approximately 35% of people over the age of 50 have an apparent deficiency in one or more important micronutrients (Chandra, 2002). In addition to a lack of micronutrient intake, the capacity to develop endogenous antioxidants is lost in the elderly (Karaousenea et al. 2011). In comparison to many other European countries, Italy, Spain, and France have had the highest COVID-19 death tolls, and the elderly in these countries have the highest prevalence of vitamin D deficiency (Manios et al. 2018; Kehoe et al. 2019). In Italy, approximately 60% of people who died from COVID-19 lived in the Lombardy region. During the cold seasons, up to 90% of the population in this area has vitamin D deficiency/insufficiency (Ferrari et al. 2019). Hospitalizations and respiratory illnesses are common in the Lombardy region, Italy's most polluted region (Carugno et al. 2016). Increased ozone levels in the atmosphere absorb ultraviolet B radiation, resulting in vitamin D deficiency (Wacker and Holick, 2013). In the United States, low vitamin D status affects more than 40% of the population (Forrest and Stuhldreher, 2011). Micronutrients play an important role in the prevention and treatment of viral infections, according to many clinical reports (Osuna-Padilla et al. 2020; Feyaerts and Luyten, 2020). Micronutrient deficiencies, such as zinc and vitamins B2, B6, B12, C, and D, were found to be widespread among Ecuadorian seniors, weakening their immune systems and increasing their risk of viral RTIs (Hamer et al. 2009). Zinc and vitamin A supplementation significantly reduced the incidence of pneumonia in children (Bhandari et al. 2002), and oral zinc supplementation can shorten the period of respiratory infection symptoms (Science et al. 2012). According to the UN's Food and Agriculture Organization, diet and antiviral drugs are equally effective in treating HIV infection, and daily micronutrient intake is critical for promoting the immune response and preserving good health in both infected and uninfected people (Thompson and Amoroso, 2011). During the Ebola virus epidemic in western Africa, early vitamin A administration decreased the mortality rate of Ebola patients (Aluisio et al. 2019).

Micronutrient supplementation increased the number of T cells and lymphocytes, improved

lymphocyte response to mitogen, increased IL-2 levels and NK cell activity, improved influenza virus vaccine response, and decreased the length of viral infections in elderly people (Maggini et al. 2018; Schmoranzer et al. 2009). Antibiotics, for example, have been linked to micronutrient depletion, including iron and vitamins A, B, and D (Karadima et al., 2016). In elderly adults, a combination of micronutrient supplementation can reduce antibiotic use while also causing a stronger post-vaccination immune response (Chandra, 2002). Surprisingly, some countries with higher COVID-19 morbidity and mortality, such as Italy and Spain, have higher antibiotic intake than other European countries (Malo et al. 2014; Barchitta et al. 2019). Antibiotic-treated mice are unable to induce cytokine release in the lungs and enhance defensive T-cell responses after infection with influenza (Ichinohe et al. 2011).

Infection by a virus whose virulence has changed as a result of replicating in a nutritionally poor host, causing a non-virulent virus to become a pathogen due to changes in its genome (Beck and Matthews, 2000). Increased mutation rates in micronutrient-deprived populations can facilitate the steady emergence of new strains of pathogen RNA viruses with new pathogenic properties, such as CoV (Beck et al. 1995). Micronutrient deficiency can increase the chances of viral mutations by making the host cell more receptive to viral replication and increasing oxidative damage to the RNA genome (Broome et al. 2019). The appearance of virulent mutated RNA viruses in the population with micronutrient deficiency could explain the outbreak of peripheral neuropathy in Cuba and the easier transmission of HIV in Africa (Broome et al. 2019; Mäs Lago et al. 1995; Audain et al. 2015).

2. CONCLUSIONS

The impact of micronutrients on host immune responses in pandemic viral infections has received little clinical attention. When considering the use of micronutrients in the prevention and/or treatment of infectious diseases like COVID-19, both the prevalence of micronutrient deficiency among affected individuals and the effect of micronutrient supplementation on the overall disease outcome may be of great importance. Furthermore, available evidence strongly suggests that the combination of unpredictable emergence of novel viral pathogens, reduced host immunity, and micronutrient deficiency presents a two-fold threat to human health in the near future. Further investigating the role of micronutrients and their replacement on immune system function, therefore, could present a highly cost-efficient and uncomplicated measure with promising long-term benefits on potential viral outbreaks. The production of new vaccines and drugs that target pathogens that cause currently prevalent diseases is often a costly and dangerous process with limited effectiveness due to their selective applications. Furthermore, due to their high costs, the use of novel vaccines and drugs is generally restricted.

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