Nutritional perspectives for the prevention and mitigation of COVID-19

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Worldwide, there is an array of clinical trials under way to evaluate treatment options against coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2. Concurrently, several nutritional therapies and alternative supportive treatments are also being used and tested to reduce the mortality associated with acute respiratory distress in patients with COVID-19. In the context of COVID-19, improved nutrition that includes micronutrient supplementation to augment the immune system has been recognized as a viable approach to both prevent and alleviate the severity of the infection. The potential role of micronutrients as immune-boosting agents is particularly relevant for low- and middle-income countries, which already have an existing high burden of undernutrition and micronutrient deficiencies. A systematic literature review was performed to identify nutritional interventions that might prevent or aid in the recovery from COVID-19. The PubMed, ScienceDirect, Cochrane, Scopus, Web of Science, and Google Scholar databases were searched electronically from February to April 2020. All abstracts and full-text articles were examined for their relevance to this review. The information gathered was collated under various categories. Deficiencies of micronutrients, especially vitamins A, B complex, C, and D, zinc, iron, and selenium, are common among vulnerable populations in general and among COVID-19 patients in particular and could plausibly increase the risk of mortality. Judicious use of need-based micronutrient supplementation, alongside existing micronutrient fortification programs, is warranted in the current global pandemic, especially in low- and middle-income economies.

INTRODUCTION

The recent coronavirus disease 2019 (COVID-19) outbreak, caused by the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), originated in China before becoming a global pandemic. As of June 23, 2020, more than 8,99 million cases of COVID-19 and more than 469 587 COVID-19–associated deaths were reported worldwide. The rate of new infections seemed to outpace both the scale of preparedness and the public health response, especially in resource-constrained economies.[1] The COVID-19 containment strategy implemented by countries like South Korea,

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Taiwan, and Singapore offers an example for the rest of the world[2,3] but may be challenging for many countries.

The possible emergence of new strains of SARS viruses that cause flu-like disease, along with the measures needed to prevent the spread of such strains, has been reported in a number of retrospective studies.[4,5] Despite these alerts, the world was unprepared for the COVID-19 pandemic. While current research is focused on the development of a vaccine and effective therapeutic agents, many scientists have also emphasized the importance of boosting the immune system through various nutritional interventions.[6] Given the potential usefulness of Bacillus Calmette-Guérin (BCG) vaccine and the worldwide clinical trials initiated to counter the COVID-19 pandemic, BCG vaccination has been suggested as a strategy to trigger immunity in patients with COVID-19.[7,8] Moreover, the use of chloroquine and hydroxychloroquine as chemoprophylaxis in COVID-19 has been extensively debated in the literature, although evidence is insufficient to recommend the routine use of any drug. Agrawal et al[9] have comprehensively summarized the various ongoing clinical trials for chemoprophylaxis in COVID-19, eg, NCT04304053, NCT04318444, NCT04251871, NCT04303507, NCT04321174, NCT04312243, and NCT04308668. Yao et al,[10] in an in vitro study, have validated antiviral activity elicited by these drugs against SARS-CoV-2. Similarly, Singh et al[11] proposed chloroquine and hydroxychloroquine to be potentially beneficial in the context of low-income and lower-middle-income countries, especially in the absence of any effective treatment option against COVID-19.

In their recent review, Zhang and Liu[12] examined a variety of treatment options for novel coronavirus infection, placing increased focus on the role of micronutrients as supportive and complementary components of treatment regimens. In a very recent report, Grant et al[13] recommended vitamin D_3 intake at 10 000 IU/d for a few weeks, followed by 5000 IU/d until the serum 25(OH)D concentration reaches 100 to 150 nmol/L, as a preventive strategy against COVID-19 among people at risk. There is existing evidence for the potential role of improved nutrition to augment the immune system. Vitamins A, B complex, C, D, and E and many trace elements, such as iron, zinc, selenium, magnesium, and copper, have been shown to elicit immune-boosting properties,[14–16] and thus deficiencies of these micronutrients could be detrimental to immune function in viral infections.[17] Likewise, supplementing diets with micronutrients has been reported as a way to improve or optimize immune function against viral infections; therefore, public health officials must consider nutritional interventions as a means to combat emerging viral infections.[6,16]

The scientific community, the various governments worldwide, and the global pharmaceutical industry, along with social and healthcare foundations and non-governmental organizations, have endeavored to find a possible solution for COVID-19, whether a medication or a safe vaccine, yet thus far their efforts have not borne fruit. The aim of this review is to highlight the potential role of nutrition in preventing and reducing the severity of COVID-19, with a focus on the role of various micronutrients.

NUTRITION AND IMMUNE DEFENSE

Micronutrients are dietary components that may contribute substantially to a robust immune system.[18] Essential micronutrients like vitamins A, D, E, C, B_6, B_{12}, and folate and trace elements such as iron, zinc, and selenium, available in a variety of fresh animal- and plant-based foods, aid the body's ability to fight infections.[19,20] Health and survival are increasingly dependent on the functioning of the immune system. Mechanistically, a rapid innate immune response occurs through phagocytes when a pathogen assaults the living system, but an adaptive immune response more specifically identifies the invading pathogen. Basically, these immune responses are controlled and coordinated by T cells, which recognize the antigens and are classified as cytotoxic T cells. Cytotoxic T cells kill infected, damaged cells and the T helper cells Th1 and Th2. These cells are involved in antiviral and cellular immune responses (Figure 1) as well as humoral and antiparasitic responses.[21] A strong immune system ensures host defense against pathogens and neoplastic cells, and balanced nutrition augments the immune system to provide optimal defense against infectious agents. Childs et al[18] explained the critical role of the immune system as well as the defense mechanisms involved in protecting the body from invading agents, particularly in the presence of appropriate nutrition. Thevarajan et al[22] reported their findings on the kinetics of the immune response to COVID-19, describing higher concentrations of follicular helper T cells, antibody-secreting cells, activated $CD4^+$ and $CD8^+$ T cells, and immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, all of which were observed to bind to coronavirus SARS-CoV-2. The results thus validate the role of a strong immune defense in patients COVID-19.

An optimally functioning immune system is closely linked to an adequate supply of micronutrients to the body, while severe deficiencies of these micronutrients lead to weakened immune responses and vulnerability to infections. Vitamins A, C, E, and B complex, along with folic acid, zinc, selenium, iron, and copper, all play important roles in boosting the immune system of the

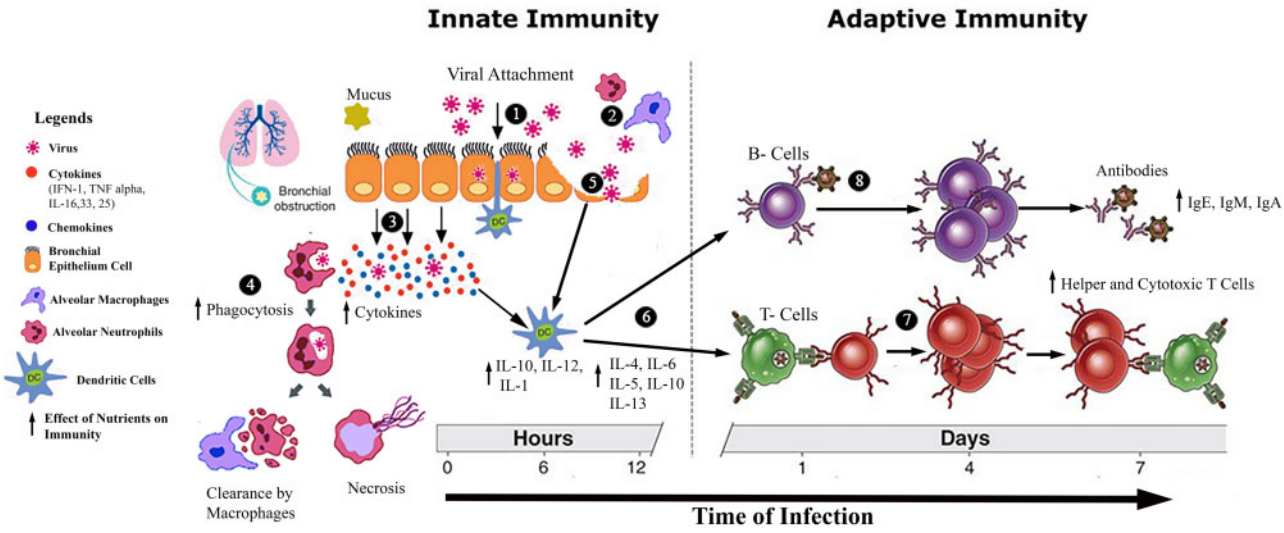
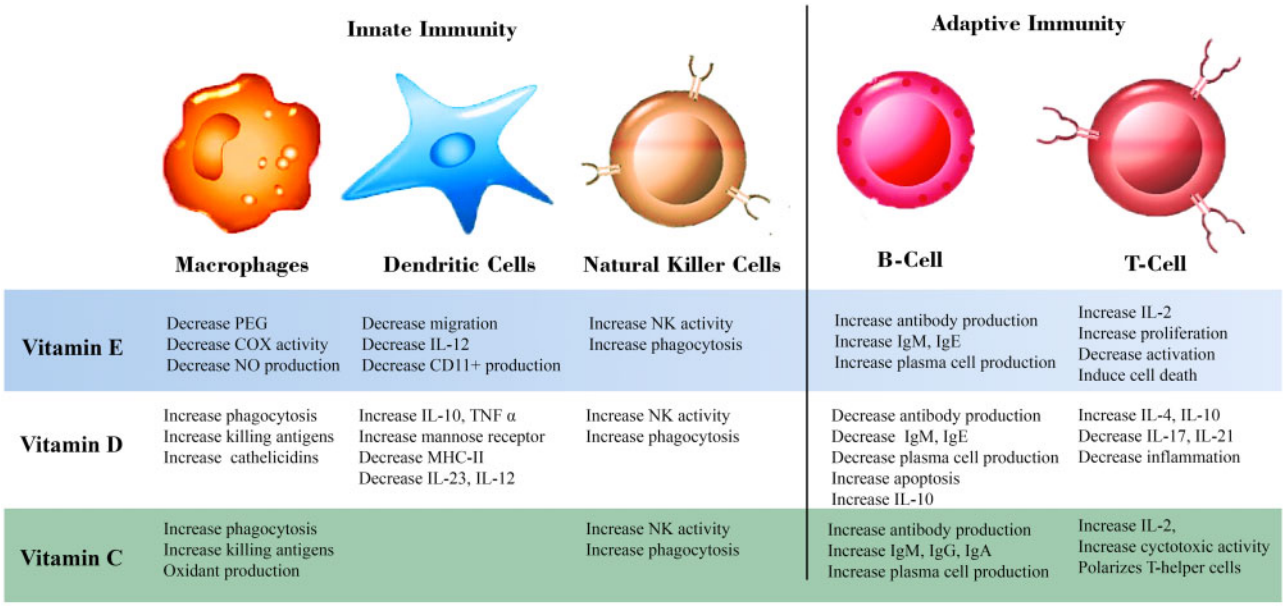


Figure 1 **Effect of nutrients on the mechanisms of innate and adaptive immunity.** (1) Virus attaches to bronchial epithelial cell layer. (2) Alveolar neutrophils and macrophages attack the virus. (3) Infected bronchial epithelial cells release cytokines (IFN-1, TNF-α, IL-16, IL-33, IL-25) to alert the neighboring cells and activate the innate immune cells, ie, neutrophils, natural killer cells, dendritic cells, and macrophages. (4) Alveolar neutrophils and macrophages engulf the virus for phagocytosis. (5) After multiple viral replications, epithelial cells burst and release new daughter viral copies, which results in activation of the dendritic cells. (6) Dendritic cells activate T-lymphocyte helper cells and B-lymphocyte cells. (7) T-helper 12 cells activate the cytotoxic T-lymphocyte cells. (8) B lymphocytes divide into memory and plasma cells, and plasma cells produce antibodies against the virus. *Abbreviations*: IFN, interferon; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.



	Macrophages	Dendritic Cells	Natural Killer Cells	B-Cell	T-Cell
Vitamin E	Decrease PEG Decrease COX activity Decrease NO production	Decrease migration Decrease IL-12 Decrease CD11+ production	Increase NK activity Increase phagocytosis	Increase antibody production Increase IgM, IgE Increase plasma cell production	Increase IL-2 Increase proliferation Decrease activation Induce cell death
Vitamin D	Increase phagocytosis Increase killing antigens Increase cathelicidins	Increase IL-10, TNF α Increase mannose receptor Decrease MHC-II Decrease IL-23, IL-12	Increase NK activity Increase phagocytosis	Decrease antibody production Decrease IgM, IgE Decrease plasma cell production Increase apoptosis Increase IL-10	Increase IL-4, IL-10 Decrease IL-17, IL-21 Decrease inflammation
Vitamin C	Increase phagocytosis Increase killing antigens Oxidant production		Increase NK activity Increase phagocytosis	Increase antibody production Increase IgM, IgG, IgA Increase plasma cell production	Increase IL-2, Increase cyctotoxic activity Polarizes T-helper cells

Figure 2 **Role of vitamins E, D, and C in innate and adaptive immunity.** *Abbreviations*: COX, cyclooxygenase; Ig, immunoglobulin; IL, interleukin; MHC, macrophage histocompatibility complex; NK, natural killer; NO, nitric oxide; PEG, polyethylene glycol; TNF, tumor necrosis factor.

population.[16,23] Several studies have confirmed that micronutrient deficiencies are associated with a weakened immune system that predisposes individuals to increased vulnerability to infections.[24,25] Gombart et al[16] demonstrated the critical role of essential vitamins and trace elements in boosting the immune system. They emphasized that micronutrients such as vitamins A, B_6, B_{12}, C, D, and E, (Figure 2) in addition to iron, selenium, and zinc (Table 1),[26–36] might work synergistically to help immune cells function appropriately. Recent research also supports a role of certain minerals and vitamins as adjunct therapeutic agents to treat microbiological infections as well as immunological and nonimmunological chronic diseases (Table 2).[37–45]

Table 1 **Role of selected minerals in innate and adaptive immunity**

Mineral	Role in innate immunity	Role in adaptive immunity	References
Folate	Supports innate immunity Increases production of NK cells	Improves cell-mediated immunity Increases expression of antigen-presenting cells Increases antibody-mediated immune response Increases antibody production Assists T-helper cell–mediated immune response	Haryanto et al (2015)[27]; McClung & Peterson (2010)[28]; Saeed et al (2016)[29]
Iron	Regulates production of cytokines Improves phagocytosis	Increases T-cell proliferationImproves cytotoxic T-cell function	Haryanto et al (2015)[27]; Weiss (2002)[30]; Xu et al (2016)[31]
Zinc	Protects cells from oxidants Helps maintain skin and mucosal cell membrane integrity	Promotes release of cytokines to mediate adaptive immunity Assists T-helper 1 cells Activates T cells	Saeed et al (2016)[29]; Wintergerst et al (2006)[32]; Maares & Haase (2016)[33]
Copper	Aids neutrophil phagocytosis Increases IL-2 production	Increases T-cell proliferation Increases antibody production Improves cellular immunity by activating cytokines and chemokines	McClung & Peterson (2010)[28]; Maggini et al (2007)[34]
Selenium	Helps selenium-dependent enzymes (sialoproteins) to resist oxidant production Supports function of NK cells and leukocytes (macrophages, neutrophils, monocytes)	Increases antibody production Promotes T-cell proliferation and differentiation	Diwakar et al (2016)[26]; Haryanto et al (2015)[27]; Avery & Hoffmann (2018)[35]; Ivory et al (2017)[36]

More recently, Calder et al[6] reviewed the association between optimal nutrition and the immune system in providing better protection against viral infections. They suggested that essential micronutrients and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic have the capacity to boost immunity against viral infections. Similarly, Chaturvedi et al[46] described the complex relationship between trace elements and viral infections, highlighting the immunomodulatory properties and antiviral activities of certain micronutrients such as iron, zinc, selenium, and copper. Apart from functioning as antioxidants, these trace elements were shown to inhibit viral replication in host cells.

Sufficient literature suggests that vitamin and mineral supplementation in conjunction with a balanced and diversified diet can be used to meet the Recommended Dietary Allowance (RDA) for essential micronutrients. Further studies have proposed supplementation with vitamin C[47,48] beyond the RDA, ie, above 0.2 g/d, as a strategy to reduce both upper and lower respiratory tract infections among older patients. In a recent report, Grant et al[13] speculated that doses of vitamin D_3 above 10 000 IU/d may be useful for treatment of patientswith COVID-19.

IMMUNE-BOOSTING ROLE OF VITAMINS

Vitamin A

Vitamin A is capable of defending the body against a variety of infections, primarily by regulating the proliferation and differentiation of immune cells. Supplementation with preformed vitamin A has been suggested to downregulate the secretion of proinflammatory cytokines like tumor necrosis factor α and interleukin 6 in response to infections.[49,50] The anti-infective role of vitamin A has been described in a number of studies that suggest all-*trans* retinoic acid to function via the nuclear retinoid acid receptor.[51,52] Retinoic acid has also been shown to exhibit immune-regulating properties, notably in humoral defense in viral infections.[53]

Vitamin A is essential for maintaining normal bodily functions, including defense against infections. An inadequate intake of vitamin A–rich food results in vitamin A deficiency, thus necessitating supplementation. In chickens infected with infectious bronchitis virus, a type of coronavirus, there was a marked difference in plasma retinol, retinol-binding protein, albumin, and transthyretin levels between those fed vitamin A–adequate diets and those fed marginally deficient diets.[54,55] The protective role of vitamin A supplementation against a variety of infections such as malaria, lung infections, and HIV has been widely reported in the literature.[49] In addition, the compromised efficacy of inactivated bovine coronavirus vaccine was attributed to vitamin A deficiency in infected calves.[56] Evidence further suggests that vitamin A supplementation in children reduces deaths associated with diarrheal and respiratory diseases.[57,58] Supplementation with preformed retinoids at a dose 100 times higher than the RDA, ie, up to 500 000 IU, may cause

Table 2 **Vitamin and mineral adjunctive therapies in viral, bacterial, and oncologic diseases**

Disease	Study design	Study year	Therapy	Findings	Reference
Glioma/ glioblastoma	Phase 2 interventional (clinical trial)	2023	Radiation, temozolomide, vitamin C	Ongoing; ending in 2023	Clinical trial NCT02344355[37]
COVID-19	Randomized, open-label phase 4 trial	2020	Hydroxychloroquine, azithromycin, zinc sulfate, doxycycline	Ongoing; ending in 2020	Clinical trial NCT04370782[38]
Leukemia	Phase 2 clinical trial	2020	Azacitidine, vitamin C	Ongoing; ending in 2020	Clinical trial NCT03397173[39]
Sepsis	–	2019	Vitamin D, standard antibiotic therapy	Vitamin D supplementation improved sepsis score and decreased levels of high-sensitivity C-reactive protein	Hagag et al (2019)[40]
Severe pneumonia	Retrospective cohort study	2018	Vitamin C, hydrocortisone, thiamine	Compared with control group, adjunctive therapy group had lower hospital mortality and higher rate of recovery from severe pneumonia	Kim et al (2018)[41]
Atopic dermatitis	Randomized, double-blind, placebo-controlled clinical trial	2018	Vitamin D_3 (5000 IU/d), baseline therapy (topical steroid, soap substitute, and emollient)	Treatment group had reduced atopic dermatitis severity score	Sánchez-Armendáriz et al (2018)[42]
Hepatitis C	Controlled randomized clinical trial	2017	Vitamin C (orange juice), pegylated interferon combined with ribavirin	Levels of liver enzyme aspartate aminotransferase decreased in patients who had high levels before the study	Gonçalves et al (2017)[43]
Ehrlich ascites carcinoma	Rodent study	2017	Selenium, cyclophosphamide	Selenium improved chemotherapeutic effect of cyclophosphamide	Bhattacharjee et al (2017)[44]
Sensorineural hearing loss	Nonblinded, noncontrolled study	2015	Vitamin A (26 000 IU), vitamin C (200 mg), vitamin E (200 IU), selenium (50 μg), methylprednisolone (1 mg/kg), trimetazidine dihydrochloride (20 mg, 3 times daily)	Treatment with vitamins A, C, and E and selenium was effective in restoring function after sudden idiopathic sensorineural hearing loss	Kaya et al (2015)[45]

hypervitaminosis in adults, while an intake of more than 10 000 IU of preformed vitamin A in first 60 days after conception may cause congenital abnormalities in infants.[59] In the current COVID-19 pandemic, researchers have suggested vitamin A supplementation as part of a tailored multivitamin solution to satisfy the RDA as a promising option to combat COVID-19 in noncritical patients.[12,60]

B vitamins

As cofactors to enzymes, B vitamins are central to the formation of, and the energy metabolism in, certain organic molecules. Multiple studies have suggested a significant role of B vitamins, eg, folic acid, B_{12}, and $B_{6,}$ in the function of the immune system. These vitamins have the ability to operate as one-carbon donors in nucleotide synthesis, and one-carbon metabolism is involved primarily in complex biochemical pathways that are responsible for donating and regenerating one-carbon units. Natural killer cells and cytotoxic $CD8^+$ lymphocytes are also influenced by these vitamins; hence, a balance of B_{12} and folate must be maintained for immune responses.[61,62] Vitamin B_6 in the form of pyridoxal phosphate is particularly important, playing an active role as a cofactor in at least 160 catalytic pathways, with some metabolites shown to exhibit immune-modulating properties.[63,64]

Scientific reports validate the significant role of vitamin B in normal function of the immune system, including the direct regulatory effects of vitamin B on immune response.[65,66] Among its myriad immune-promoting features, vitamin B_3 has been shown to inhibit neutrophil infiltration in the lungs, indicating an anti-inflammatory effect during ventilator-associated lung injury.[67] Zhang and Liu[12] reported that deficiency of B vitamins negatively influences the immune system and suggested that supplementation with B vitamins

provides defense against viral infections. Deficiency of B vitamins has been shown to weaken the host immune response; hence, B vitamins may have a role in enhancing the immune system of COVID-19 patients.

Vitamin C

A plethora of scientific literature supports the role of vitamin C as an immune booster. Besides exerting antioxidant activity, supplementation with ascorbic acid significantly affects epigenetic regulation and cell signaling.[19] The potential role of vitamin C as an antiviral agent against coronavirus has been observed in animal models by Atherton et al.[68] Carr and Maggini[14] outlined several immune-supporting features of vitamin C, including involvement in phagocytosis, antibody production, growth and functioning of immune cells, and transitioning of leukocytes at infection sites. There is also evidence for the role of vitamin C as a weak antihistamine agent to reduce symptoms of stuffy nose and swollen sinuses.[69]

An ameliorative role of vitamin C supplementation in upper respiratory tract infections has been well described in numerous studies.[47,70,71] Vitamin C has shown potential to restore the damage caused by impaired phagocytosis and respiratory burst.[14] It is also proven to reduce the duration and severity of the common cold in adults and children.[47] High-dose intravenous vitamin C, administered at 50 to 200 mg/kg/d as treatment in patients with virus-induced acute respiratory distress syndrome on extracorporeal membrane oxygenation, was reported by Fowler et al.[72] Previous studies have shown that vitamin C supplementation is associated with reduced incidence of pneumonia and lower respiratory tract infections and also offers protection against coronavirus infection by boosting the immune system.[73,74] Zhang and Liu[12] suggested supplementation with vitamin C to reduce the incidence of severe lower respiratory tract infections, such as pneumonia, and as a treatment option for COVID-19. The study by Hemilä[73] considers the findings of 3 controlled trials in humans, wherein vitamin C supplementation at doses between 0.05 and 2 g/d were reported to result in significantly fewer cases of pneumonia. In general, no adverse effects of large doses of intravenously or orally administrated vitamin C have been documented, except in patients with glucose 6-phosphate deficiency, renal insufficiency, or renal failure.[75,76]

Vitamin D

Vitamin D receptors are present on monocytes, macrophages, T- and B-lymphocytes, and other immune cells. The 25(OH)D-1α-hydroxylase available on these cells converts 25-hydroxyvitamin D [25(OH)D] to its active form, 1,25-dihydroxyvitamin D.[77] Vitamin D status is correlated with several autoimmune and inflammatory diseases. Evidence of this association could be demonstrated by the north-south gradient observed with respect to the prevalence of diabetes mellitus type I, inflammatory bowel disease, and multiple sclerosis, suggesting reduced intracutaneous synthesis of vitamin D at higher latitudes.[78,79] Vitamin D has the ability to foster differentiation of monocytes to macrophages, which destroy invading agents. The formation of special antimicrobial proteins is regulated by certain vitamin D metabolites, and these antimicrobial proteins play a substantial role in combating infections, including lung infections, by destroying pathogens.[80,81]

Respiratory tract infections can severely exacerbate chronic diseases, leading to increased risk of death. Vitamin D can act through several mechanisms to decrease the risk of respiratory infections, including pneumonia.[13] These findings are supported by the findings of Zhou et al,[82] whose meta-analysis suggests that vitamin D deficiency is associated with a heightened risk of pneumonia. A meta-analysis of individual participant data showed that vitamin D supplementation is safe and protective against acute respiratory tract infection and is most beneficial in patients with vitamin D deficiency.[15] Caccialanza et al[60] recently proposed supplementation with 25 000 IU or 50 000 IU of cholecalciferol per week to noncritical COVID-19 patients with serum 25-hydroxycholecalciferol levels of 20 to 30 ng/mL or $\leq$ 20 ng/mL, respectively. Likewise, Grant et al[13] suggested administrating 10 000 IU of vitamin D_3 per day to prevent infection among individuals at risk of influenza or COVID-19. Vitamin D_3 supplementation also seems to decrease mortality in elderly people living independently or in institutional care.[83] Recent data from countries like China have demonstrated a high number of COVID-19–infected individuals to have low serum 25(OH)D levels.[12] Likewise, fortification of foods with vitamin D is lacking in these countries, likely leading to vitamin D deficiency.[84,85] A correlation between increased incidence of COVID-19 and insufficient vitamin D concentrations in patients was further supported by Zhang and Liu,[12] who confirmed that middle-aged to elderly people recently affected by COVID-19 in China had low vitamin D levels. However, Zisi et al[86] has highlighted the need to validate whether vitamin D supplementation is beneficial for COVID-19 patients, as conflicting results were noted in some studies, while Grant et al[13] suggested vitamin D supplementation as a therapeutic option for the treatment of COVID-19.

Vitamin E

As a potential antioxidant, vitamin E has the capacity to protect cells and their functional components from

injury caused by the release of reactive oxygen species that occurs during immune reactions to invading pathogens in respiratory infections.[87] Vitamin E is involved in multiple aspects of the immune response, including phagocytosis, the production of antibodies, and T-cell proliferation. The role of vitamin E supplementation in enhancing T-cell function is well documented in the literature.[88] Vitamin E has a direct effect on T cells.[89,90] Han et al[91] confirmed that vitamin E exerts gene transcription–mediated immune-modulating effects. Vitamin E deficiency leads to a dampened immune response, though deficiency is rare in humans. Kim et al[92] recently used disease-canceling technology to investigate the role of vitamin E in attenuating coronavirus-induced patterns of gene expression. The study reported vitamin E as a top hit compound, alongside ruxolitinib and glutamine, to induce gene expression signals counteracting disease-associated signals. Double-blind, large population studies suggest a few side effects of vitamin E oral supplementation at a dose of 3200 mg/d.[93]

TRACE MINERALS FOR A WELL-FUNCTIONING IMMUNE SYSTEM

Trace minerals are an essential component of the diet. Their regulatory effects on immune function have been well defined, and inadequate levels of trace elements have been reported to alter immune competence in humans.[94,95] Prolonged dietary deficiencies of trace minerals may result in impaired immune function by influencing one or more components of the immune system.[96] Although the specific functions of minerals in protecting or boosting human immunity are not well understood, several trace elements such as zinc, magnesium, iron, copper, selenium, and manganese have gained wide recognition for their roles in maintaining optimal health.

Zinc

Zinc, as a cofactor, is an integral component of more than 300 enzymes that exert secondary effects on the human immune system.[97] Effects of zinc on the immune system are multifaceted. For example, in vivo studies on zinc deficiency have unveiled weaker immunological responses, as evidenced by reduced recruitment of neutrophils and decreased neutrophil chemotaxis, which might result in impaired function of natural killer cells, poor phagocytic activity by macrophages and neutrophils, and rapid production of reactive oxygen species, ie, oxidative burst.[98] The impact of zinc on immune mediators like enzymes, cytokines, and thymic peptides has also been reported, suggesting that recommended dietary intake or supplementation of zinc is essential to prevent functional loss.[99]

Zinc deficiency in the elderly can lead to decreased or diminished T-cell response, reduced natural killer cell activity, and depressed thymic hormone levels, thus creating substantial risk for respiratory infections and their associated morbidity and mortality.[99–102] Zinc supplementation has also been suggested to reduce the incidence of lower respiratory tract infections in zinc-deficient children,[103,104] and zinc administration within 24 hours of the onset of symptoms reduces the duration of common cold symptoms.[105] Zinc at doses of more than 75 mg/d has been suggested to have promising antiviral effects against common cold viruses, including influenza viruses, with significant reductions in the duration of the common cold reported.[106] Mild adverse effects of zinc supplementation have been reported with dosages above 200 mg/d[107,108]; hence, relatively lower dosages may also reduce the severity of COVID-19. Increasing the intracellular levels of zinc with zinc ionophores can effectively impair the replication of viral RNA. Studies have illustrated the effectiveness of zinc combined with pyrithione at lower concentrations, ie, 2μM Zn^{2+} and 2μM pyrithione, in inhibiting SARS coronavirus.[109] A recent report by Zhang and Liu[12] provides support for the immune-promoting properties of zinc, suggesting that zinc supplementation can ameliorate COVID-19–induced diarrhea and respiratory symptoms, ie, cough, sore throat, and shortness of breath. The synergistic effect of oral zinc sulfate together with BCG vaccine has been well described in the literature, providing a promising immunotherapeutic approach in communities increasingly prone to infection with the SARS-CoV-2 virus.[8]

Iron

The substantial role of iron in the immune response has been widely documented in the literature, with iron deficiency shown to lead to impairment of the host immune system. Studies have suggested that iron levels in humans must be carefully controlled to limit the availability of iron to pathogens, since iron regulates the growth and activity of a wide range of microorganisms, including viruses. Even though some information on iron regulation in COVID-19 patients is currently available, Liu et al[110] have suggested limiting the iron supply to COVID-19 patients in order to inhibit viral replication and reduce the risk and severity of infections. Iron overload in the host creates oxidative stress that increases the risk of virus mutation.[111] Mullick et al[112] considered the immune-modulating effect of iron and its deficiency to be a potential risk factor for the

development of recurrent respiratory tract infections, a notion later confirmed by Jayaweera et al.[113]

Adequate iron intake influences the innate immune response of the host by mediating the nuclear factor κB (NF-κB) and interferon γ (IFN-γ) signaling pathways in macrophages. The metal enhances the host's ability to resist intracellular pathogens.[114] Iron deficiency leads to a T-cell–mediated immune response that may be associated with reduced activity of ribonucleotidyl reductase, which in turn regulates DNA synthesis. Iron-binding proteins like transferrin and lactoferrin have been shown to have a high affinity for metal ions. Thus, iron-binding proteins do not merely lower free iron in infections but may also exhibit bactericidal properties.[115] A recent report by Wessling-Resnick[116] suggested the aforementioned mechanism as an innate immune response in humans that controls iron metabolism by limiting the availability of iron in infections. Higher concentrations of free iron are reported in people with protein energy malnutrition. Such concentrations are potentially linked to lower levels of transferrin, suggesting prudent use of oral iron therapy in infected individuals with anemia.[115] In contrast to the recommendation of Liu et al[110] to restrict iron supply in COVID-19 patients, recent updates on the management of anemia in high-risk COVID-19 patients like pregnant women and cancer patients suggest iron replacement therapy as a more promising approach than transfusion to promote erythropoiesis.[117,118] Worsening of anemia concurrent with COVID-19 in hospitalized premenopausal women not in the intensive care unit was reported to necessitate iron replacement therapy as a viable treatment approach to prevent transfusion-associated complications.[117]

Selenium

Selenium, present within selenoproteins in humans, influences cellular function by regulating redox-active proteins, antioxidant activity, and thyroid hormone metabolism.[119] The majority of the 25-member family of selenoproteins function as enzymes to catalyze redox-based reactions. However, some selenoproteins do not exert enzymatic activity; for example, selenoprotein K plays an essential role in the activation and proliferation of immune cells.[120] Selenium, as selenoproteins, supports efficient functioning of both the adaptive and the nonadaptive immune systems.[121,122] Selenium deficiency is characterized by a reduced rate of mitogen-induced lymphocyte proliferation, while leukotriene B4 synthesis, essential in neutrophil chemotaxis, is also impaired. Several studies reported selenium-deficient study participants to have a weakened humoral immune response, as demonstrated by decreased IgG and IgM titers.[26,119,121,122]

Dietary selenium deficiency increases oxidative stress, which in turn increases the virulence of benign or mildly pathogenic viruses (eg, influenza viruses) by genetic mutation and impairs the immune response.[123–125] Selenium also acts as an antioxidant for a group of enzymes that inhibit the production of free radicals and prevent oxidative damage to host cells.[125] Ma et al[126] reported an increased antibody response in chickens immunized with a live bivalent vaccine of Newcastle virus and infectious bronchitis virus administrated in conjunction with selenium and ginseng stem-leaf saponins (Se-GSLS), suggesting that Se-GSLS enhances both the proliferation of lymphocytes and the production of interleukin 4 and IFN-γ. Consistent with the above reports of the antiviral effects of selenium, a recent update on the correlation between selenium status, determined by measurement of selenium concentrations in hair, and the COVID-19 cure rate in a city population showed a significant association between poor selenium status and lower cure rates in COVID-19 patients.[127] Nevertheless, more individual-level data are needed to establish an association between infection severity and selenium status. Selenium supplementation in selenium-deficient patients, particularly those who are elderly, may be an effective option for treating COVID-19 and preventing or reducing its severe outcomes.

OMEGA-3 POLYUNSATURATED FATTY ACIDS AND IMMUNITY

Polyunsaturated fatty acids (PUFAs), like selenoproteins, also exert major effects on both the innate and adaptive immune systems. In addition to their role as a constitutive part of the cell membrane, omega-3 PUFAs and their derivatives act as signaling molecules.[128] Metabolites of omega-3 and omega-6 PUFAs are known as proresolving mediators, which are classified as prostaglandins, protectins, thromboxanes, resolvins, leukotrienes, and maresins. The synthesis of these metabolites is managed by a group of enzymes that include lipoxygenase, cyclooxygenase, and cytochrome P450.[129,130] Omega-3 PUFAs, mainly α-linolenic acid, docosahexaenoic acid, and eicosapentaenoic acid, inhibit the activation of immune cells while also supporting specific immune functions like phagocytosis and neutrophil differentiation. This suggests that omega-3 PUFAs do not repress nonspecific immunity.[128]

Protectin D1, an omega-3 PUFA–derived lipid mediator, has been reported to markedly attenuate replication of influenza virus.[131] Morita et al[131] suggested that protectin D1 levels were inversely related to the pathogenicity of influenza viruses (eg, H5N1). Infected mice

treated with protectin D1 plus peramivir were completely rescued from death due to influenza. In light of these findings on the role of PUFA derivatives in mediating immune function, omega-3 PUFA metabolites like protectin D1 may be useful as supportive dietary therapy for prevention and treatment of flu-like viral infections, including COVID-19.

IMMUNE DEFENSE AND NUTRITIONAL NEEDS OF OLDER ADULTS

Immunosenescence, or the progressive deterioration of the immune response in aging, affects both innate and adaptive immunity in various pathological conditions, resulting not only in increased susceptibility of older adults to infections but also a reduced response to various treatment regimens, including vaccines.[132,133] In 2019, the worldwide population of persons over 65 years of age was 703 million. Of this number, 260 million were from East Asia and South-East Asia, and more than 200 million were from Europe.[134] Undoubtedly, immunocompromised older adults with additional comorbidities constitute a population at high risk of infection and severe morbidity. More drastic outcomes have been observed during the ongoing COVID-19 pandemic: data confirm older adults as the most vulnerable population, with mortality reaching up to an estimated 15%.[135,136]

Older adults, compared with younger populations, are more susceptible to COVID-19–like viral infections and their associated serious outcomes. This increased susceptibility is attributable to aging-associated physiological changes, a weakened immune response, malnutrition, and multimorbidities.[137] Prolonged hospitalization to ensure the stabilization and recovery of COVID-19 patients increases the risk of malnutrition and severe loss of lean body mass and muscle function. Nutritional screening and treatment of malnutrition in older patients is therefore mandated as part of COVID-19 patient care.[138]A recent cross-sectional study from Wuhan, China, reported that 52.7% of the 182 older adult patients with COVID-19 were malnourished, with the mean Mini Nutritional Assessment score being below 17.[139] Advanced age is associated with a high risk of nutritional frailty, characterized by sudden weight loss, loss of lean body mass, and loss of physiological nutritional reserves. Nutritional frailty compromises an individual's ability to meet their nutritional needs and increases their susceptibility to disability.[140] The European Society for Clinical Nutrition and Metabolism[138] proposed several considerations for the nutritional care of older COVID-19 patients: nutritional screening; optimization of nutritional status by dietary counseling; supplementation with essential vitamins and minerals, oral nutritional supplements, and enteral and parenteral nutritional support when nutritional needs are not met; and regular physical activity in quarantine. Adverse clinical outcomes of viral infections have been linked to low intakes of micronutrients. Thus, providing the RDA of vitamins A, D, E, C, B_6, and B_{12} and iron, zinc, selenium, and omega-3 PUFAs to malnourished older adults may help prevent or treat adverse clinical outcomes of COVID-19.

SUGGESTIONS AND RECOMMENDATIONS

With the current emphasis on exploring therapeutic options to treat COVID-19, more than 100 clinical trials are under way to develop a vaccine, design effective drugs, and test novel and repurposed compounds against SARS-CoV-2. However, data from longitudinal and observational studies on the extent of micronutrient deficiencies in COVID-19 patients, along with infection severity scores, are needed. Factors predicted to be associated with high risk of severe COVID-19 include age above 50 years, male gender, smoking, chronic kidney disease, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and cerebrovascular disease. Individuals with these risk factors should be screened for micronutrient deficiencies. Supplementation to achieve adequate serological levels of the deficient nutrients may be provided in accordance with in-practice guidelines. The impact of supplementation should be evaluated relative to reductions in the severity of infection and improvements in the recovery index.

CONCLUSION

The role of optimal nutrition for managing the current COVID-19 pandemic cannot be underestimated. Nutrition has a demonstrable role in the prevention and treatment of moderate to severe respiratory and nonrespiratory infections. Adequate nutrition is even more essential for marginalized communities and in low- and middle-income countries, where deficiencies in key vitamins and minerals expose individuals to greater morbidity and mortality. Low- and middle-income countries should strategize to ensure the population at large has access to optimal nutrition to boost the immune system and should provide specific supplementation for treatment of COVID-19 patients, especially those with severe disease. Older adults represent a high-risk population and may be prioritized to receive care in nursing facilities and to receive specialized nutritional support to improve physical and mental outcomes of the COVID-19 pandemic.

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