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Review

Role of Micronutrients in the Response to SARS-CoV-2 Infection in Pediatric Patients

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Abstract: Nutrition is essential in developing and maintaining a robust immune system and is vital for immune homeostasis. The pediatric population is particularly vulnerable to dietary changes, as their growth and development require a high energy intake. Malnutrition in infants can have immediate and long-lasting effects, increasing the risk of morbidity and mortality. Under and overnutrition can slow down the immune response to infections, which can delay recovery. To effectively defend against SARS-CoV-2 infection and enhance viral clearance, it is essential to maintain a healthy diet that includes sufficient macro and micronutrients. Several studies, most of which have been performed in adults, have shown that vitamins such as C, B12, folate, D, and E, as well as the minerals selenium, copper, iron, zinc, and magnesium, can help reduce the symptoms and duration of an infection. Supplementation with micronutrients has been shown to help with childhood malnutrition and can contribute to a more favorable clinical course of COVID-19. In children with obesity, it is also essential to monitor cardiometabolic and thrombotic risks, based on data from studies in adults. This review analyses the impact of the nutritional status of pediatric patients with SARS-CoV-2 infection, its contribution to clinical severity, and potential therapeutic interventions.

Keywords: malnutrition; obesity; undernutrition; immune response; SARS-CoV-2 infection; micronutrients; pediatric population

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1. Introduction

Malnutrition is defined as deficiencies, excesses, or imbalances in energy and nutrient intake. The term malnutrition encompasses four broad groups: (1) undernutrition, (2) micronutrient-related malnutrition, (3) overweight and obesity, and (4) diet-related noncommunicable diseases [1]. Malnutrition is an umbrella term for all manifestations of poor nutrition, from extreme malnutrition to obesity. Malnutrition can lead to secondary immunodeficiency characterized by physical and chemical barrier disruption, dysfunctional phagocytosis, cell-mediated immunity, an impaired complement system, and unbalanced cytokine production [2]. In infants, these alterations increase the risk of morbidity and mortality. The effects of malnutrition on a child's immunocompetence can persist for a long time, underlining the crucial role of nutritional recovery in restoring immune competence [3,4]. In infants, these alterations increase the risk of morbidity and mortality. The effects of malnutrition on the immunocompetence of a child can persist for a long time, underscoring the crucial role of nutritional recovery in restoring immunological competence [3,4].

The role of micronutrients in immune function has been emphasized; several vitamins, including vitamins A, B6, B12, C, D, E, and folate; and trace elements, including zinc, iron, selenium, magnesium, and copper, play essential and complementary roles in supporting the innate and adaptive immune system [5–7]. Most micronutrients exhibit pleiotropic functions in supporting immune function. The degree of immunocompetence is related to the type of nutrient involved, its interaction with other nutrients, the degree of deficit, the presence of concomitant diseases, and the individual's age.

The manifestations of malnutrition differ between children and adults. In adults, malnutrition is related to unintended weight loss, chronic exhaustion, weak muscles, reduced concentration, and feeling cold all the time, independent of the ambient temperature. In children, malnutrition is related to stunted growth, delayed development, reduced energy or motivation to play, and unusual irritability or anxiousness. In both groups, children and adults lack interest in food and drink, and slow wound healing and recovery from illness are observed [8,9].

The infection of SARS-CoV-2 has affected more than 700 million people worldwide, with an approximate death toll of 1–2% of the population [10]. Children with COVID-19 are often asymptomatic or have mild symptoms, especially younger children. Symptoms can be similar to other respiratory viral infections, including fever, cough, myalgias, sore throat, headache, and malaise [11–13]. Less common symptoms include shortness of breath, gastrointestinal symptoms, neurologic symptoms, or rash [11–13]. Children with underlying medical conditions such as underweight, obese, diabetic, chronic lung disease, neurologic disorders, prematurity, and cardiovascular disease are at increased risk for severe disease [12,13]. Crespo et al. [14], from our group, conducted a cross-sectional study of the immune response in pediatric patients with COVID-19. The results suggest that nutritional status is associated with the effect on the immune response to SARS-CoV-2 infection [15]. In large populations, long-term effects of malnutrition were observed in adult and pediatric patients with severe COVID-19 [16,17].

This review examines the importance of micro- and micronutrient deficiencies in malnourished and obese children and their relationship to the immune response to SARS-CoV-2 infection. Although children are less likely to develop severe COVID-19 following SARS-CoV-2 infection, malnutrition may influence the antiviral response and viral clearance. The role of supplementation and its possible effects on the evolution of SARS-CoV-2 infection are also evaluated.

2. Childhood Malnutrition

The Director General of the World Health Organization (WHO), Tedros Adhanom Ghebreyesus, emphasized at the Nutrition for Growth Summit held in December 2021 that "Malnutrition, in all its forms, is one of the leading causes of death and disease in the world", for which the WHO reinforces its commitment in priority areas such as health and nutrition, highlighting that child malnutrition was the underlying cause of 45% of deaths in children under five years of age [18]. Developing countries face a public health issue due to malnutrition.

Malnutrition is considered a frequent, acquired, and modifiable cause of immunosuppression; infections constitute the most significant possibility of morbidity in malnourished pediatric patients. The association between malnutrition and infection risk has been documented for over 50 years. Multiple investigations have been carried out in this field, and mortality is significantly higher in malnourished children than in healthy children. Insufficient macro and micronutrients caused by economic limitations are some of the factors contributing to this problem in growing infants. The other factors are diseases associated with either undernutrition or overnutrition [16]. Different studies have evaluated the role of malnutrition on the function of the immune system, such as immune cells, tissue homeostasis, the size and function of the thymus and primary lymphoid organs, and the relationship of all these alterations with the response to infectious diseases [19–26].

Figure 1 illustrates the effects of malnutrition on different organs and its relation to immune response. The effects of malnutrition have also been related to medical conditions in adolescence and adulthood. In general terms, a proinflammatory response is observed in obese individuals and a Th2 pattern in undernourished children. However, depending on the event inducing the proinflammatory response, there may be a delayed initial inflammatory response in undernourished as compared to obese individuals. These differences may be crucial in antiviral responses and virus clearance.

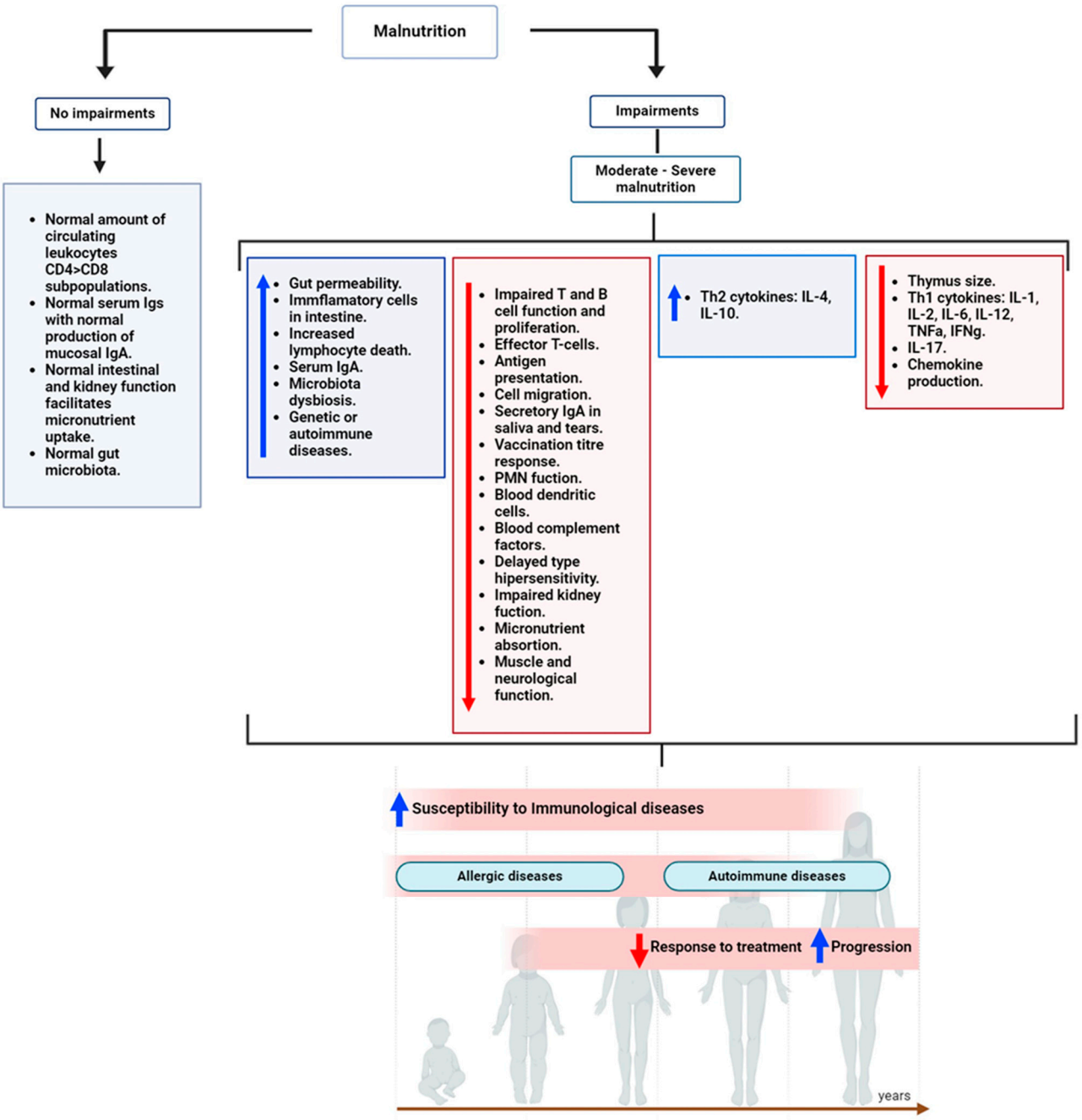

Figure 1. General effects of malnutrition on immune response.

A documented but probably not exclusive element is the decrease in thymic activity leading to an impairment of T cell responses; however, as illustrated in severe malnutrition, several other immunological parameters are compromised independently of T cell function [24]. In addition, well-designed clinical trials are required to determine the impact of nutritional status, gender, and race in different pathologies to ascertain the susceptibility or

resistance of supplementation. For example, genetic mutations are more prevalent in some populations and may not respond to supplementation. Nevertheless, what is important to mention is that malnutrition during infancy impacts immune-related diseases, from allergic reactions, atopic dermatitis, and food allergies, to autoimmune diseases [26–28].

Protein-energy and lipid malnutrition can decrease the number and function of T cells, phagocytic cells, complement pathway components, and secretory immunoglobulin A [29,30]. In the lungs, there is a reduction in the number of alveolar macrophages, which can lead to increased susceptibility to lung damage and a reduced ability to repair it. This can also lead to decreased levels of alveolar surfactant, increasing the work of breathing. These effects are influenced by micronutrient deficiencies that affect several aspects of lung maturation [31–33]. However, there is still much to be studied about the impact of malnutrition on the body's defense mechanism against infection. Additionally, few studies have evaluated the effects of nutritional interventions on improving the response to infectious diseases.

Malnutrition is closely linked to the gastrointestinal tract, where major concerns include increased permeability and decreased nutrient absorption. Conditions such as cystic fibrosis, inflammatory bowel disease, and celiac disease contribute to intestinal malabsorption [33–36]. Additionally, parasitic infections are common in children under five years old, who are especially susceptible due to their developing immune systems and their exploratory behaviors [37].

Mineral deficiency and malnutrition become a vicious circle, as the micronutrient deficiency increases the child's susceptibility to infectious diseases, leading to increased energy requirements that cannot be achieved due to the deterioration of the mucosa of the gastrointestinal tract and limiting food consumption due to the appetite suppressant effect. All these trace elements are indispensable for the organism's correct growth, development, and functioning, especially in the first stages of life. Gut microbiota may protect the mucosa from damage; however, in malnourished children, dysbiosis microbiota may prevail, facilitating intestinal impairment [38,39]. Correct microbiota dysbiosis may be challenging in adolescents compared to preschool children or infants. Similarly, environmental and social factors influence adolescent malnutrition [40].

3. Micronutrients and Immune Response to SARS-CoV-2

Patients with COVID-19 experience a wide range of symptoms, from asymptomatic forms of the disease to severe illness requiring hospitalization. Infection and poor nutrition are closely linked. The immune response to fight SARS-CoV-2 infection is associated with increased nutrient demand. Therefore, micronutrient supplementation may enhance the immune response [41].

3.1. Iron

Iron plays a crucial role in several reactions in our body, such as electron transfer, gene regulation, oxygen fixation, transport, cell differentiation, and growth regulation [42]. Iron and the immune system are intimately interconnected, as many of the genes/proteins involved in iron homeostasis, as well as cells of the innate immune system such as monocytes, macrophages, microglia, and lymphocytes, play a crucial role in controlling iron fluxes, which prevents bacteria from using iron for their proliferation. In addition, several effector molecules such as Toll-like receptors, NF-κB, hypoxia factor-1, and heme oxygenase orchestrate the inflammatory response by mobilizing various cytokines, neurotrophic factors, chemokines, reactive oxygen, and nitrogen species. Increased plasma levels of ferritin, the iron transport protein, may indicate inflammatory states and disease progression [43,44]. Imbalances in iron metabolism are also associated with severe tissue damage and impaired immune function, as ferritin is a key protein for storing cellular iron and is closely linked to iron availability and inflammation [45,46]. Iron deficiency is particularly detrimental to Th1-mediated immunity. T-lymphocytes are also most-affected by a deficiency of zinc, which is necessary for their maturation and the balance between

the different T-lymphocyte subpopulations that act as a redox signal in the regulation of many enzymes [46]. D'Alessandro et al. [47] performed a prospective observational study of a single cohort of 74 individuals (63 patients and 11 controls), which improved the understanding of anemia as an essential component of disease severity in patients infected with SARS-CoV-2.

3.2. Selenium

Selenium is also involved in redox reactions, as glutathione peroxidases and other redox enzymes are selenoproteins [48]. Selenium has unique effects on cellular immunity and resistance to viral infections; there appears to be a relationship between selenium levels and COVID-19. Several possible mechanisms have been proposed by which selenium, in one way or another, could affect the virus. Selenium has been found to down-regulate the IL-6 response, and selenium deficiency is associated with higher IL-6 levels in the elderly [48–50]. Several studies have reported heterogeneous results regarding the association of selenium deficiency with COVID-19 severity [51]. Karakaya et al. evaluated the contribution of nutrition to the progression of infection in pediatric patients diagnosed with COVID-19. No zinc or selenium deficiency was detected in any patients they assessed [52].

3.3. Magnesium

Magnesium (Mg) is involved in numerous enzymatic reactions, transport processes, and protein and nucleic acid synthesis. It stabilizes enzymes in many ATP-generating reactions, antagonizes calcium in muscle contraction, modulates insulin signal transduction and cell proliferation, and is essential for cell adhesion and membrane transport. In addition, Mg plays a critical role in innate and adaptive immune responses and the modulation of acute and chronic inflammatory processes [53,54]. Despite the physiological importance of Mg, its clinical significance is often underestimated, and serum magnesium levels are still not routinely determined. Mg deficiency is associated with the onset and worsening of the neuropsychiatric complications of COVID-19, such as memory loss, impaired cognitive abilities, loss of taste and smell, ataxia, confusion, dizziness, and headache [55]. Nouri-Majd and coworkers [56], in a cross-sectional study of adult patients with COVID-19, found that higher dietary magnesium intake was inversely associated with disease severity. There is limited information on Mg deficiency and the evolution of COVID-19 in pediatric patients.

3.4. Zinc

Zinc is necessary for nearly 100 enzymes to carry out vital chemical reactions. It is one of the main cofactors responsible for synthesizing DNA, cell growth, protein formation, damaged tissue healing, and the immune system's health. Young children are at increased risk of zinc deficiency due to the increased demand for zinc during growth [57]. Exclusively breastfed infants from mothers with adequate zinc nutrition obtain sufficient amounts of zinc during the first 5–6 months of life; after this age, supplemental foods containing absorbable zinc are necessary to meet their needs. Zinc deficiency can enhance the exaggerated release of pro-inflammatory mediators in the airways, leading to more significant airway damage [58]. Ekemen-Keleş and coworkers [59] studied patients aged between 1 month and 18 years who were attending pediatric outpatient clinics with suspected COVID-19. This study aimed to determine the clinical significance of serum zinc levels in pediatric patients with COVID-19 and to evaluate their association with disease severity [59]. They found a significantly higher incidence of hospitalization in patients with COVID-19 and low serum zinc levels, suggesting that these patients require a detailed assessment of their living environment.

3.5. Vitamin A

Vitamin A is an umbrella term for several fat-soluble substances such as retinol, retinyl palmitate, and beta-carotene. The vitamin has been associated with changes in cell differentiation, regulation of the immune response, and an increased risk of infant morbidity

and mortality from respiratory or gastrointestinal infections [60–62]. Tepasse et al. [63] conducted a prospective, observational, cross-sectional, multicenter study involving 40 hospitalized patients with SARS-CoV-2 infection. They found that in the acute phase of the disease, critically ill patients had lower plasma levels of vitamin A, which was significantly associated with acute respiratory distress syndrome and mortality.

3.6. Vitamin D

Vitamin D is a fat-soluble steroid hormone precursor produced from exposure to ultraviolet B (UVB) radiation of 7-dehydrocholesterol in the skin's epidermis [64]. This compound is then transformed into the circulating precursor cholecalciferol. In the liver, cholecalciferol is converted into 25-hydroxyvitamin D, which is further transformed into the active hormone 1,25-hydroxyvitamin D (1,25(OH)2D) in the kidneys [64]. Vitamin D plays a role in surfactant metabolism, promotes the epithelial mesenchyme, and is involved in various body systems including the innate and adaptive immune responses [65]. Vitamin D enhances innate cellular immunity by stimulating the expression of antimicrobial peptides, such as cathelicidin and defensins, which help maintain tight junctions and improve antioxidant gene expression [65]. Vitamin D promotes monocyte-to-macrophage differentiation, increasing superoxide production, phagocytosis, and bacterial killing [65]. Additionally, it can modulate the adaptive immune response by suppressing the function of Th1 cells and decreasing the production of proinflammatory cytokines IL-2 and INF-γ [65]. Vitamin D also promotes anti-inflammatory cytokines by Th2 cells and indirectly suppresses Th1 cells by diverting proinflammatory cells to an anti-inflammatory phenotype and stimulating suppressive regulatory T cells [65]. Recent epidemiological studies have shown a significant link between vitamin D deficiency and an increased incidence, or worsening, of infectious diseases and inflammatory autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis [66]. The findings of several systematic reviews and meta-analyses support the hypothesis that vitamin D deficiency is associated with an increased risk of SARS-CoV-2 infection and a worse disease prognosis [67–69].

3.7. Vitamin C

Vitamin C is the main non-enzymatic, water- and tissue-soluble antioxidant [70]. Even in small amounts, vitamin C can protect indispensable body molecules such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA) from damage caused by free radicals and reactive oxygen species (ROS) generated during normal metabolism by active immune cells and exposure to toxins and pollutants [70]. Vitamin C accumulates in leukocytes in concentrations 50–100-times higher than in plasma. During infection, vitamin C is rapidly utilized, altering the balance between antioxidant defenses and oxidant generation, which can alter multiple signaling pathways involving proinflammatory transcription factors such as NF-kB. It is difficult to visualize any single effect of a vitamin deficiency in several modes. For example, the roles played by vitamins C and D in immunity are well elucidated. Vitamin C affects several aspects of immunity, including supporting epithelial barrier function, the growth and function of innate and adaptive immune cells, the migration of white blood cells to sites of infection, phagocytosis and microbial destruction, and antibody production [71]. Many immune cells have receptors for vitamin D, which promotes the differentiation of monocytes to macrophages, increases their killing capacity, modulates the production of proinflammatory cytokines, and enhances antigenic presentation. It also regulates the production of specific antimicrobial proteins, so vitamins C and D contribute to improving responses to respiratory infections [72]. Valla and coworkers [73] found that in critically ill pediatric patients, there is a significant decrease in plasma concentrations of selenium, copper, zinc, vitamin C, vitamin E, and β-carotene as the intensity of oxidative stress increases. Very few studies have demonstrated using vitamin C as a treatment option to improve COVID-19 progression and complications [74].

3.8. B Vitamins

B vitamins are a complex of eight water-soluble vitamins. The body does not store them, so they need to be replenished daily. B vitamins are found in animal proteins, dairy products, green leafy vegetables, and legumes. Their function can generally be subdivided into catabolic metabolism, which leads to energy generation, and anabolic metabolism, which results in bioactive molecules [75]. They are critical cofactors for axonal transport, neurotransmitter synthesis, and many cellular metabolic pathways. B vitamins are also cofactors for many essential RNA and DNA biosynthesis enzymes. Vitamin B deficiencies have been identified as etiological factors in the development of various neurological disorders and a vast repertoire of pathological states [76]. Pandya et al. [77] performed a molecular dynamic (MD) simulation of the furin–vitamin B12 complex; the results indicated a robust inhibitory effect on furin, as shown by docking analysis followed by MD simulation. The above findings place vitamin B12 on the radar of therapeutic options as a micronutrient that can reduce SARS-CoV-2 virulence by hindering the entry of the virus into the cell.

Figure 2 highlights the effect of vitamins A, B12, C, D, and E on the immune response. These vitamins enhance the immune response against pathogens such as SARS-CoV-2 and recovery from COVID-19.

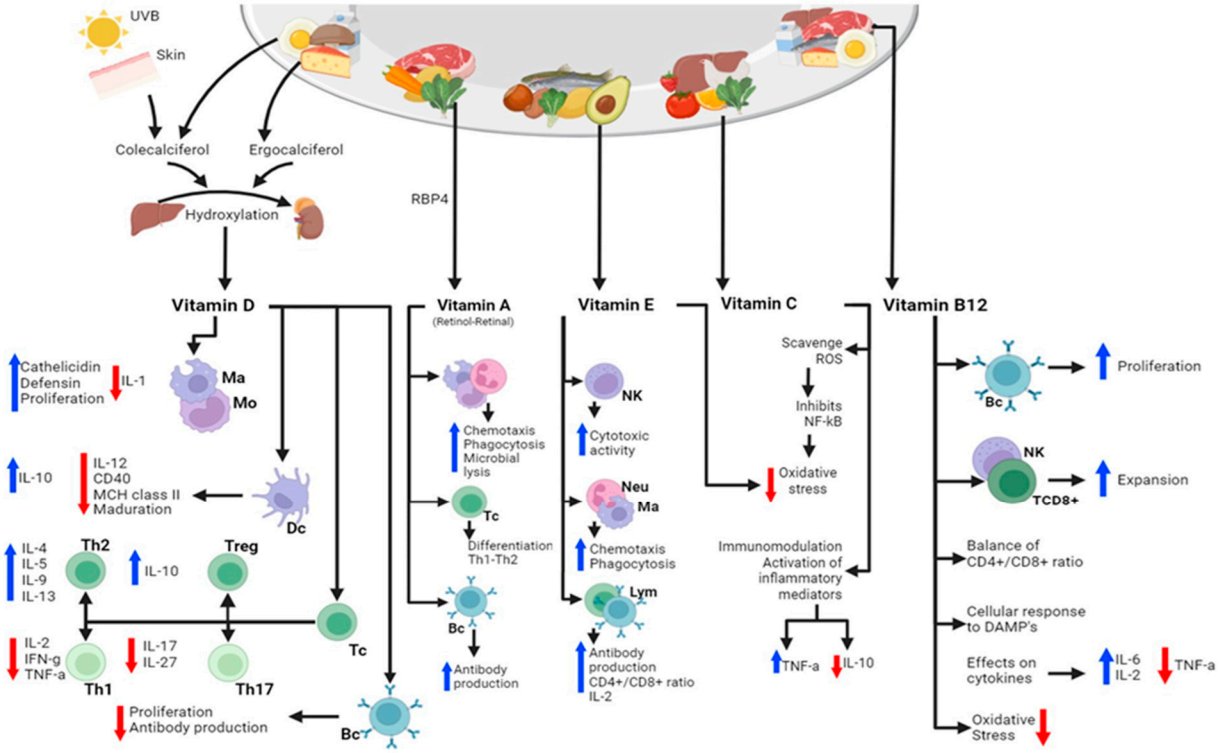

Figure 2. Effect of different vitamins on the immune response. The figure represents supplementation's role and beneficial effects on the immune response. Combined deficiencies can impair a normal cellular response, while combined supplementation may help and restore the physiological response against pathogens.

The latest clinical guidelines of the European Union Society of Clinical Nutrition and Metabolism on the Nutritional management of patients with COVID-19 emphasize the importance of ensuring sufficient levels of essential micronutrients to potentially reduce the negative impact on the disease [78]. Specific mention is made of vitamins C, D, A, E, B6, and B12, and zinc, selenium, and iron, whose potential importance is inferred from existing research on their roles in immune function and outcomes in other infectious diseases [78]. The integrity, functionality, and reactivity of the immune system and the quality of the immune response to an antigen depend on the individual's nutritional status and, by extension, on the quality of their diet [78]. The integrity of the mucous membranes requires vitamins

A and E, known for their antioxidant and cellular and tissue differentiation-promoting capacity. Additionally, the diet must provide enough trace elements, such as selenium and zinc, to preserve the antioxidant activity of ROS scavenger systems. The body's iron content also influences the constancy of the immune response [78]. A continuous intake of high biological-value proteins (rich in essential amino acids) effectively synthesizes immunoglobulins. Malnourished individuals experience secondary immunodeficiency, resulting in a depressed cellular response, while the humoral response is exaggerated, leading to micro-organisms such as SARS-CoV-2 resulting in complications. Autoimmunity occurs more frequently in patients with primary immunodeficiency than in the general population, and genetics or dietary manipulation can influence the development of autoimmune diseases. Studies on severely malnourished patients show that primary serum immunoglobulins IgG and IgM are elevated, while the secretory IgA decreases in all reports. This effect is due to the low number of plasma cells in the submucosa of the respiratory and digestive tract, reducing the production of the secretory component [79].

4. Cytokines

Malnutrition, per se, provokes an inflammatory state with cytokine production dysregulation. Figure 3 summarizes the differences in cytokines between malnourished and obese pediatric patients, and Figure 2 illustrates the effects of micronutrient supplementation. A preferential Th1 response is observed in obese children, while a Th2 response is preferred in undernourished children [80]. However, it is critical to understand that the immune response and cytokine secretion involve several physiological responses. As documented, leptin levels, which are increased in obesity, may condition the Th1 and proinflammatory responses. Even though undernourished infants produce less leptin, the inflammatory response can be present and difficult to control. Elevated levels of IL-6 and TNFα may be related mainly to infections and support the observation that an acute phase response induction is intact in malnutrition [81,82]. Woodward and co-workers [83] also analyzed the pro-tolerance model in child undernutrition based on a low response to pathogens [83]. Pereira et al. [84] evaluated children with severe malnutrition and the effects of nutritional recovery after eight weeks of intervention. The inflammatory cytokines IL-12, IL-17, IFN-γ, and TNF-α differed before and after treatment; the values were like those of healthy controls after treatment.

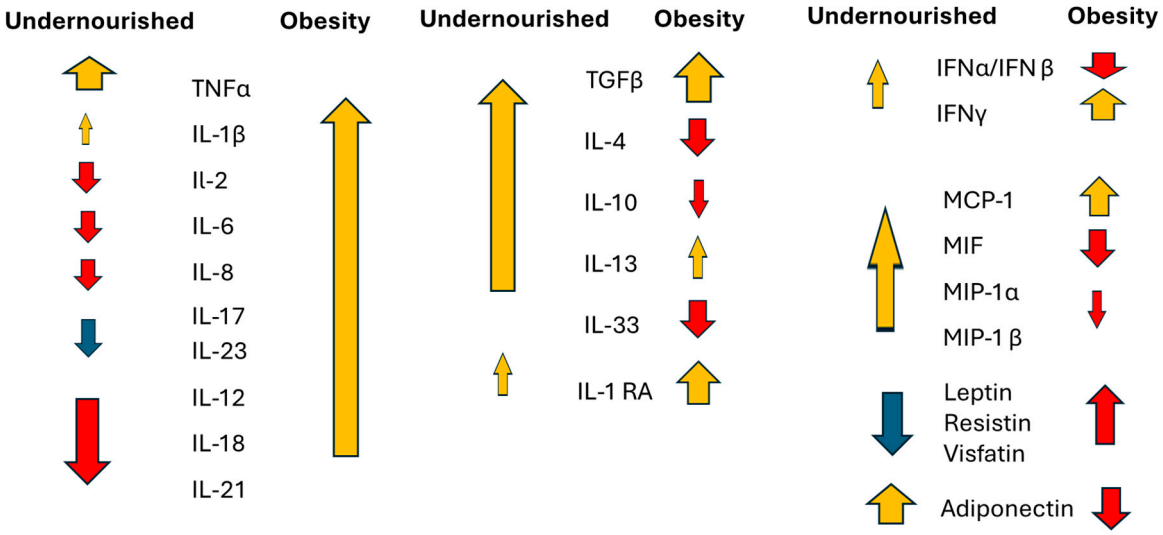

Figure 3. Comparison of cytokine levels between undernourished and obese children. The arrows refer to the general increase or decrease reported according to the literature. The size of the arrows reflects either a slight or a high increase. Yellow is considered an alert; blue is beneficial, and red is a possible detrimental effect.

IL-6 is a crucial mediator of iron metabolism in inflammation, associated with synthesizing hepcidin, the primary regulator of iron homeostasis [85]. A systematic review conducted in China by Zhang et al. 2020 [86] evaluated the supplementation of COVID-19 patients with vitamin A, B-complex vitamins, vitamin C, vitamin D, vitamin E, selenium, zinc, iron, and omega-3, with encouraging results indicating beneficial effects.

5. Obesity and COVID-19

Obesity is a form of malnutrition with low-grade systemic inflammation that may lead to metabolic syndrome [87–89]. Obese children may be more susceptible to different medical conditions. If healthy weight loss is not achieved, it may enhance a current medical condition in adulthood, such as asthma, allergy, atopic dermatitis, and obstructive sleep apnea syndrome [90]. Adipokines are the cytokines involved in maintaining adipose tissue homeostasis [91,92]. Several studies have shown that immune cells, either resident or recruited from adipose tissue, including macrophages, dendritic cells, NK cells, and B and T lymphocytes, show alterations in obese individuals [92–94]. The association between obesity and multiple micronutrient deficiencies remains unclear, although several mechanisms have been proposed. Iron, vitamins A, B, C, D, and E, folic acid, zinc, and copper are the most common deficient microelements in overweight children. Obese children may have an excess of circulating free iron and hypermagnesemia, which leads to increased radicals detrimental to a proper antiviral response [95].

Memory T cells are a critical component of immune memory, providing rapid and potent host protection against secondary challenges [96]. Caloric restriction and a high-fiber diet, but not malnutrition, enhance memory T cell function, suggesting that an appropriate balance of energy intake is required for an adequate memory T cell response. These memory T cell responses are dysfunctional in extreme nutritional states such as malnutrition and obesity. Obesity-related changes in T cell metabolism are associated with an altered T-cell response to influenza and are not reversed by weight loss [97].

Obesity is a critical risk factor for developing severe coronavirus disease. It reduces protective cardiorespiratory reserves, promotes immune system dysregulation, and can lead to organ failure [98]. Obesity also increases the risk of developing blood clots, which is essential given the link between severe COVID-19 and blood clotting issues. In addition to these risks, obesity is associated with chronic inflammation and oxidative stress, which can worsen COVID-19 symptoms. Studies suggest that children with obesity are at increased risk of developing severe COVID-19, and the inflammation associated with obesity may be one of the factors that can worsen COVID-19 symptoms in children and adults [99]. Adipose tissue expansion in obesity can lead to inflammation, and this chronic low-grade inflammation could contribute to a more severe response to the virus and the development of severe COVID-19 [100].

Studies in mice have shown that obesity increases the amount of angiotensin 2 (ACE2) receptors in lung epithelial cells and ACE2 activity and protein levels in adipose tissue. Interestingly, less information is available for humans. One study showed a trend toward increased protein expression of ACE2 in the visceral adipose tissue of obese and malnourished humans; the same trend was observed for other receptor members, such as angiotensinogen, ACE, and angiotensin 1 (AT1) receptor. Because ACE2 is expressed on endothelial cells lining blood vessels in multiple organs, SARS-CoV-2 can enter these blood vessels and activate an inflammatory response [101]. SARS-CoV-2 facilitates endothelium development in various organs in adults [102]. Histological analysis shows the recruitment of inflammatory cells, which can lead to endothelial dysfunction and apoptosis. Considering that patients with cardiovascular disease are prone to endothelial dysfunction, it is understandable that SARS-CoV-2 infection worsens the inflammatory picture and contributes to a poor prognosis. Why children with chronic ailments such as chronic lung disease and obesity are prone to develop multisystem inflammatory syndrome in children (MIS-C) is still unknown. However, one hypothesis is that local renin–angiotensin–aldosterone system activation in endothelial cells and vascular smooth muscle cells (VSMCs) means

that ACE2 is embedded in these cell membranes. Therefore, if SARS-CoV-2 can enter and replicate in these endothelial cells, it stands to reason that when the virus leaves these cells, it can infect neighboring cells. This process could increase local inflammation and worsen vasculitis [100,101].

6. Anti-Viral Treatment

Antiviral treatment against SARS-CoV-2 infection is restricted to children and adolescents older than 12 years old [103,104]. According to the FDA guidelines [105], this treatment is recommended mainly for individuals with co-morbidities who should be protected from infection. According to the results reported in mice [106], questions remain on the effectiveness of Nirmatrelvir on T cell function and memory immune response.

The effect of antiviral therapy in children with malnutrition may not be optimal unless supplementation is used. Vitamin D deficiency has been linked to a higher incidence of COVID-19 symptoms and long-term COVID-19 in different age groups [107]. However, this review states several micronutrients and vitamins are important for an efficient antiviral response. More research is needed, especially in the pediatric population under 12 years old.

7. Conclusions

It is essential to understand the role of nutrition in the immune system and infection. Proper nutrition can improve the population's overall health and strengthen the immune system through the taking of macro- and micronutrients. Studies have highlighted the link between malnutrition and morbidity, especially in pediatric patients. Tailored nutritional interventions can also help maintain immune system functions. Figure 4 summarizes the changes observed between malnutrition, the immune response against SARS-CoV-2 infection, and the effects of micronutrient supplementation.

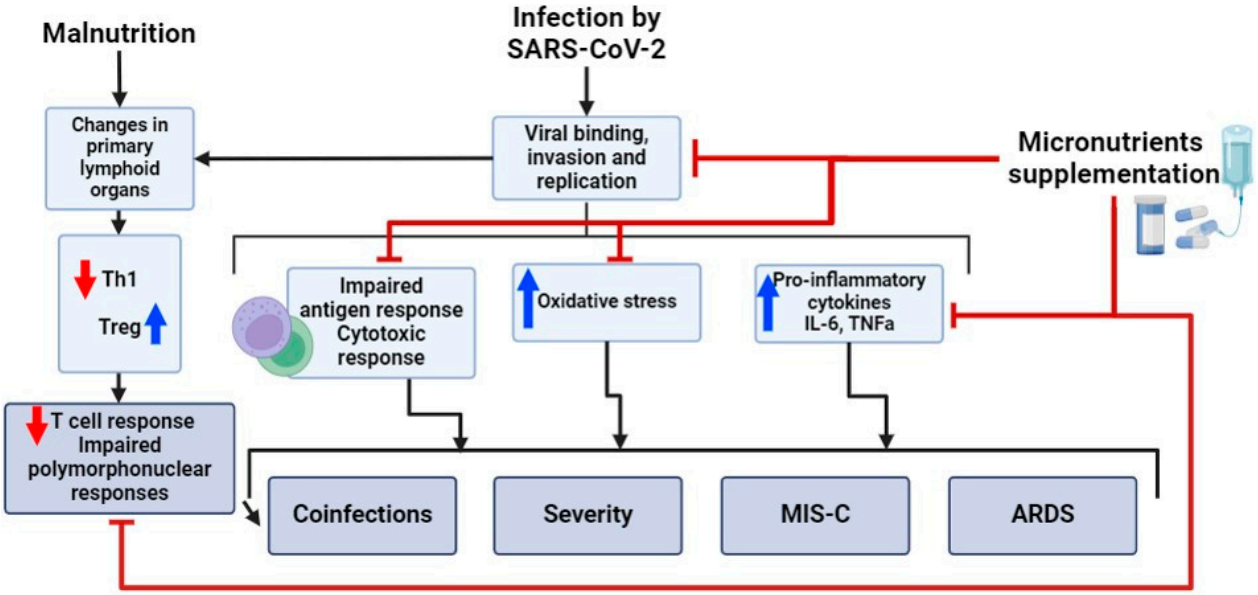

Figure 4. Immune responses in malnourished host due to SARS-CoV-2 infection and the effects of micronutrient supplementation intervention.

Numerous studies have shown that malnutrition directly impacts the severity of SARS-CoV-2 infection in children. There is a two-way relationship between COVID-19 and malnutrition: the virus can cause malnutrition by affecting nutrient uptake and weakening the immune system. In turn, the recovery of malnourished patients is worse. These patients are more likely to have a poor prognosis due to their altered immune system functions. Malnutrition and obesity are conditions that should be recognized and considered in pediatric patients with COVID-19. Early therapeutic intervention, comprehensive clinical

surveillance, and joint management with nutritional supplements are useful in reducing disease severity upon viral infection.

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