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The role of micronutrients in the management of COIVD-19 and optimizing vaccine efficacy

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ABSTRACT

Since COVID-19 was declared as a pandemic, a race between researchers has begun to deeply examine the mechanism of the virus and how to combat it. Few clinical investigations and studies have paid attention to the role of micronutrients in the disease's course and how it may affect the disease outcomes. Micronutrients have a noticeable effect on the host immune system regulation, as well as micronutrients insufficiencies where they can affect the host immune response against SARS-CoV-2 by, for example, altering the production and the function of the inflammatory cytokines such as IFN-γ, IFN-α, TNF and interleukins. Recent studies have shown that low levels of vitamin D, vitamin C, vitamin A, zinc, selenium, copper and magnesium have a great clinical impact on COVID-19 patients, where, they are linked to prolong hospital stay, increase the mortality rate and raise the complications rate related not only to the respiratory system but also to the other systems. Optimizing the need for these micronutrients will act as a productive factor by decreasing the incidence of COVID-19 infection, lowering the rate of complications, and improving the disease prognosis and outcomes. Optimal micro-nutrition supports and contributes to the efficiency of COVID-19 vaccine. The aim of this review is to highlight the role of different micronutrients in the management of COVID-19 and optimizing vaccines, and to revile the clinical effects of micronutrients deficiencies on patients with COVID-19.

1. Introduction

The nutritional status of patients with Covid-19 partly predicts the pattern of disease progression and expected outcomes. The symptomatology among corona infected patients varies because of unknown mechanisms. However, studies show that the immune system personifies a significant factor in inhibiting the progression of the disease. Micronutrients contribute significantly to immune system enhancement [1]. There has been a recent level of interest in the role of certain risk factors like age, metabolic syndrome and pregnancy in predicting the course of COVID-19 infection. Individuals with such risk factors are more inclined to develop nutritional deficiencies which ultimately affect their level of immunity and increase their susceptibility to acquire COVID-19 and develop its related complications. Although micronutrient malnutrition is highly prevalent in developing countries, some forms of nutritional deficiencies also exist in developing countries according to the World Health Organization. Bearing all of this in mind, optimization of the nutritional status through provision of diverse and well-balanced meals should be a priority during the global pandemic of COVID-19.

Deficiency of several micronutrients has been associated with prolonged hospital stay and various poor complications caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. This mainly relies on the increased production of inflammatory cytokines correlated with the low levels of different vitamins and minerals [1]. SARS-CoV-2 downregulates angiotensin converting enzyme 2 (ACE2) receptors leading to improper functioning of renin-angiotensin system, which plays a major part in the pathogenesis of "Cytokine Storm" that heralds acute respiratory distress syndrome (ARDS). In the same context, micronutrients deficiency is associated with COVID-19 infection outcomes which encompass acute respiratory distress syndrome,

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pneumonia, and the need for oxygen therapy [3,4]. There is no sufficient literature proofing a linkage between the role of dietary supplementation and the prevention of COVID-19. However, the importance of micronutrients in COVID-19 infection can be demonstrated by the fact that nutritional deficiency is associated with the increased susceptibility to viral and respiratory infections [5]. Supplementation with natural micronutrients may positively impact the course of COVID-19 and can be potentially beneficial at the level of treatment and prophylaxis as well. In the coming sections, we will discuss the mechanism of how micronutrients (vitamin C, vitamin D, vitamin A, zinc, magnesium, selenium, and copper) support the immune system and their probable benefit in the treatment and prevention of COVID-19.

2. Methods

This narrative review addresses the role of micronutrients in the management of COIVD-19 and optimizing vaccine efficacy using the best available literature. Specifically, the review attempts to cover the role of seven micronutrients (vitamin C, vitamin D, vitamin A, zinc, magnesium, selenium, and copper) in supporting the immune system and their probable benefit in the treatment and prevention of COVID-19.

Two authors, using PubMed/MEDLINE and Google Scholar, applied the following search terms to titles and abstracts: “Coronavirus” OR “COVID-19” OR “SARS-CoV-2” AND “macronutrients” OR “vitamin” OR “mineral”.

All authors separately sifted through the vast literature on these topics collected over the past two years and, by consensus, selected those papers that best answered our questions. This review used the Synthesis Without Meta-analysis (SWiM) approach to ensure unambiguous reporting [6].

3. Zinc

Zinc is highly crucial for the healthy functioning of innate and acquired immunity and moderation of cytokine production in the body [7]. The great effect of zinc in the prevention of infectious diseases can be illustrated by its antiviral actions. Zinc plays a major role in the production of IFN-γ and IFN-α, improves the function of leukocytes and mitigates the production of tumor necrosis factor (TNF) and interleukin-1β [8]. Zinc has the physical capability of virus attachment and uncoating and acts effectively against viral replication of RNA viruses through interfering with the enzymatic processes [9]. This can be exemplified by its effect in inhibiting RNA synthesis in nidoviruses [10]. Notably, SARS-CoV-2 comes under the category of nidoviruses [11]. Zinc inhibits the RNA-dependent RNA polymerase of SARS-CoV-2 by binding and elongation in Vero-E6 cells, which is an essential step in the virus’s replication process [10]. Globally, 16% of people with deep respiratory infections have zinc deficiency [12]. There are little stores of zinc in the body and inadequate intake of zinc can result in deficiency and malfunctioning of the immune system [7]. A randomized clinical trial has demonstrated the effect of supplementation of zinc in moderate doses in reducing the incidence of infections in elderly individuals [13]. Recommended dietary allowances of zinc and food sources of zinc are provided in Table 1.

Table 1
Daily recommended amount of zinc.

Micronutrient	Life Stage	Recommended Dietary Allowance (RDA)	Food Sources
Zinc	Women	8 mg	Oysters, red meat, cereals, beans, seafood, nuts, dairy products, whole grains.
	Men	11 mg	
	Pregnant Women	11 mg	
	Breastfeeding Women	12 mg	
	Birth- 6 months	2 mg	
	Infants 7–12 months	3 mg	
	Children 1–3 years	3 mg	
	Children 4–8 years	5 mg	
	Children 9–13 years	8 mg	
	Teen boys 14–18 years	11 mg	
	Teens girls 14–18 years	9 mg	

4. Vitamin D

Many lines of literature support the positive relationship between low levels of vitamin D and the incidence of respiratory tract infections [14,15]. Vitamin D is critical in the protection of the airway through its role in inducing cathelicidin and defensins and limiting respiratory epithelium damage by maintaining tight junctions [16-19]. Vitamin D reduces the risk of developing a cytokine storm by decreasing the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), tumor necrosis factor α (TNF α), and interferon-gamma (IFN-γ), which play a pivotal role in propagating “cytokine storm” [20-22]. IL-6 and IFN-γ have a negative prognosis in critically ill COVID-19 patients [23]. Supplementation with vitamin D, especially in individuals with a baseline 25-hydroxyvitamin D level of <25nmol/L, is safely effective against acute respiratory tract infections [24]. However, inadequate sunlight exposure either due to self-quarantine or hospitalization during the COVID-19 pandemic can further exacerbate vitamin D deficiency. This highlights the critical requirement for sufficient vitamin D supplementations. A meta-analysis has demonstrated that the major benefits of vitamin D supplements were obtained in individuals who received daily or weekly doses of vitamin D in comparison to those receiving bolus doses [24]. Food sources and recommended dietary allowances of Vitamin D are provided in Table 2.

5. Vitamin C

Vitamin C has been used for years to treat the common cold [25], but its efficacy is debatable. A recent meta-analysis has concluded that the beneficial effect of vitamin C supplementation on the prevention and treatment of common cold is insufficient [26], but it may help in reducing the duration of the common cold [27], which could be due to vitamin C’s virucidal effect through the neutralization of reactive oxygen species such as hydrogen peroxide and other radical species [28,29]. In neutrophils, it enhances chemotaxis and phagocytosis of microbes and modulates the process of cellular apoptosis and necrosis [30,31]. Vitamin C is a central modulator of inflammatory processes through

Table 2
Daily recommended amount of vitamin D.

Micronutrient	Life Stage	Recommended Dietary Allowance (RDA)	Food Sources
Vitamin D	Women	15 mcg (600 IU)	Mushroom, cheese, beef liver, egg yolk, fatty fish (salmon, tuna).
	Men	15 mcg (600 IU)	
	Pregnant Women	15 mcg (600 IU)	
	Breastfeeding Women	15 mcg (600 IU)	
	Birth - 12 months	10 mcg (400 IU)	
	Children 1–13 years	15 mcg (600 IU)	
	Children 14–18 years	15 mcg (600 IU)	
	Adults 71 years and older	20 mcg (800 IU)	

attenuation of inflammatory cytokines and nuclear transcription factor kappa B (NFkB) synthesis [32]. The enhanced consumption of antioxidants by white blood cells clarifies the low levels of vitamin C observed in patients with respiratory tract infections [33]. A systematic review and meta-analysis on the use of intravenous vitamin C have shown favorable outcomes in improving mortality and reducing the requirement for mechanical ventilation [34]. Besides, supplementation with vitamin C has proven its efficacy in treating and preventing respiratory tract infections and reducing the progression of pneumonia in geriatric patients which could make it a beneficial adjuvant in the treatment of COVID -19 [35]. Food sources and recommended dietary allowances of Vitamin C are provided in Table 3.

6. Vitamin A

Vitamin A deficiency can result in the disruption of the integrity of mucosal epithelium which provides an easy access of infectious agents into the human body through penetrating the mucous membranes of the eye, gastrointestinal and respiratory tract [36]. Vitamin A works as an upregulating element of the innate immune response in non-infected cells via rendering these cells to be refractory to infections in the subsequent rounds of viral replication [37] and plays a significant role in enhancing antigen non-specific immune response [38]. In patients with vitamin A deficiency, histopathological changes in the lung parenchyma and pulmonary epithelium have been observed, which marked impairment of the respiratory epithelial function [38]. Therefore, vitamin A deficiency increases the susceptibility of acquiring infections. Supplementation with vitamin A has been shown to reduce the risk of mortality in children aged 6–59 months by 20–30% [39]. However, a systematic review on the effect of vitamin A supplementation in preventing respiratory tract infections in children concluded that supplementation should be provided only in those with poor nutritional status [40]. Over intake of vitamin A can result in anorexia and further reduces the nutritional intake [40,41]. Food sources and recommended dietary allowances of vitamin A are provided in Table 4.

7. Magnesium

Magnesium has anticholinergic, anti-inflammatory and antihistaminic properties in the lung. This supports the correlation between hypomagnesaemia and improper pulmonary functioning [42]. QT interval prolongation is another complication of hypomagnesaemia which can concurrently occur with the use of medications for the treatment of SARS-CoV-2 resulting in further exacerbation of the condition [43,44]. This raises a speculation towards the negative influence of hypomagnesaemia on the course of COVID-19 and the need for investigating the use of magnesium supplementation as a therapeutic option in COVID-19 patients. Food sources and recommended dietary allowances of magnesium are provided in Table 5.

8. Selenium and copper

Selenium and copper are both essential trace elements that have an auxiliary role in the immune system. Selenium helps in the differentiation of innate immune cells and the production of antibodies. Moreover, selenium has antioxidant, anti-inflammatory, and anti-microbial effects [16,45]. Copper prevents oxidative damage, thereby preserving DNA integrity and aiding in the reduction of inflammation [46]. However, there is no enough data to support the use of copper supplements in COVID-19 patients.

9. Antioxidants

Antioxidants boost the activity of natural killer cells and

Table 3
Daily recommended amount of vitamin C.

Micronutrient	Life Stage	Recommended Dietary Allowance (RDA)	Food Sources
Vitamin C	Women	75 mg	Citrus fruits (orange, grapefruit), red and green pepper, kiwifruit, tomatoes, strawberries, broccoli, baked potato.
	Men	90 mg	
	Pregnant Women	85 mg	
	Breastfeeding Women	120 mg	
	Birth- 6 months	40 mg	
	Infants 7–12 months	50 mg	
	Children 1–3 years	15 mg	
	Children 4–8 years	25 mg	
	Children 9–13 years	45 mg	
	Teen boys 14–18 years	75 mg	
	Teens girls 14–18 years	65 mg	

Table 4
Daily recommended amount of vitamin A.

Micronutrient	Life Stage	Recommended Dietary Allowance (RDA)	Food Sources
Vitamin A	Women	700 mcg	Fruits (Apricot, mango, orange), fish (salmon), beef liver, green leafy vegetables, broccoli, carrots, dairy products.
	Men	900 mcg	
	Pregnant Women	770 mcg	
	Breastfeeding Women	1300 mcg	
	Birth- 6 months	400 mcg	
	Infants 7–12 months	500 mcg	
	Children 1–3 years	300 mcg	
	Children 4–8 years	400 mcg	
	Children 9–13 years	600 mcg	
	Teen boys 14–18 years	900 mcg	
	Teens girls 14–18 years	700 mcg	

Table 5
Daily recommended amount of magnesium.

Micronutrient	Life Stage	Recommended Dietary Allowances (RDAs)	Food Sources
Magnesium	Women	310–320 mg	Milk, yogurt, legumes, seeds, whole grains, nuts, green leafy vegetables, cereals.
	Men	400–420 mg	
	Pregnant Women	350–360 mg	
	Breastfeeding Women	310–320 mg	
	Birth- 6 months	30 mg	
	Infants 7–12 months	75 mg	
	Children 1–3 years	80 mg	
	Children 4–8 years	130 mg	
	Children 9–13 years	240 mg	
	Teen boys 14–18 years	410 mg	
	Teens girls 14–18 years	360 mg	

lymphocytes and the production of interleukin-2, which helps the immune system fight off invading microorganisms, particularly viruses [47]. Micronutrients rich in antioxidants can be found in fresh fruit and vegetables, soy, nuts [48].

10. Gastrointestinal microbiota and probiotics

COVID-19 has been shown to cause gastrointestinal mucosal inflammation and diarrhea, which aggravate the immune response and result in the production of immune modulators that worsen COVID-19 outcomes [49,50]. Therefore, probiotics supplementation may be of great importance because of its effect in modulating and maintaining a balanced immune response, improving the innate immunity in the gut, and reducing gastrointestinal permeability [51] which could prevent the complications of COVID-19.

11. Clinical impact of micronutrients on COVID-19

The clinical impact of different micronutrients among COVID-19 patients is discussed in several conducted researches. Micronutrients deficiencies can dramatically aggravate the clinical course of SARS-CoV-2 and contribute to the development of various complications.

Using vitamin C as therapeutic intervention in COVID-19 patients increases their survival rate. This is mainly caused by decreasing the over-activation of the immune response that helps in decreasing the cytokines storm [52].

The prevalence of vitamin D deficiency in Covid-19 patients requiring ICU admission is significantly higher than in Covid-19 patients who are treated in the hospital wards [53]. There was an inverse correlation between vitamin D level and clinical findings associated with Covid-19 such as pneumonia, sepsis and heart failure [54]. Vitamin D deficiency is associated with a four-fold increase in the risk of COVID-19 mortality independent of age and co-existent comorbidities [55]. This further applies to the need for invasive mechanical ventilation in COVID-19 patients with vitamin D deficiency [56]. Similarly, the mortality risk among Covid-19 patients who received a bolus dose of vitamin D one month prior to the infection was reduced by 89% [57]. Taking into consideration that vitamin D takes part in regulating thrombotic pathways; vitamin D deficiency in COVID-19 patients is associated with increased incidence of thrombotic complications [58].

Studies show that zinc level is negatively correlated with the risk factors that can lead to severe COVID-19 complications. People who are immunocompromised, obese or diabetic are more likely to have zinc deficiency. A study in South Africa showed that there was a clinical improvement among children with pneumonia who used Zinc as part of their treatment intervention compared to the placebo group. The clinical improvement was judged based on the duration of the illness, respiratory rate and oxygen saturation. It has been found that the level of zinc in COVID-19 patients is significantly lower than in the general population. Covid-19 patients with zinc deficiency are more inclined to stay longer in the hospital and develop more complications. As a result, COVID-19 patients with zinc deficiency have a higher incidence of mortality [59,60].

Magnesium is a major modulator of the cytokine storm that manifests during Covid-19 infection. Magnesium deficiency can occur as a clinical consequence of diabetes mellitus and chronic kidney disease. Thus, magnesium supplementation is highly recommended in managing patients with co-existing risk factors. Moreover, magnesium may not only be used for its prophylactic effects against COVID-19 infection but it can also minimize the side effects of the antiviral medications used for treating COVID-19 infection. Magnesium supplements can alleviate hepatotoxicity, cardiotoxicity and neurotoxicity induced by the use of antiviral medications especially chloroquine [61,62].

12. Telogen effluvium and COVID-19

There has been a recent rise in the incidence of telogen effluvium with the emergence of the novel Coronavirus-19 (COVID-19). There are different causations of telogen effluvium including psychological stress, malnutrition, vitamins and mineral deficiency, medications and hospitalization which can all occur simultaneously due to COVID-19 [63]. Besides, the activated inflammatory state which acts in response to the virus may itself provoke the pathogenesis of telogen effluvium [64]. Proinflammatory cytokines can impair anticoagulation mechanisms in the body and consequently lead to microthrombi formation at the hair follicles [64]. This highlights the role of micronutrients supplementation in meeting the increased energy requirements during infections and thus preventing nutrients deficiency. Micronutrients also play a massive effect in reducing the cascade of inflammatory process and resulting destruction of hair follicles [1].

13. Nutrition and COVID-19 vaccine

To have an adequate response to vaccines, the recipient must have a fully functioning immune system, which is dependent on a variety of factors, one of which is nutrition. The nutritional status becomes highly important in the elderly due to their malnutrition and declining immune system. It has been established that an older population has a weak response to the vaccine [65] due to a declining immune system [66,67]. A single-blind, randomized, controlled phase 2/3 trial that studied the effect of a single dose of the Oxford vaccine revealed a low level of immunoglobulin G and neutralizing antibodies in people aged (56–69) year-old and 70 years or older when compared to a younger age population (18–55) year-old [68]. Malnutrition is one of the modifiable causes of a weakened immune system and poor vaccine response in the elderly. A healthy nutritional status is required for an immune system to appropriately respond to vaccines [69].

14. Policy suggestion

Consumption of well-balanced diet meals is quite imperative during infections. Supplementation with vitamins and minerals is important but not an alternative to healthy dietary practices especially under the current pandemic of COVID-19. Certain individuals are at a higher risk of nutritional deficiency including children, pregnant and breastfeeding women, elderly, immunocompromised patients, obese individuals and those with metabolic syndrome and they accordingly need a special consideration. Achieving an optimal level of healthy nutrition and getting a wide variety of meals from different food groups is necessary to meet all energy requirements and prevent the infection with COVID-19 and the complications associated with it.

15. Conclusion

Deficiency of several micronutrients such as vitamin D, vitamin C, vitamin A, zinc, selenium, copper and magnesium play a remarkable role in COVID-19 clinical course, where they can alter the disease outcomes and prognosis. Poor outcomes have been noticeably linked to patients with malnutrition, specifically low level of these micronutrients, which can further influence the innate and humoral immune system. In contrast, available studies have suggested that sufficient level of these micronutrients can improve the diseases outcomes, decline complications and optimize the efficiency of COVID-19 vaccine. Further clinical investigations are needed to clarify the role of micronutrients in patient with COVID-19 and its impact on the inflammatory process in the host immune system. Also, guidelines and recommendations should be made to guide physicians toward testing patients for micronutrient insufficiencies and to optimize the patient's need for these micronutrients to restore normal status and function as a part of their course of treatment.

Tables 1–5 provide the food sources and daily recommended dietary allowances (RDAs) of micronutrients based on the US National Institute of Health fact sheet of dietary supplement.

Author contributions

Noor Altooq: Conception and design of the study, writing – original draft, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted.

Ali Humood: Conception and design of the study, writing – original draft, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted.

Ahmed Alajaimi: Conception and design of the study, writing – original draft, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted.

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Mohamed Janahi: Conception and design of the study, revising it critically for important intellectual content, final approval of the version to be submitted, referencing.

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Conflicts of interest

The authors declare no conflict of interest.

Declaration of competing interest

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