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# The Role of Micronutrient and Immunomodulation effect in the vaccine era of COVID-19

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**Abstract**

Different dietary nutrients have distinct effects, including enhancing immune response activity and supporting mucous membrane integrity. These effects are critical in fighting against pathogenic agents, which cover COVID-19, the coronavirus disease that shuts down globally. Recent researches have shown that micronutrient deficiency is commonly associated with compromised immune responses, respiratory tract infections, or even susceptibility to COVID-19. The relationship between Vit A and infection is its role in mucosal epithelium integrity (skin and mucous membrane), the supplementation could be an option for assisted-treating the SARS-CoV-2 virus and a possible prevention of lung infection. Vit C/ascorbic acid stimulates oxygen radical scavenging activity of the skin and enhances epithelial barrier function. Ascorbic acid alone or with other natural compounds (baicalin and theafalvin) may inhibit the expression of angiotensin converting enzyme II in human small alveolar epithelial cells and limited the entry of SARS-CoV-2. Vitamin D receptors (VDRs) can be expressed by immune cells, and different immune cells (macrophages, monocytes, dendritic cells, T cells, and B cells) can convert Vit D into its active form 1,25-$(OH)_2$ D. Oral vitamin D intake can be a readily way to restrict the viral infection through down regulation of ACE2 receptor and to attenuate the disease severity by decreasing the frequency of cytokine storm and pulmonary pro-inflammatory response. Vit E supports T-cell mediated functions, optimization of Th1 response and suppression of Th2 response. Vitamin E supplementation can lower the production of superoxides and may favors the antioxidants and benefit the progress of COVID-19 treatment. Zinc plays an essential

role in both innate and adaptive immune systems and cytokine production, and Zinc-dependent viral enzymes to initiate the infectious process have proved the Zinc levels are directly associated with symptoms relieved of COVID-19. Iron is an essential component of enzymes involved in the activation of immune cells, lower iron levels predispose to severe symptoms of SARS-CoV-2, and monitoring the status can predict the disease severity and mortality. Selenium participates in the adaptive immune response by supporting antibody production and development. Deficiency can reduce antibody concentration, decreased cytotoxicity of NK cells, compromised cellular immunity, and an attenuated response to vaccination. The COVID-19 vaccines including three broad categories, protein-base vaccines, gene-based vaccines (mRNA vaccines and DNA vaccines), combination of gene and protein-based vaccines. Micronutrients are involved in immunity from the virus entering the human to innate immune response and adaptive immune response. Micronutrients are indispensable in immune response of vaccination.

Keywords: COVID-19; Immunomodulation; Micronutrient; Vaccine.

## 1. Introduction

COVID-19 (coronavirus disease 2019), burst out from Wuhan city, China, rapidly becomes a global pandemic after the first confirmed case was identified. As of 20 May, 2021, there have been more than 160 million confirmed cases and more than 3.4 million deaths based on WHO's statistics. The pathogenic agent for the disease is severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). The primary mode for it to transmit is through air droplets in close contact that causes respiratory tract infection (RTI) with pulmonary dysfunction. Its clinical features may include asthenia, pyrexia, dyspnea, septic shock, coagulation dysfunction, and acute respiratory distress syndrome in clinically ill patients. [1] Studies have shown that malnutrition is common in certain groups of people, and among these people, micronutrient deficiency makes them susceptible to infectious diseases. [2] Therefore, to keep micronutrient balance is essential to alleviate morbidity of being infected by pathogens.

## 2. Vitamin A (Vit A)

Vit A significantly affects the regulation of the innate (via natural killer cells, macrophages, and neutrophils) and the cell-mediated immunity (via the growth and differentiation of B cells). It also plays a role in the inflammatory response when being active in cytokine signaling and humoral antibody immunity [3]. For instance, Vit A and some other retinoids can increase the efficacy of type 1 interferons (IFN-1), a significant antiviral cytokine released by the innate immune system [4]. During the early viral infection (viruses that are utilized to test against SARS-Cov-2), the innate immune system responses to it by releasing IFN-1; however, the coronavirus that

resembles SARS-CoV-2 can suppress IFN-1 activity. [5] Retinoids, which are family molecules relevant to Vit A that share immune-modulating properties, can potentially enhance the actions of IFN-1 and its most active form is found to be retinoic acid. [6] Therefore, Vit A and its related substance such as retinoid can be used to test the antiviral drugs in pre-clinical trials for COVID-19 treatment. [5]

The relationship between Vit A and infection is its role in mucosal epithelium integrity (skin and mucous membrane). Since the Vit A maintains immune function, vision, eye health, and all the growth demanding activities in bodies, the deficiency results in increased susceptibility to infection through the eyes, respiratory, and gastrointestinal tract [7-9]. There are trials of animal, and a few human clinical trials are ongoing (IRCT20180520039738N2, IRCT20170117032004N3), yet still no direct evidence suggesting Vit A supplementation as a recommended treatment for clinically confirmed cases of COVID-19 [10, 11]; however, the supplementation could be an option for assisted-treating the SARS-CoV-2 virus and a possible prevention of lung infection.[12]

**3. Vitamin C (Vit C)**

Vit C is an efficient antioxidant that not only donates electrons readily but scavenges damaging reactive oxygen species; the former strengthens the function and activity of immune cells (leukocyte function and white blood cell migration through monocyte and neutrophil mobilization) [13], and the latter prevents our cells and tissues from being damaged by oxidative agents. When the body is being infected, Vit C levels may reduce, and a person requires more of it to balance out the situation. [14] Vit C stimulates oxygen radical scavenging activity of the skin and enhances epithelial

barrier function. [13] Deficiencies impair immunity and lead to higher susceptibility to infection, which further exacerbate disease severity and increases the risk of contracting pneumonia. [15] The function of the impaired epithelial barrier of animals' lung can be reconstructed by Vit C administration. [16] Supplementing Vit C can effectively prevent and treat RTI, with being proved to reduce the frequency and span of upper respiratory tract infection (URTI) and severity of pneumonia found in hospitalized elderly. [17] However, a recent study points out that high-dose supplementation has limited effects on critically ill patients with acute respiratory distress syndrome (ARDS). [18] In adaptive immunity, Vit C can enhance the differentiation and proliferation of B and T cells.[19]

Regarding the COVID-19 treatment, an oral low dose (1-2g per day) can be helpful prophylactically, and in the severe cases, a high-dose (even very high) supplementation may be beneficial. [20, 21] Besides, ascorbic acid alone or with other natural compounds (baicalin and theafalvin) may inhibit the expression of angiotensin converting enzyme II in human small alveolar epithelial cells and limited the entry of SARS-CoV-2.[22] Vit C may play a protective role in the SARS-CoV-2 pandemic.

**4. Vitamin D (Vit D)**

Vitamin D is fat-soluble and is essential in calcium homeostasis. Our skin synthesizes Vit D endogenously as it is exposed to Ultraviolet- B (UV-B) radiations from sunlight, which 1,25-dihydroxy vitamin D [1,25-$(OH)_2$ D] is its active form. [23] It is also widely associated with suppressing the cytokine storm and strengthening the immune responses, whether innate or adaptive, which protect us against viral infection. [24] A study shows that both pro-inflammatory and anti-inflammatory

cytokines are generated by the innate immune system of people suffering from COVID-19. [25] Vitamin D receptors (VDRs) can be expressed by immune cells, and different immune cells (macrophages, monocytes, dendritic cells, T cells, and B cells) can convert Vit D into its active form 1,25-$(OH)_2$ D; this mechanism allows local regulation of the active Vit D to work at the site where inflammation happens. [26] High levels of VDRs, in particular, exist in lung epithelial cells, of which the deletion may reduce pulmonary barrier integrity and increase lung permeability. [27] Activating Vit D in the lung then may attenuate inflammatory cytokines and stimulate these antimicrobials in pulmonary barrier and lung permeability with response to viral infection.

Supplementing Vit D has been proved to effectively combat conditions such as RTI , tuberculosis , asthma , and chronic obstructive pulmonary disease [28-31].More importantly, a meta-analysis of RCTs (Randomized Controlled Trials) indicates that supplementing Vit D reduces the frequency of RTIs, by which the dosing frequency and the baseline status are found to be independent modifiers of risk. [29] Supplementation effects are most vital in patients with baseline status (<25 nmol/L) and in groups that take it daily. A study of COVID-19 cases has postulated that oral vitamin D intake can be a readily way to restrict the viral infection through down regulation of ACE2 receptor and to attenuate the disease severity by decreasing the frequency of cytokine storm and pulmonary pro-inflammatory response. [32] Therefore, the use of Vit D may become an "at-hand tool" in the fight against COVID-19.

## 5. Vit E (Vitamin E)

Vit E is a fat-soluble antioxidant that prevents cell membranes' integrity from being damaged by free radicals. Animal trials evidence demonstrates that Vit E deficiency compromises both cell-mediated and humoral immune function [33, 34]. It supports T-cell mediated functions, optimization of Th1 response and suppression of Th2 response [35]. Supplementation above the recommended levels has been displayed to strengthen immunity and increase resistance against several pathogens. [36, 37] Compared to animals, only a limited number of human trials have shown the effects of Vit E on resistance against infectious diseases. These human trials' main focus aims at the elderly, whom the groups commonly contract respiratory diseases. [38]

Studies have shown that oxidative stress is one of the main driving pathological mechanisms which support the influence of acute respiratory distress syndrome (ARDS) corresponding to COVID-19 infection. [6] Vitamin E supplementation can lower the production of superoxides and may then tilt the balance back, which favors the antioxidants and benefit the progress of COVID-19 treatment. [6]

## 6. Zinc

The body contains little Zinc, and thus inadequate intakes may result in a deficiency that can compromise immunity. [39] More specifically, deficiency is associated with immune dysfunction and increased susceptibility to infectious diseases. [40] Zinc plays an essential role in both innate and adaptive immune systems and cytokine production. It also displays antioxidant property that protects the body against reactive oxidative species; therefore, Zinc's proper status in the body acts as an anti-

inflammatory compound that optimizes immune response and further reduces the infection rate. [41]

The recent studies of Zinc-dependent viral enzymes to initiate the infectious process have proved the Zinc levels are directly associated with symptoms relieved of COVID-19.[42] Results found from four hospitalized patients diagnosed with COVID-19 have shown that their symptoms were alleviated after being treated with high-dose of zinc salts (15-23 mg/day) orally, indicating that high-dose zinc treatment may become an option for clinical recovery. [43]

**7. Iron**

Iron takes part in several immune processes, and also an essential component of enzymes involved in the activation of immune cells. [44] Its structure makes it a mediator of oxidative stress situations and a producer of highly toxic hydroxyl radicals against infectious agents. [44] Deficiency is linked to the attenuated efficacy of immune cells (NK cells and lymphocytes) and reduced cytokine production. [44] Oppositely, excessiveness can produce cellular toxicity, the titer should be monitor closely.

Concerning COVID-19, lower iron levels predispose to severe symptoms of SARS-CoV-2, monitoring the status can predict the disease severity and mortality. [45]

**8. Selenium**

Selenoprotein, which acts as cellular antioxidants, is involved in immune responses and is influenced by selenium status. [46] It mainly play a role in several components of the innate immune system by differentiation, proliferation, and normal functioning of these components. [47] Moreover, selenium also participates in the adaptive immune

response by supporting antibody production and development. Therefore, deficiency can reduce antibody concentration, decreased cytotoxicity of NK cells, compromised cellular immunity, and an attenuated response to vaccination. Supplementation of selenium can recover and also enhance the immune response to the virus. [48]

## 9. Immunity of vaccination

Vaccination seems to be the most efficient way to control the pandemic currently. According to world health organization, more than 200 vaccine candidates are in development and more than 60 of them are in clinical trials. Till 18 February 2021, at least seven different vaccines are available worldwide. COVID-19 vaccines has three broad categories, first is protein-base vaccines, such as inactivated virus vaccines and virus like particles; second is gene-based vaccines, such as viral vector vaccines, mRNA vaccines and DNA vaccines; third is combination of gene and protein-based vaccines, such as live-attenuated virus vaccines. [49] According to centers for disease control and prevention in the Unites States, three vaccines are recommended in the United States: Pfizer-BioNTech , Moderna and Johnson & Johnson/Janssen. The former two are mRNA vaccines, the later is a viral vector vaccine. Pfizer-BioNTech access an mRNA-lipid nanoparticle vaccine that encodes the S protein receptor binding domain (BNT 162b1) in humans; Moderna produced mRNA-1273 that encodes SARS-CoV-2 S protein that also encapsulated in lipid nanoparticle.[50, 51] The lipid nanoparticle entered human cell and mRNA is translated to antigenic protein in cytoplasm. The antigenic protein presented to cytotoxic T lymphocytes (CTLs) via major histocompatibility complex (MHC) I pathway and presented to helper T cells and B cells via MHC II pathway.[52] B cells can make antibodies to neutralize the virus

and CTLs can amplify the process of making antibodies. Another platform, viral vector vaccine, Ad26.COV2.S is a replication deficient adenovirus type 26 particle that contains the S protein DNA of SARS-CoV-2 made by Johnson & Johnson/ Janssen. It enters the human cell by a non-infectious adenovirus and transport DNA into the cell that will transduction to mRNA and translation to S protein. The S protein can initiate later immune response like the mRNA vaccines.[53](Figure 2)

Micronutrients are involved in immunity from the virus entering the human to innate immune response and adaptive immune response. Vitamin A, C, D, E, Fe, Zn can keep epithelial integrity and make respiratory tract barriers. Vitamin C, E, Fe, Zn, Se are efficient antioxidant. In innate immunity, Vitamin A, E, Zn, Se regulate natural killer function. Vitamin C, D can support the immune cells activities, movement and functions. In adaptive immunity, Vitamin A, E are mediated with Th1 and Th2 development. Vitamin E makes memory T cell increased. Vitamin A, C, Se help the production of antibody by B cell.[9, 19, 35, 54-56] Micronutrients are indispensable in immune response of vaccination.

In conclusion, at least as of recent studies, little evidence indicates a strong correlation between certain micronutrient supplementation and COVID-19 treatment. Prophylactic supplementation, however, has been proved in several trials to enhance our immune responses and to reduce the contraction of many infectious diseases. Depending on properties of distinct micronutrient supplementation, effects vary and some of them can backfire on body if having excessive intake. Influences of deficiency are harmful and also differ because certain vitamin or metal salt support

certain functions of body. Micronutrients do play important roles in physical barrier to innate and adaptive immunity.

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**Figure Legends**

Fig. 1. The Role of Micronutrient and COVID-19 Infection. All the micronutrients listed (Vit A, C, D, E, zinc, iron, selenium) can strengthen immune responses by enhancing immune cells activity. Vit A, C and D can improve epithelial barrier integrity. Vit C, E, zinc and selenium protect epithelium as displaying antioxidant properties. Enhanced epithelial barrier integrity, especially on ciliated cells, can be beneficial to prevent viral infection.

Fig. 2. Immune response of COVID-19 vaccination. The figure depicts the immune response of mRNA vaccine and viral vector vaccine. After entering to the human body, both of them can make S protein that present to our immune cells and have cytotoxic T cell maturation, antibody made by B cell.

Table 1. Vaccines of COVID-19

| Vaccine | Manufacturer | Platform | Dosage | Clinical stage | Storage | Overall efficacy | Approvals |
|---|---|---|---|---|---|---|---|
| **mRNA-1273** | **Moderna (US)** | mRNA | 2 | 3 | -20℃ | 92.1% after 1 dose, 94.1% after 2 doses | Approved in Switzerland, EUA in US, EU, Canada and UK |
| **BNT162b2** | **Pfizer-BioNTech (US)** | mRNA | 2 | 3 | -70℃ | 52% after 1 dose, 94.6% after 2 doses | Approved in several countries, EUA in US, EU, Canada and UK |
| **ChAdOx1** | **AstraZeneca/Oxford (UK)** | Viral vector | 2 | 3 | 2-8℃ | 64.1% after 1 dose, 70.4% after 2 doses | Approved in Brazil, EUA in WHO/Covax, UK, India and Mexico |
| **Ad26.CoV2.S** | **Janssen/Johnson & Johnson (US)** | Viral vector | 1 | 3 | 2-8℃ | 72% in US, 66% in Latin America, 57% in South Africa | EUA in US, EU and Canada |
| **Gam-COVID-Vac** | **Gamaleya National Research Center for Epidemiology and Microbiology (Russia)** | Viral vector | 2 | 3 | -20℃ or 2-8℃ | 87.6% after 1 dose, 91.1% after 2 doses | EUA in Russia, Belarus, Argentina, Serbia, United Arab Emirates, Algeria, Palestine and Egypt |
| **NVX-CoV2373** | **Novavax, Inc (US)** | Protein subunit | 2 | 3 | 2-8℃ | 89.3% in UK after 2 doses, 60% in South Africa | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **BBIBP-CorV** | **Sinopharm 1⁄2 (China)** | Inactivated virus | 2 | 3 | 2-8℃ | Unpublished reports of 79% and 86% | Approved in China, United Arab Emirates, Bahrain. EUA in WHO, Serbia, Peru, Zimbabwe |
| **CoronaVac** | **Sinovac Biotech (China)** | Inactivated virus | 2 | 3 | 2-8℃ | Unpublished reports after 2 doses, 50.38% for mild, 78% for mild to severe in Brazil, 65% in Indonesia, 91.25% in Turkey | Approved in China, EUA in WHO, Brazil, Columbia, Bolivia and other countries |
| **UB-612** | **COVAXX(US)/United Biomedical Inc, Asia (Taiwan)** | Protein subunit | 2 | 2 | 2-8℃ | | |
| **MVC-COV1901** | **Medigen Vaccine Biologics Corporation (Taiwan)/NIAID/Dynavax (US)** | Protein subunit | 2 | 2 | 2-8℃ | | |

Figure 1

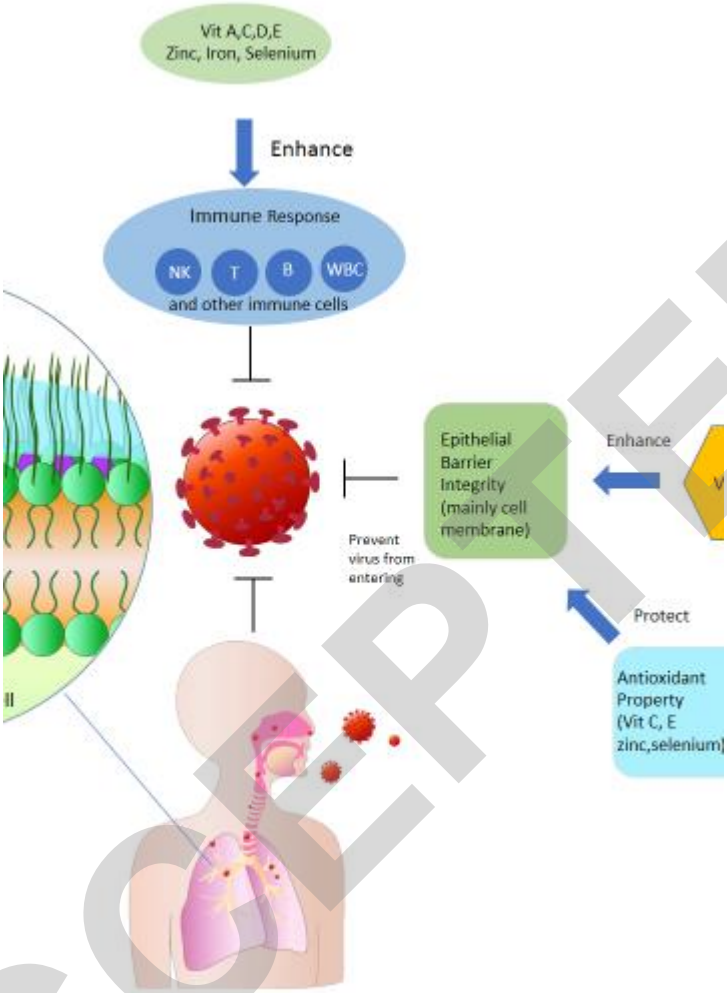

Figure 2