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Role and Effects of Micronutrients Supplementation in Immune System and SARS-Cov-2(COVID-19)

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

COVID-19 is a serious disease caused by the virus SARS-CoV-2 which is easily transmitted to humans. There are no vaccines or drugs discovered yet to control its transmission and prevent the disease. In that case, it is important to find the methods of preventing and controlling it. To fight against the virus a well-functioning immune system is necessary. The immune system is always active but if an individual becomes infected then the activity of immune system is enhanced to fight against the virus and recover the body from infection. Adequate intake of micronutrients through diet (vitamins A, B-complex, C, D and zinc, selenium, copper, iron) can help to boost up the immune system as each of the nutrients named above has roles in supporting antiviral and antibacterial defense. Although the supplementation of micronutrients can be given, it is necessary to provide the right amount of supplements after assessing the nutritional status of each individual as supplementation of micronutrient have some adverse effects. Therefore, it is recommended to follow a healthy diet to prevent COVID-19 and also assess the nutritional status of COVID-19 patients before prescribing treatments.

Keywords: Micronutrients; immune system; micronutrient supplementation; respiratory tract infection; SARS-CoV-2; COVID-19.

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ABBREVIATIONS

IL	*: Interleukin*
CD	*: Cluster of Differentiation*
COVID-19	*: Corona Virus Disease 2019*
SARS CoV-2	*:Severe Acute Respiratory Syndrome*
WHO	*: World Health Organization*
PMNL	*: Polymorphonuclear Leukocytes*
DTH	*: Delayed-Type Hypersensitivity*

1. INTRODUCTION

COVID-19, a severe acute respiratory syndrome is caused by the virus SARS-CoV-2 and WHO declared this as a global pandemic [1]. Previous epidemics related to CoV included that severe acute respiratory syndrome (SARS)-CoV was started in China in 2002 [2] and the Middle East respiratory syndrome (MERS)-CoV in the Middle East, first reported in 2012 [3]. Not all types of people are suffering from this virus. People with weak immune system are much exposed to SAS-Cov-2 [4]. There are many recommendations to prevent the spread of COVID-19 from the WHO [5], the UK [6], USA [7] governments and the European Commission [8] as well as public health agencies including the key direction of self-isolation [9]. Some potential treatment options (anti-viral, anti-malarial, herbals) are also introduced to treat COVID-19 patients [10]. Nutrition especially micronutrients play a vital role to alleviate both mortality and morbidity in COVID-19 as micronutrients boost up our immunity system. Nutritional status is an important factor influencing the outcome of patients with COVID-19 [11]. In a study, a list of nutrients were identified with possible anticoronavirus effects based on in vitro and clinical studies [11]. Several micronutrients have antioxidants feature such as Vitamin C, Vitamin E, and beta-carotene. Antioxidants increase response to influenza virus vaccine compared with placebo and also increase the number of T-cell subsets, enhance lymphocyte response to mitogen [12]. The activity of the immune system in our body is accompanied by an increasing rate of metabolism, requiring energy sources, substrates for biosynthesis, and regulatory molecules that are derived from the diet. Adequate supply of essential nutrients is required in this pandemic situation [13,14]. This review is based on published data and information and major searches were done using Google scholar and PubMed. This review aims to describe the role of specific micronutrients in supporting the immune system and also describes the effect of micronutrients supplementation in this pandemic situation.

2. ROLE OF IMMUNITY IN VIRAL INFECTION

When an individual exposed to viral infection, the immunity system becomes vital. First of all, the innate immunity system of the body such as macrophages, monocytes and dendritic cells recognize the foreign particles or pathogens. The presence of pattern recognition receptors (PRRs) and microbe-associated molecular patterns (MAMPs) help in the identification of the pathogens. TLR7 and TLR8 of innate immune system are more important for recognition of corona virus. After viral infection some cells release IFN-α and IFN-β. Natural killer cells are directly activated after viral infection to kill the infected cells. The maturation of dendritic cells is induced by PRRs signaling which functions to precess and present viral antigen. The presentation of viral antigens is resulted by upregulation of MHC I on virally infected cells which kill the virally affected cells releasing the pore forming protein like perforin. The production of IL-2 by CD4+ helper T lymphocytes and T helper 1 phenotype promotes cytotoxic T lymphocytes activity which produce antival antibodies by the differentiation of B lymphocytes to plasma cells. Then these antibodies can bind to the viruses and destroy them [15-18].

3. ROLE OF VITAMIN A IN IMMUNITY

The roles of vitamin A in the immunity system and host susceptibility to infection are identified in many studies [19-23]. The main functions of vitamin A are helping in visions, providing immunity, contributing in gene expression, etc. Vitamin A is required for immune cell maturation and functioning as boosting the immune system is the main focus to prevent the spread of COVID-19. Deficiency of vitamin A may impair barrier functions and immune response. Vitamin A and its metabolites help to modulate innate immunity along with barrier function and also control neutrophil maturation. The functions of neutrophil are to ingest and kill bacteria. Vitamin A also supports in phagocytic activity to promote bacteria killing. Vitamin A helps to increase the activity of natural killer cells which have antiviral defenses. Other functions of vitamin A are to control dendritic cell, CD4+ T lymphocyte maturation and maintaining the balance between T helper 1 and T helper 2 lymphocytes. There are various chemical forms of vitamin A and each

of the form has different activity in immune system. Movements of T lymphocyte to the gut-associated lymphoid tissue is promoted by retinoic acid and it is also required for CD8+ T lymphocyte survival and proliferation [24]. Many systemic reviews supported that vitamin A could reduce the rate of mortality and mobility from measles and improved symptoms in acute pneumonia. A systemic review study is conducted by Imdad et al. [25] found that vitamin A decreased all causes of mortality and morbidity from diarrhea and measles and decreased the incidence of diarrhea and measles. Another study found that vitamin A decreased morbidity and mortality with pneumonia and also increased the clinical response and shortened length of hospital stay [26]. Common sources of vitamin A are Liver, eggs, oily fish, fortified margarine, dairy products, carrots, orange fruits, green and yellow vegetables and tomato juice and the recommendation of vitamin A intake for adults is 3000-5000IU [27]. The adverse effects of vitamin A supplementation are identified in Table 2.

4. ROLE OF VITAMIN D IN IMMUNITY

Vitamin D is an important micronutrient for health because of its function in bone, immune etc. Several studies included the role of vitamin D in immune system [28-30]. The active form of vitamin D is 1, 25-dihydroxyvitamin D3 which has important immune-regulatory properties. However, the functions of vitamin D on the cellular components of immunity are rather complex. Vitamin D improves antimicrobial peptide synthesis in epithelial tissue [31] and also inhibits the proliferation of T cell, and production of cytokines by T helper 1 lymphocyte. It also has little impact on CD8+ T lymphocyte. Low level of vitamin D in the body has been associated with upper respiratory tract infections [32,33] including influenza [34], chronic obstructive pulmonary disease [35] and allergic asthma [36]. Many studies showed that supplementation of vitamin D can reduce the risk of viral respiratory tract infection [37] and many meta-analysis studies have been concluded this subjects. According to Bergman et al. and Martineau et al., vitamin D decreases the risk of respiratory tract infections [38,39]. A systematic review and meta-analysis conducted by Zhou et al. [40] concluded that risk of pneumonia had been increased with deficiency of vitamin D. So, vitamin D can be important micronutrients to treat COVID-19 patients. The common sources of vitamin D are sunlight, Liver, eggs, oily fish, fortified margarine and dairy products and recommendation of vitamin D intake for adults is 400-1000IU [27]. The adverse effects of vitamin D supplementation are identified in Table 2.

Table 1. Effects of vitamin and mineral supplementation on immunity

Immune system	Vitamins and minerals	Models	Effects
Macrophages	C supplementation [41]	Human	Stimulation of chemotaxis and phagocytosis
	E dietary supplementation [42]	Rat	Inhibited glomerular sclerosis
	Zinc supplementation [43]	human	Increased IL-1, IL-6, TNF-α, INF-γ
Natural killer cell	C dietary supplementation [44]	Human	Enhance activity
	E dietary supplementation [45]	Human	Enhance activity
	Zinc [46]	Human	Enhance activity
	Selenium [47]	Mouse	Enhance activity and IL-2 protein
	Iron [48]	Mouse	Decreased activity
PMNL	B_{12} supplementation [49]	Human	Increased bacterial killing
	C supplementation [50]	Human	Enhanced phagocytosis, decreased superoxide production
	C,E supplementation [51]	Human	Suppressed production of oxygen free radical
	Copper, Zinc and Iron supplementation [52-54]	Human	Increased neutrophil function
DTH	C supplementation [55]	Human	Increased
	E supplementation [56]	Human	Increased
T cell	C, E and A supplementation [57]	Human	Increased
	Zinc supplementation [58]	Human	Increased T lymphocyte

Abbreviations: PMNL: Polymorphonuclear Leukocytes, DTH: Delayed-Type Hypersensitivity

Table 2. Adverse effects of vitamin and mineral supplementation [27,59-61]

Vitamin and minerals	Adverse effects associated with supplements
Vitamin A	Hepatotoxic effects, visual change, hair and skin change, risk of lung cancer among smokers, diarrhea
Vitamin B6	Sensory neuropathy, ataxia
Vitamin B12	No upper limit unknown
Vitamin D	Hypocalcaemia, soft tissue calcifation
Vitamin C	Diarrhea, gastric
Vitamin E	Nausea, vomiting, diarrhea, headache, fatigue, blurred vision
Zinc	Nausea and vomiting, immune-suppression and impaired copper uptake
Selenium	Brittle hair and nails, peripheral neuropathies and gastrointestinal upset
Iron	Nausea, vomiting, reduced zinc uptake and constipation

5. ROLE OF VITAMIN C IN IMMUNITY

Vitamin C is a water soluble vitamin which has antioxidant properties. It plays a major role in the immune system of the human body. It is required for collagen biosynthesis and also helps in the migration of leucocytes to the sites of infection [62]. Other roles of vitamin C in immunity are phagocytosis, bacteria killing, and natural killer cells activity [62,63]. Vitamin C supplementation enhances the activity of natural killer cells [44]. Variety of studies stated that the severity of upper respiratory tract infections can be lowered by vitamin C supplementation. A meta-analysis stated that vitamin C decreased the incidence of pneumonia as well as reduced severity and morbidity from pneumonia [64]. For its functional properties, many doctors and researchers suggested to increase the intake of vitamin C to boost up the immunity and to fight against the corona virus. The common sources of vitamin C are Citrus fruits, broccoli, kiwi, yams, strawberries, melons and recommendation of vitamin C intake for adults is 60-90mg [27]. The adverse effects of vitamin C supplementation are identified in Table 2.

6. ROLE OF VITAMIN B-COMPLEX IN IMMUNITY

B vitamins are mainly involved in intestinal immune regulation and help in the gut-barrier functions. Folic acid increases the number of circulating T lymphocyte, but the activity of neutrophils appears unchanged. Vitamin B_{12} increases the phagocytic and bacteria killing capacity of neutrophils while vitamin B_6 helps in the lymphocyte proliferation and increases the number of T lymphocyte in the blood. Folic acid, vitamin B_6 and B_{12} enhanced the activity of natural killer cells which would be important in antiviral defense [65,66]. A study found that deficiency of vitamin B_6 decreased the T lymphocyte and B lymphocyte proliferation and IL-2 production [67]. The common sources of vitamin B complex are Poultry, fish, meat, nuts, legumes, whole grains, potatoes, meat, egg, seaweed etc and the recommendation of vitamin B_6 and B_{12} for adults are 1.3-2 mg and 2.4-6 µg respectively [27]. The adverse effects of vitamin B complex supplementation are identified in Table 2.

7. ROLE OF VITAMIN E IN IMMUNITY

Vitamin E acts as a scavenger of free radical by blocking the per-oxidation of polyunsaturated fatty acids (PUFA) and also acts as antioxidants. It is suggested that vitamin E is an important nutrient in the immune system [68]. Due to vitamin E deficiency, T-cell mitogenesis, IL-2 production, PMN phagocytosis, and PMN chemotaxis are decreased [56]. It is found that there is a positive association between vitamin E and cell-mediated immune responses and vitamin E supplementation appears to be beneficial for adults people [69]. Vitamin E supplementation also enhances the activity of helper T lymphocyte and improves vaccine responses [70]. Several studies identified that vitamin E supplementation reduced the risk of respiratory tract infections and decreased the duration of respiratory tract infections among adults [71]. The common sources of vitamin E are Plant oils (soya, corn, olive), nuts, seeds, wheat germ and the recommendation of vitamin E for adults people is 15-20 mg [27]. Supplementation of vitamin E also has some adverse effects which are identified in Table 2.

8. ROLE OF ZINC IN IMMUNITY

In this COVID-19 situation, zinc is considered as a supportive treatment therapy as it has direct antiviral effects [72]. It is found that zinc supplementation may have positive effects in the

treatment of COVID-19 patient [73]. The role of zinc in immunity is explained in many studies [74-76]. Zinc deficiency can cause loss of T helper cells and also responsible for atrophy of thymus and spleen. Zinc increases the IgM plaque response and IgG response. Cell mediated immunity is also increased with zinc supplementation. T lymphocyte proliferation is also maintained by proper dietary intake of zinc [77]. Some meta-analysis found that zinc decreased the prevalence and incidences of pneumonia as well as duration of common cold [78,79]. The common sources of zinc are meat, cheese, cereals and grains, shellfish etc.

9. ROLE OF SELENIUM IN IMMUNITY

Selenium has important effect on both innate and acquired immunity. Selenium enhances the function of T lymphocyte and B lymphocyte and also increases the activity of natural killer cell [80,81]. A study found that selenium supplementation improved immune function in the human body [82]. The common sources of selenium are fish, meat, egg and nuts. Supplementation of selenium also has some adverse effects on the body.

10. ROLE OF COPPER IN IMMUNITY

Some studies described the importance of copper in the immune system. Copper has antimicrobial properties, and also increases the activity of natural killer cell and neutrophils, monocyte function [83,84]. Some studies showed that lymphocyte proliferation and IL-2 production are promoted by copper [85]. A systematic review found that respiratory tract infection can be reduced by copper supplementation [86]. The common sources of copper are nuts, shellfish and some vegetables.

11. CONCLUSION

Nutrition is very important for every steps of life and proper intake of both micronutrients and macronutrients can help to prevent and treat several infectious diseases. All nutrients named above have special role in immune system of the body, and consumption of adequate amount nutrients is necessary to boost up our immune function. Immune system can also be boosted up by supplementation of these nutrients. However, there are some adverse effects of micronutrients supplementation in case of overdosing. Many studies showed both positive and negative effects of micronutrients supplementation on immune response and human health. However, there are no published studies which described the function of micronutrients for the prevention and treatment of corona-virus but some studies showed that intake right amount of micronutrients can reduce the duration of the disease severity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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