

Review Article

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

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 that are 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, its activity is enhanced. Therefore, Adequate intake of micronutrients through diet (vitamins A, B, complex, C, D and zinc, selenium, copper, iron) can help lead to boost up the enhance the activity of immune system as each of the nutrients named above has roles in supporting the antiviral and antibacterial defense. Although the sSupplementation of micronutrients can be given. However, it is necessary to provide an adequate amount of supplement as supplementation of micronutrient have some adverse effects which may lead to toxicity. 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

ABBREVIATION:

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 include severe acute respiratory syndrome (SARS)-CoV started in China in 2002 (2) and- the Middle East respiratory syndrome (MERS)-

Comment [RG1]: Not clear? I think it should be re-written - if the individual becomes infected then the immune system needs to work more as it has to fight with the virus to prevent and recover the human body from the infection.

Comment [RG2]: Right amount of supplements after assessing the nutrition status of every individual

Comment [RG3]: All citations to be linked with the bibliography as not able to refer

CoV in the Middle East, first reported in 2012 (3). Not all types of are suffered from this virus. People with a weak immunity 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). Nutrition, especially micronutrients plays a vital role to prevent both mortality and morbidity in COVID-19 as micronutrients boosts up our immunity system. Nutritional status is a important factor influencing the outcome of patients with COVID-19(10). In a study, a list of nutrients are identified with possible anti coronavirus effects based on in vitro and clinical studies(10). 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 (11). The activity of the immune system in our body is accompanied by an increase rate of metabolism, requiring energy sources, substrates for biosynthesis and regulatory molecules which are derived from diet. Adequate supply of essential nutrient supply is required in this pandemic situation(12, 13). The aim of this review is to describe the role of specific micronutrients in supporting immune system and also describing the effect of micronutrient supplementation in this pandemic situation.

2. ROLE OF VITAMIN A IN IMMUNITY:

The role of vitamin A in immunity system and in host susceptibility to infection are identified in many studies(14-18). The main functions of vitamin A are helping in vision, provide immunity, helping in gene expression etc. Vitamin A is required for immune cell maturation and function as boosting immune system is the main focus to prevent the spread of COVID-19. Deficiency of vitamin A may impaired 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 cell which has 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 form of vitamin A and each of the forms have different activity in immune system. Movements of T lymphocyte to the gut associated lymphoid tissue are promoted by retinoic acid and it is also required for CD8+ T lymphocyte survival and proliferation(19). There are many systemic reviews which supports that vitamin A can reduce the rate of mortality and mobility from measles and improved symptoms in acute pneumonia. A systemic review study conducted by Imdad et al(20) found that vitamin A decreased all cause 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 (21). Common sources of vitamin A are Liver, eggs, oily fish, fortified

Comment [RG4]: Methodology is missing. Author needs to write about the methodology in brief like he has done the literature review and all together how many researches/studies/guidelines he has reviewed, etc.

margarine and dairy products and recommendation of vitamin A intake for adults is 3000-5000IU(22). The adverse effect of vitamin A supplementation identified in Table 2.

Comment [RG5]: All are animal source products. What about the plant sources i.e. vegetarian sources? Please include those.

3. 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 (23-25). The active form of vitamin D is 1,25-dihydroxyvitamin D₃, which has important immune-regulatory properties. However, the function of vitamin D on the cellular components of immunity are rather complex. Vitamin D improves antimicrobial peptide synthesis in epithelial tissue (26) 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 have been associated with upper respiratory tract infections (27, 28) including influenza(29), chronic obstructive pulmonary disease(30) and allergic asthma(31). Many studies showed that supplementation of vitamin D can reduce the risk of viral respiratory tract infection(32) and many meta-analysis studies have been concluded this subjects. According to Bergman et al and Martineau et al, vitamin D decreased the risk of respiratory tract infections(33, 34). A systematic review and meta-analysis conducted by Zhou et al(35) concluded that risk of pneumonia had been increased with deficiency of vitamin D. The common sources of vitamin D are Liver, eggs, oily fish, fortified margarine and dairy products and recommendation of vitamin D intake for adults is 400-1000IU(22). The adverse effect of vitamin D supplementation identified in Table 2.

Comment [RG6]: Sunlight should also be included as a great source of Vitamin D which is missing here. Secondly, it has a role in calcium absorption in the body which is also missing. Hence, to be included.

Table 1: Effects on vitamin and mineral supplementation on immune response

Immune system	Vitamins and minerals	Models	Effects
Macrophages	C supplementation(36)	Human	Stimulation of chemotaxis and phagocytosis
	E dietary supplementation(37)	Rat	Inhibited glomerular sclerosis
	Zinc supplementation(38)	human	Increased IL-1, IL-6, TNF- α , INF- γ
Natural killer cell	C dietary supplementation(39)	Human	Enhance activity
	E dietary supplementation(40)	Human	Enhance activity
	Zinc (41)	Human	Enhance activity
	Selenium(42)	Mouse	Enhance activity and IL-2 protein
PMNL	Iron(43)	Mouse	Decreased activity
	B ₁₂ supplementation(44)	Human	Increased bacterial killing
	C supplementation(45)	Human	Enhanced phagocytosis, decreased superoxide production
	C,E supplementation(46)	Human	Suppressed production of oxygen free radical

	Copper, Zinc and Iron supplementation(47-49)	Human	Increased neutrophil function
DTH(delayedtype Hypersensitivity)	C supplementation(50)	Human	Increased
	E supplementation(51)	Human	Increased

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

Table 2: Adverse effects of vitamin and mineral supplementation (22, 52-54)

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	Hypercalcemia, soft tissue calcification
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

4. ROLE OF VITAMIN C IN IMMUNITY:

Vitamin C is a water soluble vitamin which has antioxidant properties. It plays a major role in immune system of the human body. It is required for collagen biosynthesis and also helps in migration of leucocyte to the sites of infection(55). Other roles of vitamin C in immunity are phagocytosis, bacteria killing and natural killer cell activity(55, 56). Vitamin C supplementation enhances the activity of natural killer cell(39). Variety of studies stated that 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 decreasing severity and morbidity from pneumonia (57). 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(22). The adverse effect of vitamin C supplementation identified in Table 2.

5. ROLE OF VITAMIN B COMPLEX IN IMMUNITY:

B vitamins are mainly involved in intestinal immune regulation and helps in the gut barrier functions. Folic acid increase the number of circulating T lymphocyte but the activity of neutrophils appears unchanged.

Vitamin B₁₂ increases the phagocytic and bacteria killing capacity of neutrophils while vitamin B₆ helps in the lymphocyte proliferation and increase the number of T lymphocyte in the blood. Folic acid, vitamin B₆ and B₁₂ enhanced the activity of natural killer cells which would be important in antiviral defense(58, 59). A study found that deficiency of vitamin B₆ decrease the T lymphocyte and B lymphocyte proliferation and IL-2 production(60). 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 B₆ and B₁₂ for adults are 1.3-2mg and 2.4-6µg respectively(22). The adverse effect of vitamin B complex supplementation identified in Table 2.

6. ROLE OF VITAMIN E IN IMMUNITY:

Vitamin E acts as a scavenger of free radical by blocking the per-oxidation of polyunsaturated fatty acid (PUFA) and also acts as antioxidants. It is suggested that vitamin E is an important nutrients in immune system (61). Due to vitamin E deficiency, T-cell mitogenesis, IL-2 production, PMN phagocytosis, and PMN chemotaxis decreased(51). It is found that there is a positive association between vitamin E and cell-mediated immune response and vitamin E supplementation appears to be beneficial for adults people(62). Vitamin E supplementation also enhances the activity of helper T lymphocyte and improves vaccine responses(63). Several studies identified that vitamin E supplementation can reduce the risk of respiratory tract infections and decrease the duration of respiratory tract infections among adults (64). 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 15-20mg(22). Supplementation of vitamin E also has some adverse effects which are identified in Table 2.

7. ROLE OF ZINC IN IMMUNITY:

In this COVID-19 situation, zinc is considered as a supportive treatment therapy as it has direct antiviral effects(65). It is found that zinc supplementation may have positive effects in the treatment of COVID-19 patient (66). The role of zinc in immunity is explained in many studies (67-69). Zinc deficiency can cause loss of T helper cell and also responsible for atrophy of thymus and spleen. Zinc increase 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 (70). Some meta-analysis found that zinc decreases the prevalence and incidences of pneumonia as well as duration of common cold (71, 72).

8. 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 functions and also increases the activity of natural killer cell(73, 74). A study found that selenium supplementation improve immune function in the human body(75). Supplementation of selenium also has some adverse effects on the body.

9. ROLE OF COPPER IN IMMUNITY:

Some studies described the importance of copper in immune system. Copper has antimicrobial properties and also increase the activity of natural killer cell and neutrophils, monocyte function(76, 77). Some studies showed that lymphocyte proliferation and IL-2 production are promoted by copper(78). A systematic review found that respiratory tract infection can be reduced by copper supplementation(79).

10. CONCLUSION:

Nutrition is very important for very 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. Many studies showed the 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 in the context of COVID-19 virus, but some studies showed intake of right amount of micronutrients can reduce the duration of the disease.

Comment [RG7]: In case of overdosing.

Comment [RG8]: Positive effect or negative effect. Please clarify

Comment [RG9]: Not clear? Are you talking about the decease caused due to covid 19 virus? To be clarified further for the readers.

CONSENT

Not applicable

ETHICAL APPROVAL

Not applicable

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