

ROLES OF VITAMINS IN IMMUNITY AND COVID-19: A LITERATURE REVIEW

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ABSTRACT

SARS-CoV-2 is a severe acute respiratory virus that causes Coronavirus Disease-19 (COVID-19). Even before the COVID-19 pandemic, diet was undeniably important in immunity. In order to be more resilient during and after the pandemic, understanding the role of vitamins is crucial. This review aims to explore the role of vitamins in supporting the immune system and its correlation to COVID-19. The article search was done using five electronic databases (i.e., Google Scholar, Semantic Scholar, ScienceDirect, PubMed, and PMC). Some of the keywords utilized in the literature search were “vitamin A and immunity” OR “vitamin B and immunity” OR “vitamin C and immunity” OR “vitamin D and immunity” OR “vitamin E and immunity” OR “vitamin A and covid19” OR “vitamin B and covid19” OR “vitamin C and covid19” OR “vitamin D and covid19” OR “vitamin E and covid19”. A total of 51 articles was assessed in this literature review. Research finds vitamin A plays a role in both innate immune system cell function and humoral immunity by regulating, differentiating, and maturing immune system cells. Vitamin B complex primarily reduces inflammation by lowering serum C-reactive protein levels (CRP), while vitamin C strengthens epithelial barriers, phagocytes, T and B lymphocytes, and inflammatory mediators, to improve the immune system. Vitamin D acts as a mediator in the vitamin D receptor (VDR), an inner immune system component that regulates the humoral and adaptive immune systems through unique genetic transcriptions. Finally, vitamin E acts as an antioxidant, lowering the production of reactive oxygen and nitrogen species (ROS and RNS). In conclusion, all vitamins are essential in improving individual’s immune system that prevent from infectious diseases including COVID-19.

Keywords: COVID-19, immunity, infectious disease, vitamin

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is a respiratory disease caused by SARS-CoV-2) virus. Droplets from the respiratory system secretions easily propagate COVID-19 causing fever, dry cough, dyspnea (shortness of breath), headache, disorientation, fatigue, vomiting, and diarrhea (Huang et al., 2020; Shi et al., 2020). Within three months of its discovery, the World Health Organization (WHO) designated COVID-19 a pandemic. Until this paper was written, there were 523 million confirmed cases worldwide according to the WHO, with more than six million deaths (WHO, 2020). As many as 87% of COVID-19 patients aged 30–79 had one or more comorbidities, such as cardiovascular disease, diabetes mellitus, and hypertension. Those with comorbidities had a greater death risk than those without (Mungroo et al., 2020).

It is unarguable that nutrition plays a crucial role in immunity, even before the COVID-19 pandemic. The cells in the body, particularly those in the immune system, require adequate nutrients to function at their best. However, the degree of malnutrition, especially micronutrient deficiency was still high. Despite recent efforts in the prevention and control of micronutrient deficiency, vitamin A, iodine, and/or iron deficiencies indicate that over two billion individuals worldwide are at risk (Ramakrishnan, 2002). Pregnant women and young children are most at danger in Southeast Asia and Sub-Saharan Africa, where the frequency is exceptionally high. For example, the number of pregnant anemic women in Indonesia accounted for 48.9% (Ministry of Health, 2019).

Micronutrient status, host immune response, and virus pathogenicity all have complicated and multidimensional relationships. One

of the major roles of micronutrients is for the coordinated recruitment of innate and adaptive immune responses to viral infections, as well as the modulation of pro- and anti-inflammatory host responses (Gorji & Ghadiri, 2021).

Several vitamins and minerals, such as vitamins A, B, C, D, E, folate, zinc, iron, selenium, and copper, play a role in supporting both innate and adaptive immunities. The deficiency of the nutrients further influences the immune system functions and decreases the resistance against infections (Calder et al., 2020; Gombart et al., 2020). Malnourished people have a higher risk of having infectious diseases and impaired wound healing, which increases the morbidity and mortality. Some studies have discussed the role of vitamins and minerals within the immune system and their relation to infectious diseases (Gombart et al., 2020; Wintergerst et al., 2007). Furthermore, insufficient micronutrients not only decrease the immune system's ability to fight viral infections, but also contribute to the formation of more virulent strains by altering the viral genome's genetic makeup (Beck & Levander, 2000). This review explores the role of vitamins in supporting the immune system and its correlation to COVID-19.

METHOD

Article searching was done using five electronic databases (i.e., Google Scholar, Semantic Scholar, ScienceDirect, PubMed, and PMC). The keywords used were “vitamin A and immunity” OR “vitamin B and immunity” OR “vitamin C and immunity” OR “vitamin D and immunity” OR “vitamin E and immunity” OR “vitamin A and covid19” OR “vitamin B and covid19” OR “vitamin C and covid19” OR “vitamin D and covid19” OR “vitamin E and covid19”. The purpose of this literature review is to answer the research question, “How do vitamins affect immunity and COVID-19?” Only English-language research was taken into consideration. The data was delivered narratively. Fifty-one articles were included in this paper. Articles in line with the study objective were included.

RESULTS AND DISCUSSION

Vitamin A

Vitamin A is a fat-soluble vitamin that was discovered in 1928 and has a role in the immune system that is called “anti-infective” vitamin (Green & Mellanby, 1928). Three active forms of vitamin A in the body are retinol, retinal, and retinoic acid, in which the latter has the most prominent biological activity. Vitamin A's mechanism of action toward immunity still cannot be fully understood; however, some literature disclosed the possibility of mechanisms that make vitamin A stimulate the immune system. In the innate immune system, furthermore, retinoic acid plays an indispensable role in the regulation of differentiation, maturation, and the innate immune system cell functions.

The innate immune cells consist of macrophage and neutrophil, which start a direct response on the pathogenic invasion through phagocytosis and “natural killer” T cell activation that performs immunoregulatory functions through cytotoxic activities (Chang & Hou, 2015; Wynn & Vannella, 2016). Moreover, vitamin A also plays a role in humoral immunity by immunoglobulin synthesis. Prior research revealed that retinoic acid synergizes with gut-associated lymphoid tissues of dendritic cells from IL-6 or IL-5 to secrete IgA (Huang et al., 2018). Besides IgA, retinoic acid also plays a role in increasing the IgG antibody production by activating Th2 response through the increase in expression of costimulatory molecules, CD86, and natural killer T cell population (NKT) that is correlated with IL-4 secretion increase (Ross & Restori, 2013).

Studies regarding the provision of vitamin A to COVID-19 patients have not yet been found; nonetheless, numerous researches have concluded that vitamin A provides positive effects on many types of infectious diseases. Semba et al. (1999), for example, reported that vitamin A supplementation is capable of reducing morbidity and mortality of various infectious diseases, including measles, diarrhea, measles pneumonia, HIV, and malaria with numerous

mechanisms of activation of innate and adaptive immune cell responses. The administration of vitamin A supplementation can also increase the antibody response toward vaccines and protect life-threatening complications due to infection, including lung disease, malaria, and HIV (Jayawardena et al., 2020; Zhang & Liu, 2020). Studies on animals indicated that chickens fed with a low amount of vitamin A are more susceptible to coronavirus infection than those fed with a high amount of vitamin A (Zhang & Liu, 2020).

The Recommended Dietary Allowance (RDA) of vitamin A is 900 mcg for adult males and 700 mcg for adult females (Institute of Medicine, 2000). Several foods recognized as containing high amount of vitamin A are chicken liver (23,000 mcg), mango (16,400 mcg), papaya leaf (18,250 mcg), moringa leaf (10,020 mcg), and carrot (7,125 mcg) (Ministry of Health, 2018).

Vitamin B

Vitamin B is a water-soluble vitamin that also has a role as a cofactor and coenzyme. Vitamin B can be obtained from the diet and the microbial synthesis such as intestinal microbiota (Yoshii et al., 2019). A study in animals revealed that vitamin B6 deficiency decreases the proliferation and differentiation of lymphocyte T cells, reduction in IL-2, and the increase in IL-4 (Qian et al., 2017). Cross-sectional studies from the NHANES 2003-2004 data and HIV-infected people data showed a correlation between vitamin B intake and inflammation. A higher niacin, pyridoxine, or cobalamin intake is related to the lower serum C-reactive protein (CRP) level (Morris et al., 2010; Poudel-tandukar, 2016). The provisions of a high dose of vitamin B6, namely 50 mg/day for critically ill patients for 14 days can increase the immune responses, including lymphocyte T cells, T-helper, and T-suppressor increases (Cheng et al., 2006).

Folate deficiency can affect the immune response, especially cell-mediated immunity, by reducing the lymphocyte T cells circulation and its proliferation. Folate deficiency also reduces the capacity of CD8⁺ cell proliferation in response to mitogen activation (Shetty, 2010). Meanwhile, vitamin B12 deficiency reduces the amount of lymphocyte and CD8⁺ cells as well as its proportion to CD4⁺. A low CD4⁺/CD8⁺ ratio

can reduce the activity of NK cells (Shetty, 2010). An *in silico* study revealed that vitamin B12 could obstruct the viral replication by inhibiting the RNA-dependent-RNA polymerase activity of nsp12 from SARS-CoV-2 (Narayanan & Nair, 2020). This study brings up an opportunity to be continued to *in vitro*, *in vivo* studies and clinical studies. Vitamin B12 contributes to the immune response through T cells CD8 and NK cells. The provision of vitamin B12 to anemic patients with vitamin B12 deficiency increases the number of lymphocyte cells and CD8⁺ besides the CD4/CD8 ratio and the suppressed activity of NK cells (Tamura et al., 1999). In the meantime, the *in vitro* study suggested that riboflavin and ultraviolet light reduce the infectious titer of MERS-CoV and SARS-CoV-2 in human blood plasma (Keil et al., 2016; Ragan et al., 2020). During COVID-19, it is recommended as much as 100% RDA for age and gender in addition to a well-balanced diet (Fernandez-Quintela et al., 2020).

Vitamin C

Vitamin C can optimize the immune system through some mechanisms; namely, increasing epithelial barriers, phagocyte, T and B lymphocytes, and inflammatory mediators (Carr & Maggini, 2017). In its relation to the epithelial barriers increasement, vitamin C functions in the stabilization of collagen, the protection against ROS-caused damages, triggering keratinocyte differentiation and lipid synthesis, the increase in proliferation and fibroblast migration, and the decrease in wound healing time (Kishimoto et al., 2013; Lauer et al., 2013; Mohammed et al., 2016).

The role of vitamin C in phagocytic function begins by increasing the neutrophilic migration as a response toward chemotaxis increases. Lacking vitamin C conditions, thus, can affect the decrease in phagocytic function to migrate to the infected cells. After that, the phagocytosis process is continued with the ROS increase and pathogenic killing. The chemotaxis neutrophil ability during the phagocytosis process is also influenced by the antihistamine function from vitamin C. After the phagocytosis and pathogenic killing processes, neutrophils undergo a process of programmed cell death called apoptosis. Vitamin C then continues

to the apoptosis process by increasing the uptake and clearance by macrophage as well as preventing the occurrence of necrosis and excessive tissue damage (Fisher et al., 2012).

B and T lymphocytes also accumulate vitamin C in high doses through sodium-dependent vitamin C transporter 2 (SCVT2). It is further elaborated that vitamin C plays a vital role in modulating T cells' maturation. Moreover, vitamin C also functions in increasing antibody levels (IgM and IgG) (Tanaka et al., 1994). The last role of vitamin C in the immune system, additionally, is the modulator of inflammation, which is also known as cytokines. Cytokines are further explained as primary cells signaling molecules secreted by various immune cells, both innate and adaptive, in response to infections and inflammation consisting of multiple molecules, including chemokines, interferons (IFNs), interleukin (IL), lymphokines, and TNF that modulate the humoral and cellular-based immune responses. Cytokines, moreover, can generate both pro-inflammation and anti-inflammation responses (Carr & Maggini, 2017). Vitamin C, therefore, roles as a potent antioxidant toward the occurrence of oxidative stress caused by COVID-19; hence, it can prevent inflammation and cell damage besides enhancing the phagocytic ability of the immune system cells and contributing to the demolition of hazardous pathogens (Hancer et al., 2020). In other words, vitamin C helps in easing the cytokine storm in COVID-19 patients.

The role of vitamin C in improving the coronavirus symptoms has been exposed since 1978 in a study that concluded that vitamin C increases the endurance of chicken embryo trachea toward avian coronavirus (Atherton et al., 1978). An observational study carried out to 17 moderate-severe COVID-19 patients disclosed that the administration of intravenous vitamin C for as many as 1 gram per eight hours for three days as part of COVID-19 medication reduces the inflammatory markers, which include ferritin, D-dimer, and the fraction of inspired oxygen (FiO₂). Therefore, it can be affirmed that, clinically, it is feasible to administer intravenous vitamin C to moderate-severe COVID-19 patients (Hiedra et al., 2020). However, research regarding intravenous vitamin C provision for as many as 12 grams, compared to the placebo to severe pneumonia

patients due to COVID-19 twice a day for seven days, is still being carried out as of September 2020 (Clinical trials identifier: NCT04264533). As a consequence, the effects of vitamin C administration cannot yet be enforced.

The recommended vitamin C intake for adult males is 90 mg and 75 mg for adult females with daily addition of 35 mg for smokers (Institute of Medicine, 2000). There is also a recommendation of vitamin C intake up to 200 mg to avoid infections (disease susceptibility and the maintenance of an adequate immune function); and 1–2 g/day for infected patients (Fernandez-Quintela et al., 2020). Some foods are high in vitamin C (per 100 gr), such as cashew fruit (197 mg), soybean (121 mg), mustard greens (102 mg), ketip bananas (95 mg), and guava (87 mg) (Ministry of Health, 2018).

Vitamin D

Vitamin D is one of the fat-soluble vitamins that can be synthesized by the body with the help of UVB rays, or obtained from food. Vitamin D is acknowledged as having an essential role in the immune system. Vitamin D has a role as the mediator in the Vitamin D Receptor (VDR), an inner part of the immune system to modulate the humoral and adaptive immune system through specific-genetic transcriptions (Koivisto & Hanel, 2020). VDR can be found in almost all immune cells, for instance, B and T lymphocytes, monocytes, macrophage, and dendritic cells.⁹⁰ In the humoral immune system, VDR plays a role in cathelicidin antimicrobial peptides (CAMP) and defensin β 2 formations (Koivisto & Hanel, 2020). Besides, VDR is a component of the pattern-recognition receptor (PRR) and used to suppress inflammatory cytokines release.⁹² Furthermore, vitamin D through VDR also influences the adaptive immune system activity by suppressing the T helper cell production and T1 by stimulating T2 release. These activities, then, will enhance the adaptive immune system activation (Dimitrov & White, 2016; Sassi et al., 2018).

Some studies argued that vitamin D has a negative correlation with respiratory tract infections. Pham et al. (2019) revealed that subjects with serum 25 (OH)D levels of less than 37.5 mg have a higher risk for acute respiratory infections. Zitterman et al. (2016) added that vitamin D

deficiency increases the risk of severe airways infection. A study conducted to workers in Japan showed that vitamin D level was related to the risk for influenza to the subject group that did not get vaccinated (Nanri et al., 2016). The same pattern, additionally, was found in a recent study involving COVID-19 patients in Switzerland, which revealed that a lower 25(OH)D level was found more in PCR-positive patients than in PCR-negative patients in SARS-CoV-2 examinations (D'Avolio et al., 2020). Furthermore, vitamin D deficiency is discovered more in high-risk groups for COVID-19, such as obese, smokers, and elderly (de Jongh et al., 2017; Ghosh et al., 2020; Jiang et al., 2016; Roizen et al., 2019; Zhang et al., 2016).

Due to its significant functions in the immune system, numerous researchers assumed vitamin D provides protective effects toward SARS-CoV-2 infections (Grant et al., 2020; McCartney & Byrne, 2020), which hypothesizes the assumption of using vitamin D metabolic pathways in the immune system. Vitamin D increases Angiotensin Converting Enzyme 2 (ACE2) production in the alveolus cells that can reduce lung tissue damages. ACE2 is an enzyme in the Renin-Angiotensin, which functions to regulate lung vasodilation besides acting as the SARS-CoV-2 receptor. The bond between ACE2 and SARS-CoV-2, causing a decrease in the number of ACE2 in lung cells, which will lead to an increased risk of lung damage and pneumonia (Mahdavi, 2020). Vitamin D also produces cathelicidin in alveolar epithelial cells that can reduce viral replication by activating the mechanism of autophagy (Chieosilapatham et al., 2018; Crane-godreau et al., 2020; Grant et al., 2020; Jiang et al., 2020). Cathelicidin can also minimize lung damage due to hypoxia (Jiang et al., 2020).

Vitamin D can suppress the cytokine storm through suppression of Th1 cytokines and interferon γ formulations (Grant et al., 2020). As a result, vitamin D plays a role in preventing COVID-19 severity by suppressing the cytokine storm. Although vitamin D has a promising effect for COVID-19 treatment, until recently, there have been no studies confirming the outcome of the optimal dose of vitamin D supplementation under COVID-19 conditions. Thus, further research is needed to prove the role of vitamin D as a strategy

for the prevention and treatment of COVID-19. For recommendation intake, 10,000 IU over few weeks, followed by 5000 IU (until 25-hydroxyvitamin D concentrations rise above 40–60 ng/mL (equivalent to 100–150 nmol/L) (Fernandez-Quintela et al., 2020).

Vitamin E

Vitamin E is one of the fat-soluble vitamins consisting of tocopherol and tocotrienol that also has a role as an antioxidant. Nonetheless, only the α -tocopherol form can meet human needs since α -tocopherol has 5–10 times of bioavailability and a better metabolism than γ -tocopherol (Dayong Wu et al., 2019). Amongst the foods containing vitamin E are beans, seeds, vegetable oils (soybean, sunflower, corn), and green leaves (spinach and broccoli) (Lee & Han, 2018; Muscogiuri et al., 2020; Wu et al., 2019).

Several studies on humans and animals discovered that vitamin E deficiency can damage the immune system (Wu & Meydani, 2018). Vitamin E increases the immunity by taking oxygen in oxidants to reduce oxidative stress so that it can reduce the impact of inflammatory damage (Lee & Han, 2018; Wu & Meydani, 2018). Other roles of vitamin E are protecting PUFA in membrane cells from the oxidation, managing the ROS and reactive nitrogen species (RNS) productions, and controlling the transduction signal (message delivery) so that when the body undergoes inflammation, it will automatically respond to it (Coquette et al., 1986; Wu et al., 2019).

In the elderly, increasing vitamin E intake is beneficial for better immune function by giving resistance to infection and reducing pain due to infection (Gavazzi et al., 2011; Hemilä, 2016; Meydani et al., 2018). The elderly tend to experience diseases due to the decreased immune system caused by old age (immunosenescence) (Ginaldi et al., 2001). Therefore, the administration of vitamin E and combining it with vitamin C is highly possible for antioxidant therapy in complications due to COVID-19 (Wang et al., 2020).

The study carried out by Meydani et al. (2004) argued that a high dose of vitamin E (800 mg/day in one study and 60, 200, and 800 mg/day in other study) increases the T-helper 1 in the cellular

immunity. Another study added that the provision of vitamin E supplementation (200 IU/day or 135 mg/day) for a year reduces the risk of respiratory tract infections in the elderly (Meydani et al., 2004). Although vitamin E is highly recommended as a potential nutrient to fight against COVID-19, nevertheless, until recently, the estimated exact dose for a specified target has not yet been discovered. Therefore, further studies regarding the proper doses for vitamin E supplementation for every age group need to be carried out (Zhang & Liu, 2020). An RCT study in Iran was conducted to analyze the impact of administering vitamin A, B, C, D, and E supplementations to the mortality rate of COVID-19 patients in the ICU (Beigmohammadi et al., 2020).

CONCLUSION

In conclusion, all vitamins are essential in improving an individual's immune system that prevents from infectious diseases including COVID-19. Even though the pandemic has almost come to an end, maintaining adequate vitamin intake should be reached because maintaining the immune system is not only for preventing COVID-19 but other hundreds of infectious diseases. Thus, in order to be more resilient after pandemic, vitamin intake should reach requirements. Strengthening the immune system becomes one of the goals in preventing or reducing illness severity as well.

The role of vitamin A both in innate immune system cell function is by regulation, differentiation, and maturation of immune system cell functions and also synthesizing immunoglobulin as the humoral immunity. Vitamin B complex mainly plays a role in reducing inflammation level by lowering serum C-reactive protein (CRP). Vitamin C improves the immune system by strengthening epithelial barriers, phagocytes, T and B lymphocytes, and inflammatory mediators, among other things. Vitamin D functions as a mediator in the Vitamin D Receptor (VDR), an inner element of the immune system that regulates the humoral and adaptive immune systems via unique genetic transcriptions. Last but not least, vitamin E acts as an antioxidant, reducing the generation of reactive oxygen and nitrogen species (ROS and RNS).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We would like to thank Universitas Airlangga for funding this research (No. 532/UN3/2020).

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