International Journal of Medical Laboratory 2023;10(2):120-126.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Review Article

The Importance of Antioxidant/Anti-inflammatory Vitamins during the SARS-CoV-2 Infection

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ABSTRACT

Article history
Received: 17 Dec 2022
Accepted: 31 May 2023
Available online: 15 Jun 2023

Keywords
COVID-19
Dietary supplements
SARS-COV-2
Self-immune system
Vitamins

Coronavirus 2019 (COVID-19), an epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has spread worldwide since it was first identified in Wuhan, China, in December 2019, leading to outbreaks of epidemics. Due to the increasing spread of this disease, definitive treatment and approved vaccines have not been found for it. In this study, we reviewed recent articles on the effect of vitamins (including vitamins A, B, and E) for treating coronavirus. This result suggests that some dietary supplements such as vitamins (A, B, C, D, E, etc.) have antiviral, antioxidant, and anti-inflammatory effects. Dietary supplements consisting of vitamins and individual dietary habits can therefore be used as adjunctive therapy along with antiviral drugs in the treatment of COVID-19 disease.

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[DOI: 10.18502/ijml.v10i2.12945]

Introduction

A large group of viruses that cause illnesses ranging from the common cold to more acute illnesses, such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-COV) are coronaviruses (CoV). The new virus was unknown until December 2019, when it emerged in Wuhan, China [1-3]. The ongoing coronavirus disease 2019 (COVID-19) pneumonia pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is spreading worldwide [4]. SARS-CoV-2 causes severe inflammation and damage to endothelial cells in the heart, liver, kidney, and gut, suggesting vascular infection rather than pure respiratory disease [5, 6]. An overactivated and misdirected immune response can cause these symptoms. High levels of interleukin (IL)-6 followed by a cytokine storm without an adequate response to interferon types I and III are associated with severe COVID-19 disease [7-12]. Patients with major underlying medical conditions, especially those with chronic conditions such as hypertension, diabetes, coronary artery disease, and cancer, are susceptible to SARS-CoV-2 due to their low systemic immunity due to the disease itself and its treatment [13]. Therefore, strengthening the autoimmune system is particularly vital. The key ways to strengthen an individual's immunity are maintaining personal hygiene, a healthy lifestyle, and proper food intake [14, 15]. Dietary supplements may be beneficial in managing SARS-CoV-2 infection [16]. In general, vitamins act as modulators of immune function. SARS-CoV-2 causes stress on infected host cells by increasing levels of pro-inflammatory cytokines in the blood [17]. Antioxidant and anti-inflammatory effects are natural functions of many vitamins (including vitamins A, C, and E). Oxidative stress thus happens in a series of imbalances between the production of free radicals and the organism's ability to detoxify these molecules/ molecular fragments, resulting in cellular damage [18, 19]. Conversely, antioxidants are low- or high-molecular-weight substances (vitamins, minerals, enzymes, etc.) that counteract the harmful properties of free radicals and help prevent or repair cellular damage [20-22]. Therefore, paying attention to your diet during this period is important by following a healthy and balanced dietary pattern that includes adequate amounts of minerals, antioxidants, and vitamins. Fruits and vegetables containing micronutrients such as vitamins A and B, E, and C have been reported to boost immune system function. Antioxidants increase the number of T-cell subsets, increase lymphocyte response to mitogens, increase IL-2 production, and enhance natural killer cell activity [23]. Vitamins A, C, D, E, B6, and B12 are important for maintaining the structural and functional integrity of physical barriers (skin, gastrointestinal mucosa, airways, etc.) and, thus, the differentiation of innate immune cells. Important to proliferation, function, and migration processes. Vitamins C and E, on the

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[DOI: 10.18502/ijml.v10i2.12945]

other hand, and selenium protect cells from free radical damage during increased oxidative stress through differentiation, proliferation, and normal function of T and B cells. These nutrients also affect antibody production and function, contribute to cell-mediated immunity, and aid in pathogen recognition and destruction [24]. This review mentions the importance of antioxidant/anti-inflammatory vitamins during the SARS-CoV-2 infection by potentiating the immune system.

Vitamin A

As a fat-soluble vitamin, vitamin A refers to several substances, including retinol, retinal, retinoic acid, retinoids, and carotenoids. Vitamin A's main benefits and functions are antioxidant effects, role in night vision, correct color discrimination, role in antibody formation and immune system support, and skin integrity [25]. The most common sources of vitamin A are liver and fish oil. Other sources of vitamin A include milk and eggs, green leafy vegetables, orange and yellow vegetables, tomatoes, fruit, and some vegetable oils [26]. Vitamin A (also known as the "anti-infective" vitamin) has anti-inflammatory roles related to improving immune system function and mucosal integrity, protecting the body from infection [27]. Jee et al. announced that diets low in vitamin A may have reduced the effectiveness of inactivated coronavirus vaccines in cattle and increased the susceptibility of calves to infections [28]. The effects of contamination with infectious bronchitis virus, a coronavirus, were more pronounced in chickens with severe vitamin A malnutrition than in vitamin A-rich chickens [29]. Vitamin A has been suggested to treat coronaviruses and prevent lung infections [30]. Vitamin A improves the phagocytic and oxidative function of macrophages. Vitamin A helps regulate the number and function of natural killer (NK) cells and also helps to regulate the production of IL-2 and the pro-inflammatory tumor necrosis factor alpha (TNF- α), which activates the microbial action of macrophages. Vitamin A is also involved in developing and differentiating T helper (Th)1 and Th2 cells [24].

Vitamin B

B vitamins (e.g., B1, B2, B3, B6, B7, B9, and B12) play crucial roles in the immune system [31-36]. Vitamin B1 (thiamine), through its effects on proapoptotic proteins, mitochondrial membrane integrity, cytochrome C release, P38 mitogen-activated protein kinase activity, and oxidative stress-induced nuclear factor-κB (NF-κB) mediated several has anti-inflammatory effects. Vitamin B1 insufficiency can cause inflammation, T-cell infiltration, and overexpression of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6 [37]. The main role of vitamin B2 (Riboflavin) is to regulate the energy metabolism of all cells [38]. Keil et al. have reported that ultraviolet light and vitamin B2 effectively reduced the titer of MERS-CoV in human plasma products [39]. Vitamin B3 (Niacin) produces T cells and interleukins [40]. Vitamin B3, also known as nicotinamide, could enhance the destruction of *Staphylococcus aureus* through a myeloid-specific transcription factor [41]. Moreover,

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[DOI: 10.18502/ijml.v10i2.12945]

vitamin B3 treatment significantly inhibited neutrophil infiltration into the lungs during ventilator-induced lung injury with a strong anti-inflammatory effect [41, 42]. Vitamin B6 (Pyridoxine) has a role in lymphocyte maturation [24], and vitamin B6 deficiency has been associated with a dramatic depletion of thoracic duct lymphocytes and a reduction in lymphocyte proliferation [40]. Vitamin B12 (cobalamin) can act as an immunomodulator and increase the number of cytotoxic T cells against viral infections [24, 43]. In sepsis and systemic inflammatory response syndrome, it is believed that vitamin B12 may also be used as a therapeutic compound. Vitamin B12 helps maintain normal macrophage activity. It also has several anti-inflammatory effects, such as regulating NF-κB, a key activator of pro-inflammatory signaling pathways. It also has a proven role in bacteriostasis and phagocytosis [41, 42, 44]. Therefore, B vitamins can be selected as a basic option for COVID-19 treatment. The best sources of B-complex vitamins are whole grains, lean meats, fish, poultry, eggs, milk, seeds, beans, nuts, and various fruits. etc. [26].

Vitamin E

Vitamin E is an antioxidant in reducing oxidative stress by binding free radicals [45]. Vitamin E deficiency stimulated myocardial injury in mice infected with RNA viruses and coxsackievirus B3 [46, 47]. Furthermore, vitamin E deficiency significantly increases the risk of bovine CoV infection in calve [48]. Vitamin E strengthens the immune system, fights pathogens such as bacteria and viruses with its powerful antioxidant properties, and maintains the integrity of T-cell membranes [49, 50]. In addition, vitamin E performs many important functions in the immune system, including cell-mediated destruction of microorganisms and antibody production [51, 52]. However, a recent study showed that vitamin E shortened the duration of influenza virus infection [53]. Meydani et al. reported that the group treated with vitamin E (received 200 IU daily) had fewer cold days per person per year [54]. These studies suggest mechanisms involved in the effects of vitamin E in the reduction of Prostaglandin E2 production by the inhibition of cyclooxygenase-2 activity mediated through decreasing nitric oxide production, the improvement of effective immune synapse formation in naive T cells and the initiation of T cell activation signals. Moreover, more activity of the NK cells and lower IL-12 production/migration were induced by vitamin E, but the underlying mechanisms need to be further elucidated [52]. Numerous foods, such as nuts, seeds, vegetable oils, corn, etc., provide vitamin E [26].

Conclusion

This study investigated the effects of vitamins on the disease of COVID-19. Corona 2019 is an acute respiratory disease caused by a new coronavirus called SARS-COV2. This disease is spreading rapidly in the cities of China and other countries. The prevalence of this disease is very high. The disease is mainly transmitted through droplet transmission and close contact with the patient. The most important ways to increase personal safety are personal hygiene, health protocols, social distancing, wearing a

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[DOI: 10.18502/ijml.v10i2.12945]

mask, and washing hands regularly. Dietary supplements, along with health tips, can help prevent disease. SARS-COV virus increases plasma levels of pro-inflammatory cytokines. Many vitamins (A, C, E, etc.) have antioxidant and anti-inflammatory properties. Therefore, patients should consume a healthy, balanced diet containing sufficient antioxidants and vitamins. Antioxidants also increase the production of IL-2 and the activity of NK cells. Vitamins A, C, E, B6, and B12 are important for innate immune cells' differentiation, proliferation, function, and migration. Vitamin B6 may play a role in improving coronary heart disease by suppressing the development of a cytokine storm.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgment

None.

References

[1]. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020; 26(3): 368.

[2]. Goumenou M, Sarigiannis D, Tsatsakis A, Anesti O, Docea AO, Petrakis D, et al. COVID-19 in Northern Italy: An integrative overview of factors possibly influencing the sharp increase of the outbreak. Molecular Medicine Reports 2020; 22(1): 20-32.

[3]. Tsatsakis A, Petrakis D, Nikolouzakis TK, Docea AO, Calina D, Vinceti M, et al. COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence. Food and Chemical Toxicology 2020; 141: 111418.

[4]. Fedullo AL, Schiattarella A, Morlando M, Raguzzini A, Toti E, De Franciscis P, et al. Mediterranean diet for the prevention of gestational diabetes in the Covid-19 era: Implications of Il-6 in diabesity. International Journal of Molecular Sciences 2021; 22(3): 1213.

[5]. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet 2020; 395(10234): 1417-418.

[6]. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. New England Journal of Medicine 2020; 383(6): 590-92.

[7]. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. China medical treatment expert group for Covid-19: Clinical characteristics of coronavirus disease. N Engl J Med. 2019; 382(18): 1708-720.

[8]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020; 395(10223): 497-506.

[9]. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immuno-suppression. The Lancet 2020; 395(10229): 1033-1034.

[10]. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host & Microbe 2020; 27(6): 992-1000.

[11]. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of Clinical Investigation 2020; 130(5): 2620-629.

[12]. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020; 181(5): 1036-1045.

[13]. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncology 2020; 21(3): 335-37.

[14]. Yoshikawa TT, High KP. Nutritional strategies to boost immunity and prevent

[Downloaded from ijml.ssu.ac.ir on 2024-09-16]

[DOI: 10.18502/ijml.v10i2.12945]

infection in elderly individuals. Clinical Infectious Diseases 2001; 33(11): 1892-900.
[15]. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. Progress in Molecular Biology and Translational Science 2015; 135: 355-80.
[16]. Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. Nutrients 2020; 12(6): 1562.
[17]. Fung TS, Liao Y, Liu DX. Regulation of stress responses and translational control by coronavirus. Viruses 2016; 8(7): 184.
[18]. Kolahi S, Hejazi J, Mohtadinia J, Jalili M, Farzin H. The evaluation of concurrent supplementation with vitamin E and omega-3 fatty acids on plasma lipid peroxidation and antioxidant levels in patients with rheumatoid arthritis. Internet J Rheumatol. 2011; 7: 1-7.
[19]. Jamilian M, Dizaji SH, Bahmani F, Taghizadeh M, Memarzadeh MR, Karamali M, et al. A randomized controlled clinical trial investigating the effects of omega-3 fatty acids and vitamin E co-supplementation on biomarkers of oxidative stress, inflammation, and pregnancy outcomes in gestational diabetes. Canadian Journal of Diabetes 2017; 41(2): 143-49.
[20]. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochemistry Cell Biol. 2007; 39(1): 44-84.
[21]. Gorrini C, Harris IS, Mak TW. Modulation of oxidative stress as an anticancer strategy. Nature Reviews Drug Discovery 2013; 12(12): 931-47.
[22]. Poprac P, Jomova K, Simunkova M, Kollar V, Rhodes CJ, Valko M. Targeting free radicals in oxidative stress-related human diseases. Trends in Pharmacological Sciences 2017; 38(7): 592-607.
[23]. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet-London, 1992; 340: 1124-129.
[24]. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutrients 2020; 12(1): 236.
[25]. Ianoşi S, Ianoşi G, Neagoe D, Ionescu O, Zlatian O, Docea AO, et al. Age-dependent endocrine disorders involved in the pathogenesis of refractory acne in women. Molecular Medicine Reports 2016; 14(6): 5501-506.
[26]. Khan MMI, Shill LC, Purba NH, Chakma M, Prosad V, Rumel AR. Prevention, possible treatment, and control of corona virus (SARS-CoV-2). Asian Journal of Immunology 2020: 8-19.
[27]. Stephensen CB. Vitamin A, infection, and immune function. Annual Review of Nutrition. 2001; 21(1): 167-92.
[28]. Jee J, Hoet AE, Azevedo MP, Vlasova AN, Loerch SC, Pickworth CL, et al. Effects of dietary vitamin A content on antibody responses of feedlot calves inoculated intramuscularly with an inactivated bovine coronavirus vaccine. American Journal of Veterinary Research. 2013; 74(10): 1353-362.
[29]. West CE, Sijtsma SR, Kouwenhoven B, Rombout JH, van der Zijpp AJ. Epithelia-damaging virus infections affect vitamin A status in chickens. The Journal of Nutrition. 1992; 122(2): 333-39.
[30]. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. Journal of Medical Virology 2020; 92(5): 479-90.
[31]. Mazur-Bialy AI, Buchala B, Plytycz B. Riboflavin deprivation inhibits macrophage viability and activity–a study on the RAW 264.7 cell line. British Journal of Nutrition 2013; 110(3): 509-14.
[32]. Bozic I, Savic D, Laketa D, Bjelobaba I, Milenkovic I, Pekovic S, et al. Benfotiamine attenuates inflammatory response in LPS stimulated BV-2 microglia. PLoS One 2015; 10(2): 118372.
[33]. Kunisawa J, Sugiura Y, Wake T, Nagatake T, Suzuki H, Nagasawa R, et al. Mode of bioenergetic metabolism during B cell differentiation in the intestine determines the distinct requirement for vitamin B1. Cell Reports 2015; 13(1): 122-31.
[34]. Kuroishi T. Regulation of immunological and inflammatory functions by biotin. Canadian Journal of Physiology and Pharmacology 2015; 93(12): 1091-1096.
[35]. Zhang P, Tsuchiya K, Kinoshita T, Kushiyama H, Suidasari S, Hatakeyama M, et al. Vitamin B6 prevents IL-1β protein production by inhibiting NLRP3 inflammasome activation. Journal of Biological Chemistry 2016; 291(47): 24517-4527.
[36]. Kruman II, Kumaravel T, Lohani A, Pedersen WA, Cutler RG, Kruman Y, et al. Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models ofAlzheimer's disease. Journal of Neuroscience 2002; 22(5): 1752-762.
[37]. Spinas E, Saggini A, Kritas S, Cerulli G, Caraffa A, Antinolfi P, et al. Crosstalk between vitamin B and immunity. J Biol Regul Homeost Agents. 2015; 29(2): 283-88.

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[DOI: 10.18502/ijml.v10i2.12945]

[38]. Powers HJ. Riboflavin (vitamin B-2) and health. The American Journal of Clinical Nutrition 2003; 77(6): 1352-360.
[39]. Keil SD, Bowen R, Marschner S. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. Transfusion 2016; 56(12): 2948-952.
[40]. Qian B, Shen S, Zhang J, Jing P. Effects of vitamin B6 deficiency on the composition and functional potential of T cell populations. Journal of Immunology Research 2017; 2197975: 1-12.
[41]. Kyme P, Thoennissen NH, Tseng CW, Thoennissen GB, Wolf AJ, Shimada K, et al. C/EBPε mediates nicotinamide-enhanced clearance of Staphylococcus aureus in mice. The Journal of Clinical Investigation 2012; 122(9): 3316-329.
[42]. Jones HD, Yoo J, Crother TR, Kyme P, Ben-Shlomo A, Khalafi R, et al. Nicotinamide exacerbates hypoxemia in ventilator-induced lung injury independent of neutrophil infiltration. PloS One 2015; 10(4): 123460.
[43]. Tamura J, Kubota K, Murakami H, Sawamura M, Matsushima T, Tamura T, et al. Immuno-modulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clinical & Experimental Immunology 1999; 116(1): 28-32.
[44]. Romain M, Sviri S, Linton D, Stav I, van Heerden PV. The role of Vitamin B12 in the critically ill: A review. Anaesthesia and Intensive Care 2016; 44(4): 447-52.
[45]. Galmés S, Serra F, Palou A. Vitamin E metabolic effects and genetic variants: a challenge for precision nutrition in obesity and associated disturbances. Nutrients 2018; 10(12): 1919.
[46]. Beck MA, Kolbeck PC, Rohr LH, Shi Q, Morris VC, Levander OA. Vitamin E deficiency intensifies the myocardial injury of coxsackievirus B3 infection of mice. The Journal of Nutrition 1994; 124(3): 345-58.
[47]. Beck MA. Increased virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency. The Journal of Nutrition 1997; 127(5): 966-70.
[48]. Nonnecke B, McGill J, Ridpath J, Sacco R, Lippolis J, Reinhardt T. Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. Journal of Dairy Science 2014; 97(9): 5566-579.
[49]. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. IUBMB Life 2019; 71(4): 487-94.
[50]. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 2020; 12(4): 1181.
[51]. Salehi B, Rescigno A, Dettori T, Calina D, Docea AO, Singh L, et al. Avocado–soybean unsaponifiables: a panoply of potentialities to be exploited. Biomolecules. 2020; 10(1): 130.
[52]. Lee GY, Han SN. The role of vitamin E in immunity. Nutrients 2018; 10(11): 1614.
[53]. Galabov AS, Mileva M, Simeonova L, Gegova G. Combination activity of neuraminidase inhibitor oseltamivir and α-tocopherol in influenza virus A (H3N2) infection in mice. Antiviral Chemistry and Chemotherapy 2015; 24(3-4): 83-91.
[54]. Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. JAMA 2004; 292(7): 828-36.

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