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Nutrition and immunity during COVID-19 pandemic

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ABSTRACT

Introduction: After the influenza pandemic since 1918, the world is experiencing another viral challenge by a coronavirus (SARS-CoV-2). One of the most important strategies is to enhance the immune system.

Results: Having an optimal nutritional behavior, following a balanced dietary pattern is essential for immune enhancement and reduce the risk of infectivity. Cytokine release syndrome (CRS) is hypothesized as one of the main causes of inflammation and consequently, lung damage in this viral infection. Undernutrition or overnutrition as the result of nutritional status can affect the immune system. Multivitamin and Minerals (MVM) intake can be beneficial in vulnerable populations such as the elderly, having a regular diet with the priority of healthy food portions can supply all daily requirements.

Conclusion: According to the WHO recommendations for consumption of fresh fruits and vegetables and also diets which have been hypothesized as an immune enhancer, the Mediterranean diet may involve all nutrients needed for improvement of the immune system.

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Introduction

After the influenza pandemic since 1918, the world is experiencing another viral challenge by a coronavirus (SARS-CoV-2). Resistance to probable therapies and ascending prevalent trends of this infection will pressure us to live with this virus, perhaps for a long time. This virus can infect almost all group ages, particularly adults. As of the seventeen of July, the World Health Organization (WHO) has reported 14.1 million confirmed individuals worldwide have 603,000 death (1). Recent studies from Wuhan have reported that around 15% of confirmed individuals infected by this virus progress to the severe respiratory dysfunction; this probability becomes more highlighted in adults over 65 years(2). Correspondingly, Neurologic consequences could be affected by SARS-Coronavirus-2 (3, 4). Since there is no specific treatment for this novel virus, it is essential to find alternative solutions to

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prevent and control infection or at least minimize the spread of this virus.

One of the most important strategies is to enhance the immune system as the first and the most effective weapon against viral infections. A healthy immune system depends on several factors, of which one of these is healthy, balanced nutrition that reach by receiving adequate vitamins and trace elements necessary for optimal immune function (5). From another overview, malnutrition due to unhealthy diets or inadequate nutrient intake, can increase the rate of infections and, subsequently, increase morbidity and mortality (6,7). Also significant economic burdens due to these consequences are one of the challenge that should be considered (8). Thus, having an optimal nutritional behavior, following balanced dietary patterns containing an adequate amount of micronutrients, antioxidant, vitamins, and minerals, is essential for immune enhancement and reduces the risk of infection.

This review will discuss the possible roles of nutrients and selective dietary patterns according to hypothesized mechanisms revealed for SARS-CoV-19 infection, which can promote immunity and reduce infectivity during this pandemic.

COVID-19 and immune system

Immune response due to SARS-CoV-2 infection has not been clearly understood. During early stages of infection (Incubation or mild manifestation of symptoms), an adaptive immune response is obligated to prevent the disease from progression to severe stages of the disease. This protection in early stages depends on appropriate general health, and well-nourished status; until the host can obtain antiviral immunity (9). On the other hand, when an optimal immune response cannot confront the virus activity, enormous destruction of affected tissues will occur, especially in tissues with ACE 2 expression (such as kidney and intestine). The damage can initiate an inflammatory pathway, which can cause advanced respiratory dysfunction at severe stages of disease (10).

One of the inflammatory mechanisms regarding the SARS-CoV-2 virus is cytokine release syndrome (CRS), which is hypothesized as one of the leading causes of inflammation and, consequently, lung damage in this viral infection. Cytokine release syndrome (also called cytokine storm) is a systemic inflammatory reaction that can be initiated by several factors such as infection(11). Observational studies on Influenza infections (as a respiratory viral disease) have shown rising levels of chemokines and cytokines in individuals affected by viruses, especially those who died. Also, it has been reported that virulence load correlates with this cytokine storm(12). Similarly, in an analysis of 150 confirmed SARS-CoV-2 patients, elevated IL-6 ($p<0.0001$) was detected as a biomarker of inflammation(13); so it is notable that blocking inflammatory cytokines such as IL-1, IL-6, and TNF may beneficial and should be considered in the management of disease through preventable or treatable strategies.

Diet and immunity

At the individual level, the particular trait that demonstrates the role of nutrition and dietary recommendations to fight against COVID-19 depends on the link between diet and immunity.

An optimal diet enriched with adequate nutrients is required for cells functioning in the immune system; this becomes highlighted when the immune system is activated or ready for activation when confronting SARS-CoV-2. An optimal diet should support immune cells to start effective responses against pathogens, while reduces immune activity after optimal response to minimize likelihood of any chronic inflammation or even autoimmunity. Some dietary elements have particular roles in this regard; as an example, vitamin C, which is known in collagen synthesis, has antioxidant effects and also improve proliferation and differentiation in B- and T-lymphocytes; regulates cytokine production and decreases histamine excretion(14). Roles of minerals such as zinc have been demonstrated in their deficiencies; lymphopenia, impaired cellular and humeral immune response, and impaired wound healing are consequences of zinc deficiency (15, 16).

Undernutrition or overnutrition as the result of nutritional status can affect the immune system; obesity was described for the first time as an independent risk factor in the 2009 H1N1 influenza pandemic. Around 33% of infected patients were obese. Severe obesity (Body Mass Index> 40 kg/m2) was severely correlated with the risk of admission in hospitals and also death from H1N1 influenza, while this correlation was independent of other comorbid factors (17). Also, it has been reported that obesity (BMI>30 kg/m2) was a considerable factor detected for mortality among individuals older than 20 years. However, this result was not significant for all-cause death but was correlated with length of stay in intensive care units and prolonged mechanical ventilation (18). In this regard, a systematic review implied that obesity plays an important role in the pathogenesis of COVID-19 (19). Also Stefan et al., reported that individuals with obesity are at risk of more severe course of COVID-19 (20).

Undernutrition as a result of food scarcity or famines (which is a concern of the remaining quarantine period for COVID-19 pandemic in developing countries) makes the population vulnerable to infections. The spectrum of immune dysfunction relies on the severity of the nutrient deficiency, nutrient interactions, and age of the person (21). Chronic protein-energy malnutrition (PEM) can debilitate immunity by affecting thymus function, T cell proliferation and differentiation, macrophage function, and complement activation (22).

Not only micronutrient deficiencies can result in impaired immunity, but also excessive intake of some nutrients can adversely affects immunity; for example, iron overload by supplementation may reduce antibody mediated phagocytosis by macrophages and monocytes, changes in T-lymphocyte subgroups, and alteration of lymphocyte scattering in a different part of the immune system (23).

During mouse model reports, new evidence has been reported, which suggests that the energy-restricted diet (ER) and diet-induced obesity (DIO) have harmful immune responses due to influenza infection. Higher susceptibility and mortality were consequences of both ER and DIO mice, which had been affected by the influenza virus. This study demonstrated that ER has considerable effects on innate responses of immunity, while DIO has pronounced effects during both innate and adaptive responses. These adverse effects include Natural killer cell dysfunction and altered inflammation(24).

We can investigate the role of undernutrition in individuals suffering from eating disorders such as Anorexia Nervosa (AN). There are several metabolic alterations due to anorexia nervosa, which results in organ system impairment, such as the immune system. Several authors believe that malnutrition induced immune deficiencies are consequences of anorexia nervosa; significant reductions on the t-lymphocyte percentage have been demonstrated. This reduction is reversed, and also an increase in CD8 cell count was observed by a complete nutritional diet (25).

We should take into consideration that there is evidence of the role of foods for improving the immune system, especially in viral infections such as influenza. Among them, garlic, cranberry, broccoli sprout, and oily fish are the most available options and affect antiviral defense responses by increasing virus-induced peripheral blood NK cell granzyme B production (26-29).

Micronutrients and immunity

All cells, as well as immune system cells, need adequate and appropriate nutrition to function optimally. The presence of nutrients is a necessity for the best immunological results and allow immune cells to initiate effective responses.

Vitamin A

Vitamin A is a fat-soluble vitamin that is recognized as an "anti-infective" vitamin that has previously been shown to effects the immune system. Vitamin A is also critical for intestinal lymphocyte trafficking and mucosal immune functions (30). Researches demonstrated that an adequate supply of vitamin A could reduce morbidity and mortality of different infectious diseases such as malaria, measles-related pneumonia, diarrheal diseases, and human immunodeficiency virus (HIV) infection (31). Studies showed that vitamin A

supplementation can reduce the recurrence of bronchopneumonia and time of remission after non-measles pneumonia in children (32). Additionally, Villamor et al. had reported that vitamin A supplementation provides protection against some infectious diseases, including lung diseases, HIV and malaria (33). Jee et al. revealed the association between low vitamin A consumption and inadequate production of IgG in calves. Authors reported that it is due to an inactivated bovine coronavirus vaccination, and calves receiving a diet supplemented with vitamin A produce more IgG compared to calves with low consumption of vitamin A (34).

Vitamin A and retinoids have been shown to inhibit the replication of the measles virus by increasing elements of the innate immune response and uninfected bystander cells, making them resistant to productive infection throughout the following sequence of viral replication (35). These findings suggest that vitamin A may be beneficial for the prevention and management of COVID-19 and lung infection.

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin and a wide-spectrum antioxidant essential for humans. Vitamin c also affects the immune system, such as the production of interferon, the transformation of T lymphocytes, and the function of phagocytes (14). Mostly high-quality evidence showed a significant reduction in duration, severity, and the time of confinement indoors of the common cold after supplementation with vitamin c in children and adults. This evidence also indicated that vitamin c supplementation can relieve the cold symptoms, including chest pain, fever, and chills (36, 37). some researches indicated that one of vitamin c functions is protection against infection caused by a coronavirus (38, 39). One study conducted by Hemila et al. demonstrated the utility of Vitamin C to reduce the risk of pneumonia in adults and children. Besides, the author suggested that the duration of pneumonia may also be reduced after vitamin C supplementation in adults (40). Another study supports that supplementation with vitamin c may minimize the risk of upper respiratory tract infection in athletes (41). A recent study suggested that a high intravenous dose of vitamin C is safe to prevent and treat COVID-19 infections (42). However, further clinical studies should be established to develop standard protocols.

B vitamins

B vitamins are water-soluble vitamins that play a significant role in the body's immune system (43). Vitamin B1, also called thiamine, affects as an anti-inflammatory factor and suppresses oxidative stress-induced NF-kappa B activation. Deficiency of thiamine may lead to immune system dysfunction and impairment of oxidative metabolism (44). Vitamin B2 (riboflavin) has a vital role in energy production (45). Keil et al. suggest that vitamin B2 and UV light potentially decrease the titer of MERS-CoV in human plasma products (46). Niacin (nicotinic acid), another vitamin of B-complex, has important modulatory effects on the production of inflammatory mediators. Also, one study suggests that nicotinamide treatment during ventilator-induced lung injury could significantly inhibit neutrophil infiltration into the lungs (47). In general, a low level of vitamin B group or low intakes are related to adverse clinical outcomes during viral infections and may attenuate host immune response (48).

Vitamin D

Vitamin D, a fat-soluble prohormone, is synthesized in the skin from exposure to sunlight. Mounting evidence suggests that vitamin D can reduce the risk of viral infections (49). Two meta-analyses reports indicated that the risk of respiratory tract infection can reduce by vitamin D (300–3653 IU/day) in adults and children (50, 51). In a review by Ahanchian et al. 2012, vitamin D deficiency was related to increased risk of respiratory infection, asthma, and wheezing in children (52). Recent evidence indicates that vitamin D supplementation has a beneficial effect on reducing the risk of upper respiratory tract infection, tuberculosis and influenza in children and adults (53). Evidence suggesting the role of vitamin D in

reducing the risk of COVID-19 includes when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest and a time when vitamin D deficiency contributes to ARDS. These studies proved that to increase 25(OH)D concentrations, 10,000 IU/d of vitamin D3 should be administered to people at risk of influenza and/or COVID-19 for a few weeks, followed by 5000 IU/d to decrease infection potential. The goal should be to increase the serum level of vitamin D above 40–60 ng/mL (100–150 nmol/L). For the treatment of individuals who become infected with COVID-19, higher vitamin D3 supplements might be beneficial (54). One of the mechanisms that reduce the risk of COVID-19 includes enhancement of innate immunity by vitamin D. Then, innate immunity generates both anti-inflammatory and pro-inflammatory cytokines in response to viral infections, as observed in COVID-19 patients (55). Vitamin D also enhances innate cellular immunity by inducing defensins and cathelicidin that can lower viral replication rates (56). According to this finding, vitamin D supplementation may have some utility for the treatment of COVID-19.

Vitamin E

Vitamin E is the main lipid-soluble antioxidant in the human body and is the general term for all tocopherols and tocotrienols. These compounds have distinct antioxidant activities that inhibit the production of reactive oxygen species molecules. Vitamin E plays an important role in increasing phagocytic functions and enhancing cell and humoral immune responses (57). Vitamin E as an antioxidant enhances response to influenza virus vaccine by producing interleukin-2 and increasing the number of T-cell subtypes (58). Evidence reported that supplementation with vitamin E (200 IU/day) for 1 year reduced the risk of upper respiratory tract infections in the elderly. Still, another study did not report a significant effect of vitamin E supplementation (200 mg/day) on the incidence and severity of respiratory infections (59). Therefore, Randomized controlled trials studies should be conducted to the evaluated effect of vitamin E supplementation in COVID-19 infection. However, dietary intake of vitamin E such as canola, walnut and vegetable oil is appropriate.

Zinc

Zinc is one of the dietary trace elements which could be consumed to reduce the intensity of COVID-19 infection and perhaps inhibit the replication of severe acute respiratory syndrome (SARS) coronavirus (60). Zinc is considered the potential effective compound in the therapy of COVID- 19 infection, especially its direct antiviral effect and immune-modulatory effect (61). Earlier studies have indicated that zinc deficiency could affect B lymphocyte development with low IgG production, leading to increased susceptibility to different viral and bacterial infections and higher mortality (60). It has been reported that zinc has an antiviral effect by inducing the generation of (IFN)-α and IFN-γ. It could be consumed to reduce the respiratory tract infection and perhaps lessen the intensity of COVID-19 infection (60, 62).

Selenium

Selenium is another trace element that is a crucial nutrient for immune function. Selenium is essential for selenoproteins' functions, which act as cellular antioxidants and redox regulators and thus are critical for Natural Killer cells and leukocytes functions. Selenium with glutathione peroxidase plays a role in protecting cells from oxidative stress and damage of free radicals (63). Selenium deficiency has been associated with an increased risk of poor immune function, cognitive decline, and mortality, while higher selenium levels have antiviral effects (64). Ma et al. reported that selenium combined with ginseng stem-leaf saponins could promote an immune response against the vaccination of infectious bronchitis coronavirus in chickens (65). Moghaddam et al. implied that covid-19 patients present low concentration of selenium in blood, low enzymatic activity of the secreted GPx3 and have deficiency in selenium transporter SELENOP (66). Another study by Zhang et al., found an association between the selenium status and cure rates for COVID-19 (67). Some studies evaluated

the role of selenium in viral infection and suggest that selenium supplementation could be used in viral infections (e.g., HIV, type A influenza virus) as safe adjuvant therapy up to 200 g/day (i.e., higher than the RDA of 55 g/day in adults) (68).

Magnesium

Magnesium plays a crucial role in modulating immune function by impacting antibody-dependent cytolysis, immune cell adherence, leukocyte activation, antigen-binding to macrophages, and regulation of apoptosis (69). Moreover, magnesium stabilizes the structure of nucleic acids and involved in DNA replication and repair (69). Evidence from human studies show that low intake of dietary magnesium could affect the occurrence and management of upper respiratory tract infections like asthma (70, 71). A previous study proposed that magnesium supplementation in adult subjects with asthma have little or no effect on the improvement of pulmonary function or measures of inflammation (72). Another study shows that supplementation of magnesium helps to provide better control of asthma symptoms in podiatric patients (73). Although some in-vivo and in-vitro studies indicate that magnesium is related to the immune response against viral infections (74), we could not found any RCTs that showed a beneficial impact on magnesium supplementation in immunity against viral infections.

Omega-3

Dietary long-chain PUFA, derived from fish oil, is shown to have anti-inflammatory properties. Long-chain PUFA such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) appear to be most beneficial. Both EPA and DHA inhibit T-cell proliferation and decrease the production of T-helper 1 type cytokine and inflammatory cytokines. Besides, omega-3 can increase the production of inflammation, resolving resolvins and protectin (74). Protectin D1 could attenuate influenza virus replication (75). The ability of omega-3 to decrease inflammation has been shown in numerous studies under different conditions. A study by Healy et al. high-dose omega-3 supplementation is shown to be useful in asthma patients (76). The results from one study identify the endogenous lipid mediator D1, which inhibits influenza virus replication and improves severe influenza (75).

On the other hand, Schwerbrock et al., suggest that fish oil consumption was associated with increased severity of an influenza virus infection (77). Therefore, omega-3 supplementation may not be safe and should be cautiously considered on a case-by-case approach. However, dietary intake of n-3 PUFA, such as canola, walnut, salmon, and sardine, is appropriate.

Diets and multivitamin supplements during COVID-19 pandemic

Considering a diet to minimize getting SARS-COV2 should be based on the reduction of inflammation besides improvement immunity in front of respiratory viral diseases. During the influenza pandemic in 1918 and 1919, US Public Health Service announced that being alkalinized with bicarbonates can reduce attacks of disease. Pieces of evidence have been shown that coronavirus can be quite stable at a pH of 6.0 and a temperature of 37°C. Still, they can irreversibly become inactive in a mild treatment at a pH of 8 and a temperature of 37°C(78). Although the normal range for arterial blood pH is between 7.35 to 7.45, alkaline-based diets could have a slight alteration through normal upper ranges of pH (alkalosis). According to this evidence, coronaviruses can be weaker and potentially have less infectivity. It should be taken into account that studies are controversial in this regard. Studies in vitro have indicated no adverse effect on leukocyte function in pH lower than 7.4(79). It is better to consider the role of pH status for immune enhancement in clinical studies of acidosis and ketoacidosis. Overall, clinical academia goes along with immunodeficiency, such as reduction in white cell counts, Gamma globulins, impaired inflammatory response, and retard phagocytosis. These changes are reversed due to the correction of acidosis. Therefore. There are lack of evidence to demonstrate that changes in pH environment is beneficial for immune enhancement or not(80); however, alkaline foods mostly include fruits

and vegetables which have their beneficial effects on immunity at least due to their nutrients not just for their alkaline context.

As discussed above, inflammation is the initiator of cytokine storm. Diets consist of elevated refined starches. saturated and trans fatty acids, poor in omega 3 fatty acids, fibers and antioxidants can increase pro-inflammatory cytokines production while reducing anti-inflammatory cytokines, which are initiators of the innate immune response. Epidemiological reports since the 60s have revealed healthy characteristics of the Mediterranean diet(81); this dietary pattern consists of high consumption of fruits, vegetables, olive oil, whole grains, legumes, nuts and seeds(82). This dietary pattern can reach almost all nutrients needed to minimize risk of infection to respiratory viral disease such as COVID-19. Observational studies have revealed that adherence to the Mediterranean diet is associated with 20% and 17% reduction in CRP and IL-6 levels, respectively(83).

Determining a special diet for the enhancement of immunity is difficult. Considering a hygienic lifestyle and ideal dietary behaviors are the priorities of preventive strategies in front of COVID-19. According to WHO guidelines, each person should have at least five portions of fruits and vegetables daily, starchy carbohydrates, particularly with whole grains, and also two or three portions of meats or other protein-rich foods. Although Multivitamin and Minerals (MVM) intake can be beneficial in vulnerable populations such as the elderly, having a regular diet with the priority of healthy food portions can supply all daily requirements. Also, MVM intake in short durations such as COVID-19 pandemic may be advantageous due to the several financial and logistic limitations during self-quarantine. Individuals can receive well-balanced nutrients and ensure their daily intakes of at least their micronutrients. However, this becomes more important for individuals who are malnourished or at risk of malnutrition; preventative care should be taken into account to ensure adequate energy, protein, and micronutrient intakes in these groups(84). In this situation, an expert dietitian is needed to adjust an appropriate diet with consideration of socio-economic limitations. Micronutrient deficiencies should be detected and treated by a therapeutic dose of micronutrient. Otherwise, each malnourished person without clinical symptoms of malnutrition should receive MVM daily(85).

On the other hand, as discussed above, obesity is a risk factor for impairment of immune system. Weight loss of at least 5% during 12 weeks in people with the Body Mass Index higher than usual (BMI>25kg/m2) is recommended to enhance their immunity(86). Meal distribution, which is the essential part of a diabetic lifestyle, should be considered in patients with diabetes mellitus instead of foods with a low glycemic index, limiting the intake of high saturated fatty acids and simple sugars(87).

In the current pandemic with related limitations, it is difficult to prescribe a general diet for all populations. According to the WHO recommendations for consumption of fresh fruits and vegetables and foods which have been hypothesized as immune enhancers, the Mediterranean diet may involve all nutrients needed for improving the immune system.

Conclusion

In the pandemic situation of COVID-19 in where there is no exact cure and treatment, the use of preventable strategies should be taken into account. In this regard, nutrition and a healthy diet are priorities that should be considered and trained by health care providers, especially for vulnerable populations. Also, in these similar situations, it should be emphasized on malnourished individuals and those at risk of malnutrition. As discussed above, MVM is recommended in vulnerable individuals and those who do not receive adequate nutrients through diet. Also, weight loss for overweight individuals is necessary to improve their immunity and reduce the causes of susceptibility to infection due to obesity.

Abbreviations

CRS: Cytokine release syndrome, **MVM:** Multivitamin and Minerals, **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2, **WHO:** World Health Organization, **ACE2:** Angiotensin converting

enzyme, **COVID-19:** Coronavirus Disease 2019, **IL:** Interleukin, **TNF:** Tumor necrosis factor, **PEM:** Protein-energy malnutrition, **ER:** Energy-restricted diet, **DIO:** diet-induced obesity, **MERS-CoV:** Middle East respiratory syndrome, **IFN:** Interferon, **RCTs:** Randomized clinical trials, **PUFA:** Poly unsaturated fatty acid, **DHA:** Docosahexaenoic acid, **EPA:**Eicosapentaenoic acid, **MVM:** Multivitamin and Minerals

Conflict of interest

The authors have no conflict of interest to disclose.

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