An Overview of Vitamins and Minerals in the Prevention of COVID-19 Infection

COVID-19 Enfeksiyonunun Önlenmesinde Vitamin ve Minerallere Genel Bakış

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ABSTRACT

The COVID-19 pandemic originated from infection of SARS-CoV-2, is an important international public health concern, threatening to human life. Infection with SARS-CoV-2 can be asymptomatic or can progress to severe disease with crucial respiratory symptoms and important pulmonary changes. The pathological mechanisms underlying of COVID-19 are still unknown, and to date, suitable vaccines or antivirals have not been found for effective treatment for COVID-19. Therefore, reduction of the incidence or severity of infection are of vital importance, and alternative approaches should be explored like nutritional strategies for supporting immune functions. Nutrients with antioxidant and anti-inflammatory properties, may be preventive or attenuant the inflammatory outcomes related to COVID-19. In this review, an overview of some vitamins and minerals is presented in the prevention and management of COVID-19 infection. In particular, we focused on the potential role of micronutrients such as vitamin D, vitamin C, zinc and selenium in all therapeutics, including prevention strategies and mitigation interventions for COVID-19.

Key Words: COVID-19, immune response, micronutrients, SARS-CoV-2, trace elements, viral infection

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ÖZET

SARS-CoV-2 enfeksiyonundan kaynaklanan COVID-19 pandemisi, insan yaşamını tehdit eden önemli bir uluslararası halk sağlığı sorunudur. SARS-CoV-2 enfeksiyonu asemptomatik olabilir veya önemli solunum semptomları ve önemli akciğer değişiklikleri ile ciddi hastalığa ilerleyebilir. COVID-19'un altında yatan patolojik mekanizmalar hala bilinmemektedir ve bugüne kadar COVID-19'un etkili tedavisi için uygun aşılar veya antiviraller bulunamamıştır. Bu nedenle, enfeksiyon insidansının veya şiddetinin azaltılması hayati öneme sahiptir ve bağışıklık fonksiyonlarını desteklemek için beslenme stratejileri gibi alternatif yaklaşımlar araştırılmalıdır. Antioksidan ve antienflamatuar özelliklere sahip besinler, COVID-19 ile ilişkili enflamatuar sonuçları önleyici veya hafifletici olabilir. Bu derlemede, COVID-19 enfeksiyonunun önlenmesi ve tedavisinde bazı vitamin ve minerallere genel bakış sunulmaktadır. Özellikle, COVID-19 için önleme stratejileri ve hafifletme müdahaleleri de dahil olmak üzere tüm terapötiklerde D vitamini, C vitamini, çinko ve selenyum gibi mikrobesinlerin potansiyel rolüne odaklanılmıştır.

Anahtar Sözcükler: COVID-19, immün cevap, mikrobesinler, SARS-CoV-2, eser elementler, viral enfeksiyon

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INTRODUCTION

In December 2019, many serious respiratory illness and death were reported in Wuhan, Hubei province, China. After that, the number of cases increased dramatically, and it spread all around the world due to transmit readily among humans. The World Health Organization (WHO) firstly named the disease as "2019-nCoV", or "Wuhan Coronavirus", but then, the disease was officially declared as "coronavirus disease 2019 (COVID-19)". It was revealed that new coronavirus is phylogenetically close to severe acute respiratory syndrome coronavirus (SARS-CoV) by the genome analysis. Therefore, it was subsequently called as SARS-CoV-2 by the coronavirus Study Group of the International Committee on Virus Taxonomy (1,2).

Infection with SARS-CoV-2 can be asymptomatic or can exhibit mild to severe symptoms (3). COVID-19 has been demonstrated to have an average incubation duration of approximately 5.2 days and a mean period from the initiation of symptoms to death of 14 days (1,4). At the onset of the illness, symptoms seen most common are fever, cough, and fatigue or myalgia, while symptoms seen less common involves headache, sputum production, lymphopenia, haemoptysis, diarrhoea, and dyspnoea (4,5). Particularly, in patients with older age and those with pre-existing illness, infection with SARS-CoV-2 can progress to severe disease with crucial respiratory symptoms and important pulmonary changes visible *via* imaging techniques. The changes involve interlobular involvement, alveolar exudates, ground glass opacities, patchy consolidation, and finally prognosticating deterioration (6). Infection is transmitted via respiratory droplets formed during coughing and sneezing by patients with symptoms, however, can also occur from asymptomatic people and before onset of symptoms. It can be transmitted *via* aerial droplets and contact. To date, vaccine or antiviral treatment for human coronavirus could not be found (7). Hand hygiene and the usage of personal preventive materials like surgical masks have been advised in the prevention of COVID-19 (1). Some countries have adopted "stay in home" to prevent spread of COVID-19 (8).

There are different important risk factors including the presence of poor nutritional status and pre-existing non-contagious diseases such as chronic lung diseases, cardiovascular diseases (CVD), diabetes mellitus, obesity, and varied other diseases that render the host immunocompromised for severe COVID-19 (8). In maintaining immunity, balanced nutrition play an essential role for prevention and management of viral infections (9). In this review, while the properties and effects of important micronutrients are evaluated in relation to the current COVID-19 outbreak, an overview of vitamins and minerals is given in the prevention of COVID-19 infection.

Structure Of Sars-Cov-2 and Pathogenesis of COVID-19

Coronaviruses are enveloped, 150 to 160 nm in size, pleomorphic or spherical particles, related to positive-sense, single stranded RNA, non-segmented, capsid, matrix, nucleoprotein, and S-protein. Nucleocapsid (N) protein, envelope (E) protein, membrane (M), and spike (S) protein are crucial viral proteins playing important roles in virus entry and virus replication in the host cell (10). Coronaviruses are a member of the family Coronaviridae and order Nidovirales and commonly spread among humans and other mammals which lead to neurologic, hepatic, enteric, and respiratory diseases (5,11).

The family comprises of two subfamilies, Coronavirinae and Torovirinae. The members of the subfamily Coronavirinae are subdivided into four genera including alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus. Betacoronavirus contains HCoV-HKU1, HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) (12).

Although most of the human coronavirus infections are mild, SARS-CoV-2 is one of the betacoronaviruses like two highly pathogenic viruses that originated from bats including SARS-CoV that caused SARS with mortality rates of 10%, in 2002, and MERS-CoV that caused MERS with mortality rates of 37%, in 2012 (2,5,12). The mortality rate of SARS-CoV-2 (approximately 3.4%) is lower than that of SARS-CoV or MERS-CoV (1). Similarities of genetic sequence between SARS-CoV-2 and SARS-CoV have been shown as over 80%, whereas similarities between SARS-CoV-2 and MERS-CoV have been demonstrated as 50% (4). Although the precise pathological mechanisms underlying of COVID-19 are unknown, these genomic similarities of between SARS-CoV-2 and SARS-CoV could aid to understand the emerging inflammatory response that may result in the initiation of severe pneumonia (1). COVID-19 acute respiratory distress syndrome (ARDS) patients and SARS patients have characteristic ARDS pathology in the lung. ARDS is a disease with high mortality, and angiotensin-converting enzyme 2 (ACE2) act as a protector in this kind of acute lung injury (ALI) (13). ACE2 is expressed in lungs, kidneys, intestine and heart its major functional role is the maturation of angiotensin (Ang) (14). It is a very important constituent of the renin-angiotensin system (RAS). ACE2 antagonizes RAS system activation and prevents organ damage (13). The spike protein of SARS-CoV-2 binds to the ACE2 receptor, with a 10-20 fold higher affinity than does S-protein of SARS-CoV, and then enters host cells (3). The SARS-CoV-2 primary generally infects lower respiratory tract and binds to ACE2 on alveolar epithelial cells (11). Both SARS-CoV-2 and SARS-CoV are effective inducers of inflammatory cytokines leading to organ damage. The postulated mechanism is defined as "cytokine storm". The viral infection induces immune cells and stimulates the release of inflammatory cytokines and chemokines into pulmonary vascular endothelial cells (11) and may result in pulmonary damage and reduced lung capacity (8).

COVID-19 patients demonstrated higher numbers of leukocyte, abnormal respiratory outcomes, and enhanced proinflammatory cytokines levels (4). Huang et al. indicated that patients with COVID-19 had high values of proinflammatory cytokines including IFNγ, IP10, IL1B, and MCP1, presumably leading to induced T-helper-1 (Th1) cell responses. Furthermore, intense care unit (ICU)-admitted patients had higher levels of MCP1, GCSF, MIP1A, IP10, and TNFα than did those non-ICU patients, propounding that the cytokine storm was related to severity of the disease. Moreover, infection with SARS-CoV-2 triggered increased release of T-helper-2 (Th2) cytokines such as IL4 and IL10, that inhibit inflammation, as varied from infection with SARS-CoV. Authors reported that further research is required to characterise the Th1 and Th2 responses in SARS-CoV-2 infection and to clarify the pathogenesis (5).

Nutritional status, and nutrients that have anti-inflammatory and immunomodulatory effects have potential effects on homeostasis and dysregulation of the immune system (Fig 1).

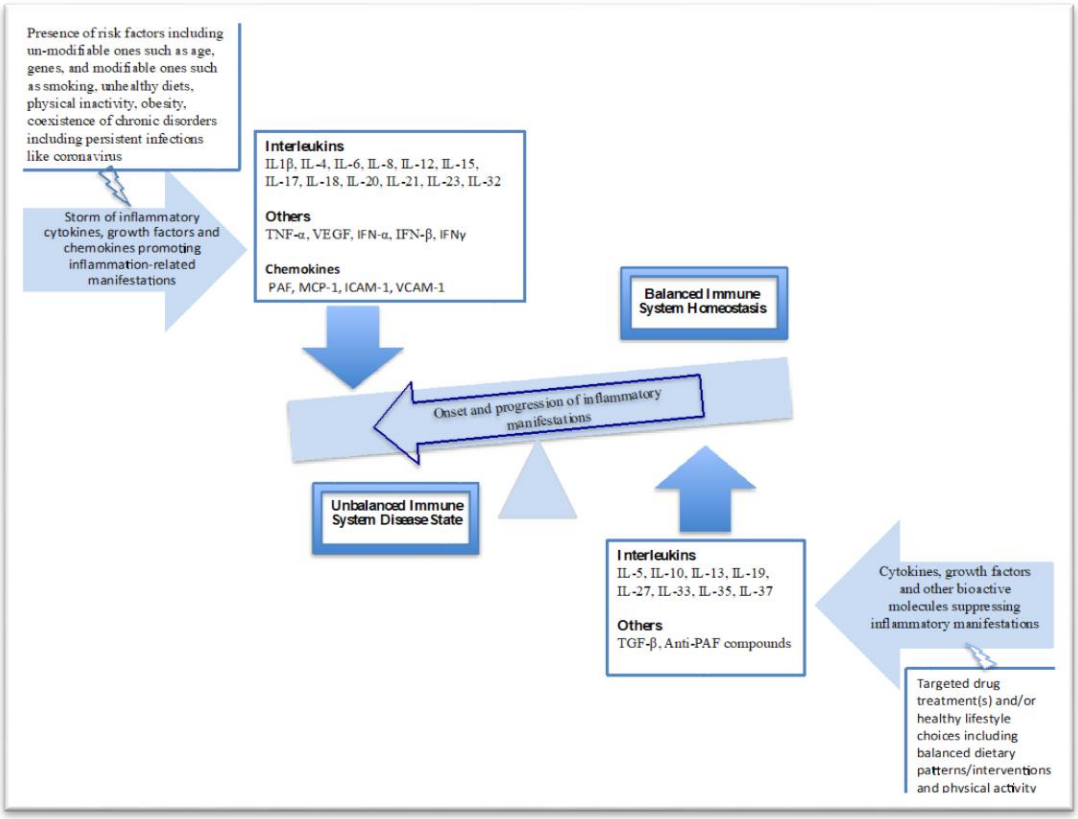

Figure 1. The inflammatory molecules involved in infection and immun system regulation (8).

Micronutrients

Vitamins, minerals and phytochemicals that have beneficial effects, have been investigated for their potential benefits related to respiratory and inflammatory conditions (8). In this section, healthy micronutrients are examined in relation to the current COVID-19 outbreak.

Vitamin D (1,25 dihydroxycholecalciferol, calcitriol)

In humans, vitamin D requirement is supplied from the diet, or it is synthesized in the skin. Vitamin D3 (cholecalciferol) is generated from 7-dehydrocholesterol in the skin by ultra-violet B radiation exposure. In the liver, vitamin D3 or dietary vitamin D is converted to 25-hydroxyvitamin D (calcidiol) by 25-hydroxylation and then to the 1,25(OH)2D (calcitriol), hormonal metabolite, that mediate the biological actions of vitamin D. Calcidiol is the main and stable circulating calcitriol metabolite and level of calcidiol in the serum is the best indicator of vitamin D status. Serum 25(OH)D concentration lower than 20 ng/ml constitutes deficiency (15). Calcitriol metabolizing enzymes and vitamin D receptors exist in numerous cell types including diverse immune cells such as B cells, T cells, monocytes and antigen-presenting-cells (16).

Vitamin D has crucial functions including modulation of the innate and adaptive immune responses in addition to bone and calcium homeostasis (17). The biosynthesis of the active metabolite calcitriol by peripheral tissues and immune cells has been speculated to have immunomodulatory properties similar to locally active cytokines (16). The influence of calcitriol on the immunity includes the inhibition of B cell proliferation and differentiation, blocking immunoglobulin secretion, suppression of T cell proliferation. Moreover, vitamin D has effects on T cell maturation, induces regulatory T cells and alters cytokine secretion pattern resulting in reduced generation of inflammatory cytokines such as IL-17, IL-21 with increased generation of anti-inflammatory cytokines such as IL-10. Calcitriol also inhibits monocyte generation of inflammatory cytokines including TNFα, IL-1, IL-6, IL-8, and IL-12. It additionally inhibits dendritic cell differentiation and maturation (17,18). Furthermore, calcitriol is a negative regulator of RAS and suppresses renin expression and formation. It can increase the expression and levels of ACE2 and have a potential preventing role *versus* ALI/ARDS (19).

Deficiency of vitamin D has been associated to an increased respiratory infections risk including influenza, tuberculosis and respiratory syncytial virus infection (20). Low serum concentrations of vitamin D have been related to enhanced risk and severity of viral respiratory infections involving community acquired pneumonia, whilst there is data that supplementation of vitamin D which increases its serum concentrations above 50 nmol/l may ameliorate this risk (21).

Hong et al. observed inverse trends between vitamin D supplementation frequency with infants and respiratory tract infection risk (22). Previous studies reported relationship between low vitamin D levels and predisposes to respiratory tract infections (15,18). The preventive effect of calcitriol has been reported in pneumonia (23,24).

Although there is no clinical evidence to validate vitamin D supplementation will decrease the incidence of COVID-19, several studies have suggested that vitamin D has a potential role in the reduction of the respiratory tract infections risk, particularly in the influenza and also COVID-19 (25,26). Among the proposed preventive effects of vitamin D are several which may decrease the COVID19 infection risk, or which may alleviate the immunological sequelae responsible for its severe respiratory effects (21). Vitamin D has some benefits such as decreasing the generation of proinflammatory cytokines (27). Marik et al. reported that vitamin D deficiency may enhance the cytokine storm, which may be especially lethal in patients infected with SARS-CoV-2. Authors declared that further studies are required to validate their hypothesis (20). In addition, Zemb et al. reported that vitamin D deficiency is a readily alterable risk factor of acute respiratory infections, despite insufficient data regarding the effect of vitamin D status on COVID-19 infection. On the other hand, they accepted that more reliable data are required to show the benefit of vitamin D supplementation in the prevention of COVID-19 (28). Important crude association between vitamin D concentrations and the number of COVID-19 cases, particularly the mortality due to infection, was found. Vitamin D levels are notably low in aging population that is the most undefended group for COVID-19. It was demonstrated that vitamin D protects *versus* acute respiratory infections and is safe. It was advised to make researches related to vitamin D concentrations in COVID-19 patients with diverse degrees of disease severity (29).

In addition to observational studies, it was suggested that targeting the regulation of RAS and ACE2 with vitamin D in SARS-CoV-2 infection may be a potential therapeutic approach to struggle with the growing of COVID-19 and induced ARDS (19). However, one of the previous study demonstrated that vitamin D did not supply an advantage upon placebo as regards 90-day mortality or other non fatal outcomes among severely ill patients with vitamin D deficit. Further studies are required to understand the probable advantages of vitamin D supplementation in acute critical illness (30).

Vitamin C (ascorbic acid)

Vitamin C has effects on immunity, including sustaining epithelial barrier function, both innate and adaptive immune cells growth and function, migration of white blood cell to locations of infection, generation of antibody, and phagocytosis and microbial killing (31). In addition to these pleiotropic roles in the immune system, vitamin C is also well-known for its antioxidant features, and antioxidants are usually accepted as an adjuvant therapy for severely ill patients, whose vitamin C concentrations are substantially reduced (32,33).

In numerous diseases, the balance between oxidants and antioxidants is changed, with severe outcomes. Viral infection causes an increase in the intrapulmonary oxidative load. The pathophysiological mechanisms by which free radicals compose different stress types result in lung inflammation and an altered immune response. Antioxidants may play a major role against lung oxidative stress. Therefore, it was suggested that antioxidants have protective role in lung infection and inflammation (34). It was reported that vitamin C supplementation results in a significantly lower incidence of pneumonia, comending that vitamin C may affect sensibility to lower respiratory tract infections (35). It is believed that the main cause of COVID-19's effect on humans is pulmonary insufficiency (ARDS) (36). Acute respiratory distress syndrome is an important factor of fatality. Significantly enhanced oxidative stress due to the trigger of free radicals and cytokines is the feature of ARDS which causes cellular damage, organ dysfunction and death. An effective treatment for these patients may be early use of high dosage antioxidants, such as vitamin C (36,37). Vitamin C promote the resistance against coronavirus and may affect the sensitivity to lower respiratory tract infections under certain circumstances (38). The use of intravenous vitamin C has shown promising results in the treatment of COVID-19, leading to a marked increase in immune system response, a decrease in cytokine storm or an increase in antiviral activities through other unknown mechanisms (36). However, in a study of sepsis and ARDS patients, it was found that vitamin C infusion did not significantly ameliorate organ function disorders or change indicators of inflammation and vascular damage. Therefore, authors reported that further studies are required to interpret the role of vitamin C for other results in sepsis and ARDS (39).

Zinc

Zinc is an essential trace mineral of the diet that is significant for maintenance and development of cells in immune systems (both the innate and adaptive), and also a critical cofactor for many enzymes including antioxidant defense, especially SOD and antiinflammatory proteins, and for zinc-finger transcription factors implicating in DNA and RNA synthesis (8,9,31,40). Zinc deficiency can affect immunity resulting in impaired stimulation, production and maturation of lymphocytes, disruption of the intercellular communication through cytokines, and attenuation of the innate host defense (31). Zinc supplementation in healthful individuals has been demonstrated to lower oxidative stress concerned byproducts, block TNF-α and IL1β induction, protect *versus* NFκβ (nuclear factor-κβ) activation in mononuclear cells and regulate intracellular killing and cytokine generation via macrophages (41). It was suggested that insufficient zinc stores might be a risk factor for pneumonia in the elderly (42). Moreover, a study on children with pneumonia indicated that zinc supplementation improved the clinical status, the respiratory rate, and the oxygen saturation. In the zinc group, it was observed that IFNγ and IL-2 increase after treatment. Authors concluded that zinc supplementation ameliorated some clinical symptoms in children with pneumonia in fewer hours and triggered a cellular immune response (43). Zinc has been demonstrated to be significant for maintenance of skin and integrity of mucosal membrane, and also has antiviral effects such as on rhinovirus replication *in vitro*. An increased risk of viral infections has been associated with a low zinc status (40). Inhibition of corona- and arterivirus replication by increased $Zn2^{+}$ levels has been reported in cell culture (44). Furthermore, zinc has antiviral properties versus several viral species such as HIV or HCV, and its deficiency leads to increased risk of acquiring infections. Despite limited number of mechanistic studies, zinc seems to block virus attachment, infection, uncoating, and also viral protease and polymerase enzymatic processes. Nevertheless, these mechanisms have not been well-elucidated in clinical studies on zinc supplementation against viral infections (45). To date, there are no studies evaluating zinc for COVID-19 management, despite a few trials testing zinc as a part of diet to treat COVID-19 (46).

Selenium

Selenium is a trace element that has antioxidant effect *via* selenoproteins and also antiinflammatory properties (9,47). Low selenium levels have been related to an increased risk of mortality, attenuated immune function, and cognitive reduction, whereas, antiviral effects have been demonstrated in a higher selenium level or selenium supplementation (9). Deficiency of selenium causes enhanced oxidative stress levels in the host can change a viral genome, thereby, an ordinarily benign or mildly pathogenic virus becomes highly virulent. This condition leads to a reduced immune response against viruses and an increased mutation rates of RNA viruses (47,48). In deficiency of selenium, benign species of Coxsackie and influenza viruses can alter to highly pathogenic species, due to mutations (49). An increase of selenium intake by otherwise healthy individuals with relatively low concentrations of plasma selenium levels lead to improve the cellular immunity. Also, selenium supplementation seemed to clear an oral live attenuated poliomyelitis vaccine more quickly and sequence analysis of the viral genome displayed lower numbers of mutations. These findings suggested that insufficient nutrient status in the host population could cause the outbreak of more pathogenic types of viral diseases, thus rising the risks and burdens related to these illnesses (31,40). Sodium selenite, a chemical form of selenium, can be used for increase blood selenium concentrations. It can oxidize thiol groups in the virus protein disulfide isomerase, thus, prevents the virus penetration to the healthy cell membrane. Kieliszek et al. believed that sodium selenite usage in the treatment of anticoagulation, may decrease the blood clots risk forming in COVID-19 patients, particularly, at risk for its severe clinical course. Hence, this chemical compound can potentially be utilized in the combat *versus* coronavirus epidemic (50).

CONCLUSION

COVID-19 is a global pandemic with increasing mortality rates worldwide. Unfortunately, there is no vaccine or effective antiviral drug for the prevention or treatment of infection with SARS-Cov-2. About COVID-19, a viral-based disease, vaccination studies and effective treatment options are being explored. A strong immune system occupies an important place both in preventing and alleviating diseases. The strength of the immune system is influenced by many factors, including heredity, age, gender, nutritional status, cigarette-alcohol, stress, activity, hormones, vaccines, and infections. Balanced nutrition is the most important among these factors. Oxidative explosion, proliferation and inflammation are the three important components of the immune response. The antioxidant and anti-inflammatory foods we mentioned about protecting immune cells and control oxidative explosion. They play an effective role in the production and development of all new cells in the body, including immune cells.

To date, there is no known evidence-based therapeutic or therapeutic strategy to prevent the incidence or severity of COVID-19 infection. In this review, we reviewed the potential effects of micronutrients such as vitamin D, vitamin C, zinc and selenium, in all therapeutics including prevention strategies and mitigation interventions, for COVID-19. We conclude that micronutrients known to affect immunity and infection risk, may be protective and show promise in the prevention and management of COVID-19. Therefore, investigation of possible effects of micronutrients on COVID-19 should be encouraged along with the several other potential treatments. However, it is also of great importance that it is supported by randomized controlled clinical trials involving large series of cases.

Conflict of interest

No conflict of interest was declared by the authors.

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