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COVID-19 Pandemisi Sürecinde Takviye Kullanımına Genel Bakış
Overview of The Use of Supplements in The COVID-19 Pandemic Process

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Özet

Koronavirüs, şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), Dünya Sağlık Örgütü tarafından Mart 2020'de pandemi ilan edilen, yeni keşfedilen yüksek derecede patojenik bir virüstür. Covid-19'un şiddetli belirtilerinin patogenezinde bağışıklık sistemi ve inflamatuar yanıtın rolü iyi bilinmektedir. COVID-19'un yönetimi için bağışıklık sistemi üzerinde aktif olan farklı tedaviler kullanılmaya devam etmektedir ve besin takviyeleri de antimikrobiyal ve immünomodülatör aktivitelerinden ve viral yayılımın önlenebilmesi için umut vericidir. Sağlıklı beslenmenin sürdürülmesi, özellikle bağışıklık sisteminin güçlü olmasının gerektiği Covid-19 gibi bir dönemde çok önemlidir. Dengeli ve sağlıklı bir beslenme düzenine sahip olmak, insan vücudunun virüslerle savaşmada önemli olan bağışıklık sistemini güçlendirmeye yardımcı olabilmektedir.

COVID-19 hastalarında takviye kullanımları hakkında sınırlı sayıda veri bulunmasıyla birlikte, D vitamini, C vitamini ve çinkonun rolü ilgi çekicidir. Besin takviyeleri, günümüzde en hızlı büyüyen sağlık kategorilerinden birisi olarak gösterilmektedir. Bunun yanında birçok klinik çalışma, enfeksiyon hastalıklarından korunma ve bu hastalıkların tedavisinde özellikle mikronütrientlerin önemini vurgulamaktadır. Mikro besin öğelerinin eksikliği, olumsuz tablolara hız kazandırırken, belirli dozlarda alımlarının proflaksi ve tedavide yeri olduğu bilinmektedir.

Bu derlemenin amacı, besin takviyelerinin temel özelliklerini ve COVID-19'un önlenmesi ve tedavisinde potansiyel uygulanabilirliklerini tartışmaktır.

Anahtar kelimeler: COVID-19, İmmün Sistem, Mikronütrientler, Takviye, Beslenme

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Abstract

Coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a newly discovered highly pathogenic virus that was declared a pandemic by the World Health Organization in March 2020. The role of the immune system and inflammatory response in the pathogenesis of severe manifestations of Covid-19 is well established. Different treatments active on the immune system continue to be used for the management of COVID-19, and nutritional supplements are also promising for their antimicrobial and immunomodulatory activities and prevention of viral spread. Maintaining a healthy diet is very substantial , especially in a period like Covid-19 when the immune system needs to be strong. Having a balanced and healthy diet can help strengthen the human body's
immune system, which is substantial in fighting viruses.

The role of vitamin D, vitamin C and zinc is of interest, with limited data on the use of supplements in COVID-19 patients. Nutritional supplements are shown as one of the fastest growing health categories today. For good measure, many clinical studies emphasize the importance of micronutrients in the prevention and treatment of infectious diseases. While the lack of micronutrients accelerates the negative picture, it is known that their intake in certain doses has a place in prophylaxis and treatment.

The purpose of this review is to discuss the main properties of nutritional supplements and their potential applicability in the prevention and treatment of COVID-19.

Keywords: Pregnancy, Dietary supplements, Vitamins, Supplements

Introduction

The Covid-19 pandemic has quickly turned into a global pandemic that poses deadly threats. While the epidemic still maintains its negative effects on human health, it is seen that it causes lifestyle changes. Among these lifestyle changes, people's controlled or uncontrolled use of supplements is one of the prominent topics.

Consumption of nutritional supplements is increasing globally (Binns et al., 2018: 405). Supplements, unlike drugs, require minimal regulation during their manufacture and do not require a prescription for use by individuals (Binns et al., 2018: 403-404). Such factors create a positive environment for the widespread distribution and market growth of supplements (Binns et al., 2018: 412).

Nutrition is crucial to every stage of life, and proper intake of both micronutrients and macronutrients can help prevent and treat a variety of infectious diseases. Adequate consumption of nutrients is necessary to strengthen our immune function (Chowdhury, 2020: 51). Nutritional supplements ensure reinforcement of nutrients that cannot be taken in sufficient quantities (Kourkouta et al., 2016: 18). However, supplements should not be thought of as a substitute for nutrients.

Micronutrients play an substantial role in boosting the immune system. For this reason, it has been stated that a correct nutritional support containing micronutrients can have a positive effect on the treatment and prophylaxis of COVID-19 (AbdAllah et al., 2020: 1).

COVID-19 is a serious illness caused by the SARS-CoV-2 virus, which is easily transmitted to humans. No vaccine or drug has yet been discovered to fully control its transmission and prevent disease altogether. In this case, it is substantial to find methods of preventing and controlling it (Chowdhury, 2020: 47).

The immune system can be strengthened by supplementation of nutrients. However, there are some negative effects of micronutrient supplements in case of overdose. Many studies have shown both positive and negative effects of micronutrient supplementation on immune response and human health. However, there are no published studies describing the function of micronutrients for the prevention and treatment of coronavirus, although some studies have shown that the right intake of micronutrients can reduce the duration of the severity of the disease (Chowdhury, 2020: 51).

1. Nutritional Supplements

Nutritional supplement can be described as any vitamin, mineral, additional chemical, herbal product, amino acids or other digestible preparation added to the diet to profit human health. Food supplements represent a broad product category that can be distinguished from conventional food and medicines. Scientists and health experts agree that nutritional supplements can be beneficial to human health under certain conditions; however, these supplements should not replace the daily balanced diet required for a healthy diet (Valavanidis, 2016: 60).

Vitamin and mineral supplements are the most widely used nutritional supplements by people worldwide (Fang Zhang et al., 2020: 1). However, there are many herbal supplements that are widely used around the world. Calcium, Echinacea, fish oil, ginseng, Glucosamine and / or Chondroitin sulfate, garlic, vitamin D, St. John's Wort, dwarf palm, Ginkgo, green tea are the examples of some other common nutrional supplements (U.S. Food & Drug Administration, 2020).

1. The Relationship between Common Food Supplements and Immune System During the Covid-19 Pandemic Process

1.1. Vitamin D

Vitamin D regulates proliferation, differentiation, apoptosis and cell growth of many cells in the body. It also modulates gene expression associated with inflammation, neuromuscular and immune function and helps regulate antimicrobial peptides. It is accepted that many cells in the body express vitamin D receptors (VDR) (Sassi et al., 2018: 1656-1664). Some cells involved in immune function also express VDR and CYP27B1. This shows that 1,25(OH)2D, the biologically active form of vitamin D, can control immune function at different levels (Sassi et al., 2018: 1656). It is 1,25(OH)2D, which is the biologically active form of vitamin D. 1,25(OH)2D modulates innate and adaptive immunity through regulation of at least 15 genes by the VDR (Koivisto et al, 2020: 1140).

VDR signaling has a suppressive role and anti-inflammatory effect on autoimmunity, promotes dendritic cell and regulatory T cell differentiation, and decreases Th 17 cell response and inflammatory cytokine secretion (Covid-19-induced cytokine storm). Vitamin D is thought to have a regulating effect on innate immunity. There is no general consensus on the desired 25 (OH) D level to achieve immunomodulatory effects; therefore, there is no current indication for vitamin D supplementation in specific infections and/or autoimmune diseases (Matsui, 2020: 328).

Prospective studies have reported inverse correlations between 25(OH)D serum levels and cardiovascular diseases, serum lipids, inflammation, glucose metabolism disorders, weight gain, mood disorders, decreased cognitive function, and Alzheimer's disease. However, no effect of vitamin D supplementation has yet been demonstrated for these results (Matsui, 2020: 324-325).

First recommended more than 30 years ago, vitamin D is now often referred to as a "well-known" regulator of innate immunity (Sassi et al., 2018: 1657). The obvious mechanism for this is that vitamin D remaines the production of defensin β2 and cathelicidin antimicrobial peptides (CAMP) and their antimicrobial activity (Wei & Christakos, 2015: 8252-8253).

It is possible that vitamin D may play a role in COVID-19; because it has been believed for over 100 years that there is a link between vitamin D deficiency and respiratory disease (Matsui, 2020: 327).

Observational studies have reported a relationship between low serum concentration of 25-hydroxyvitamin D, the inactive precursor of vitamin D, and susceptibility to acute respiratory infections. These relationships are independent relationships (Jung et al., 2018: 2003-2004).

Vitamin D deficiency is substantial in pneumonia patients. In deficiency pneumonia patients, acute respiratory distress syndrome (ARDS) is associated with an remained risk of hospitalization and death (Dancer et al., 2015: 617).

A systematic review and meta-analysis of 25 randomized controlled trials in the literature Martineau et al. (2017: 12). As a result of this research, it found that vitamin D generally protects against acute respiratory infection.

Is low vitamin D status to disease for related non-skeletal conditions; or whether the disease causes a low vitamin D state is unknown. The same uncertainty applies in the case of diseases such as multiple sclerosis, Alzheimer's disease and even ARDS (Matsui, 2020: 328).

The immunomodulatory role of Vitamin D is known. A randomized placebo-controlled trial is available to shed light on the effect of therapeutic vitamin D3 supplementation (high-dose oral cholecalciferol supplementation) on viral clearance in SARS-CoV-2 infection. Inclusion criteria were individuals with asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficiency (25(OH)D <20 ng/ml). The search was completed in a total of 40 SARS-CoV-2 RNA positive vitamin D deficient patients in 16 randomly selected intervention and 24 control groups. As a result, it was stated in the search that a greater proportion of vitamin D deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative, with a significant reduction in fibrinogen observed as a result of high-dose cholecalciferol supplementation (Rastogi et al. : one).

A multicenter, double-blind, randomized, placebo-controlled search was conducted to investigate the effect of a single high-dose vitamin D3 vitamin on hospital stay in patients with COVID-19. 240 patients with moderate to severe illness and hospitalized Covid-19 patients were included in the search. Patients were randomly assigned to receive a single oral dose of 200,000 IU of vitamin D3 containing placebo, 120 in the intervention group (n = 120) or 120 in the control group (n = 120). As a result of the research; Among hospitalized Covid-19 patients, a single high dose of vitamin D3 compared to placebo is said to not significantly decrease length of hospital stay, with the findings not supporting the use of high-dose vitamin D3 for the treatment of moderate to severe Covid-19 (Murai et al., 2021: 1053) .

It has been shown that vitamin D receptor activation expressed in immune cells directly decreases the secretion of inflammatory cytokines such as interleukin-6 and indirectly affects C-reactive protein. In a clinical case series, the effect of vitamin D

supplementation was investigated to investigate the importance of the vitamin D pathway in patients diagnosed with Covid-19. 4 patients with vitamin D deficiency received 1000 IU (standard dose) cholecalciferol (D3) per day or 50,000 IU (high dose) ergocalciferol (D2) daily for 5 days. Clinical results indicated that patients receiving high doses of vitamin D supplements had shorter clinical recovery and hospital stay with a reduction in inflammatory marker status. Vitamin D supplementation may be a valid alternative to decrease acute respiratory distress syndrome, randomized clinical trials are said to ensure guidance (Ohaegbulam et al., 2020: e485).

In a parallel pilot randomized open-label, double-blind clinical study, the effect of oral calcifediol (25-hydroxyvitamin D3) supplementation on ICU admission and death rates in 76 Covid-19 patients was investigated. It has been shown that the administration of high doses of calcifediol (25-hydroxy vitamin D3), the main metabolite of the vitamin D endocrine system, significantly decreases the need for intensive care treatment of patients hospitalized beacuse of Covid-19. As a result of the study; calcifediol seems to decrease the severity of the disease, but larger trials with appropriately matched groups are required for a definitive result (Castillo et al., 2020: 1).

1.2. Vitamin A

Vitamin A is involved in the regulation of innate immune response (natural killer cells, macrophages and neutrophils) and cell-mediated immunity (growth and differentiation of B cells). It is also active in humoral antibody immunity and cytokine signaling; therefore, it has a role in the inflammatory response (Alpert, 2017: 200).

In vitamin A deficiency, mucosal epithelial integrity is compromised. This means that deficiency may predispose to the invasion of various pathogens in the eyes, respiratory system and gastrointestinal tract (Alpert, 2017: 200).

1.3. C vitamin

Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune systems. It is an effective antioxidant because it can easily donate its electrons. It supports epithelial barrier function against pathogens (Carr & Maggini, 2017: 1).

Vitamin C deficiency causes to impaired immunity and higher susceptibility to infections. Infections, on the other hand, significantly affect vitamin C levels beacuse of metabolic requirements and remained inflammation. In addition, it is stated in the literature that vitamin C supplementation can both prevent and treat respiratory tract and systemic infections (Carr & Maggini, 2017: 1).

As is known, vitamin C must be included in the diet for health and in many cases supplemented. The absorption of vitamin C from the diet is dependent on many factors: facilitated diffusion and substrate transport mechanism states involving specific transporters of ascorbates, etc. (Rossetti et al., 2020: 146). In this regard, there are many

formulations containing ascorbic acid for the oral route, but parenteral administration is required when high doses are required. In critically ill patients (sepsis), plasma vitamin C concentrations are usually below normal (Wilson, 2009: 5). The vitamin C concentration is inversely proportional to the multi-organ failure state (Borrelli et al., 1996: 392). And vitamin C concentration is directly related to survival (Galley, 1996: 143). All these emphasize the importance of vitamin C in the treatment of such patients (Evans, 2008: 751).

In critical illness, the requirements for these micronutrients can remain significantly. This is especially true for vitamin C, which is severely depleted in critically ill patients. Severe respiratory infections such as pneumonia are a common complication of severe vitamin C deficiency. And pneumonia is one of the most common causes of death in patients with severe vitamin C deficiency. These results suggest a substantial link between vitamin C levels and respiratory infections. Although the vitamin C status of COVID-19 patients has not yet been reported in the literature, it is known that the vitamin C status of patients with community-acquired pneumonia is severely depleted and is associated with remained oxidative stress. However, it is not yet known whether vitamin C deficiency is a cause and/or consequence of severe infection (Carr, 2020: 349).

Clinical searches are quickly being conducted to investigate the effect of vitamin C infusion in the treatment of Covid-19 (Liu et al., 2020: 1), (Moskowitz et al., 2020: 642), .. However, there have been completed studies investigating the place of vitamin C supplementation in the treatment of Covid-19. If we investigate a few clinical studies;

A randomized clinical trial of 214 outpatients with SARS-CoV-2 infection investigated whether high-dose oral zinc and/or ascorbic acid supplementation reduced the severity and duration of symptoms among patients. As a result of the search, it is said that this new form of treatment tried did not significantly reduce the duration of symptoms compared to standard care (Thomas et al., 2021: 1).

In a retrospective cohort search investigating the condition of Covid-19 patients treated with a formulation containing a combination of vitamin C and nutraceuticals to reduce symptomatology and improve prognosis; By following the recovery process of 39 patients, it is said that the formulation is potentially promising as an adjuvant treatment, especially the symptoms of fever, dry cough, dyspnea, headache, diarrhea and malaise have shortened the recovery period compared to the control group (Hernández et al., 2020: 1). Based on these results, it is stated that a controlled, double-blind, randomized clinical trial is currently being conducted in a larger population (Hernández et al., 2020: 12-13).

In a randomized controlled clinical search investigating the therapeutic effect of oral vitamin E and vitamin C supplementation in addition to standard treatment in patients with Covid-19 pneumonia, 38 patients for the intervention group and 34 patients for the control group received 1000 mg oral vitamin C and 400 IU oral vitamin E supplements daily. . As a result, it is stated that the oral vitamin combination taken in this way does not have a

beneficial effect in Covid-19 patients (Hakamifard et al., 2021: 1).

1.4. Vitamin E

Vitamin E is a term used to describe 8 different fat-soluble tocopherols and tocotrienols; alpha-tocopherol is the most biologically active form. Vitamin E acts as an antioxidant that protects cell membranes from oxidative damage (Okebukola et al., 2017: 4).

Vitamin E has the potential to affect both innate and adaptive immunity, with alpha-tocopherol shown to specifically remain the weakened immune response associated with aging (Wu & Meydani, 2014: 283-284). This aspect may also be substantial when focusing on high-risk groups and preventive healthcare in the Covid-19 era.

1.5. Zinc

Zinc is an essential trace element that is crucial for immune function (Read et al., 2019: 696). The body has very little zinc stores, which means that insufficient intakes can easily cause zinc deficiency. And zinc deficiency is associated with weakened immune function (Ibs & Rink, 2003: 1452S). The role of zinc in immunity has been described in many studies (Read et al., 2019: 696-710).

In the case of Covid-19, zinc is considered a supportive therapy as it has direct antiviral effects (Zhang & Liu, 2020: 481). It has been found that zinc supplementation can have positive effects in the treatment of the Covid-19 patient (Chowdhury, 2020: 50-51).

A randomized clinical trial in 214 outpatients with Covid-19 investigated whether high-dose oral zinc and/or ascorbic acid supplementation decreased the severity or duration of symptoms among patients. Compared to standard care, this option has been said to fail to yield significant results (Thomas et al., 2021: 1).

There is an uncontrolled research investigating the effect of high-dose zinc salt lozenges on the course of the disease in 4 patients diagnosed with Covid-19. As a result, it is stated in the research that symptoms decrease within 24 hours (Finzi, 2020: 307).

1.6. Selenium

Selenium has a significant effect on both innate and acquired immunity (Huang et al., 2012: 706). It remaines the function of T/B lymphocytes (Huang et al., 2012: 717-722). In one search, selenium supplementation was found to improve immune function (Kiremidjian-Schumacher et al., 1996: 227). Selenium supplementation is also said to have some adverse effects on the body (Chowdhury, 2020: 51).

1.7. Omega-3

Omega-3 polyunsaturated fatty acids play a substantial role in inflammation and adaptive immunity. And they can remain the anti-inflammatory response (Doaei et al., 2021: 2). Recent studies have shown that omega-3 polyunsaturated fatty acids, including

eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and α-linolenic acid (ALA), can remain cell membrane stability, regulate immune function, and block hyperinflammatory reactions (Zhao & Wang, et al. 2018: 2).

EPA and DHA replace arachidonic acid in phospholipid membranes. When oxidized by enzymes, EPA and DHA contribute to the synthesis of less flammable eicosanoids and specific pre-solvent lipid mediators such as solvents, preservatives. This decreases inflammation. In contrast, some studies have reported that EPA and DHA make cell membranes more susceptible to non-enzymatic oxidation mediated by reactive oxygen species, leading to the formation of potentially toxic oxidation products and increasing oxidative stress. Although EPA and DHA may contribute to the recovery of patients infected with SARS-CoV-2, clinical studies on supplementation of Omega-3 fatty acids are recommended (Rogero et al., 2020: 190).

Based on the thesis that omega-3 polyunsaturated fatty acids may have beneficial effects on the immune system in patients with viral infections, a double-blind, randomized clinical trial was conducted to investigate the effect of omega-3 polyunsaturated fatty acids supplementation on inflammatory and biochemical markers in critically ill patients with Covid-19. The search was conducted on a total of 128 Covid-19-infected critically ill patients, 42 randomly assigned to the intervention group and 96 for the control group. As a result of the study, he says that omega-3 supplementation improves the levels of various respiratory and kidney function parameters in critically ill patients with Covid-19, and that more clinical studies are needed on the subject (Doaei et al., 2021: 1).

2. Safety of Food Supplements

Dietary supplements are not regulated as strictly as drugs. For this reason, the reliability of their effectiveness is a controversial issue (Ghosh et al., 2018: 695).

When people use supplements instead of prescription drugs, or take multiple supplements together, the harmful effects of supplements can occur. (Ghosh et al., 2018: 697).

Today, the use of food supplements is very popular. In particular, the presence of contaminants in supplements raises some concerns about the quality and safety of these products (Costa et al., 2019: 1113).

The most prominent reinforcement pollutant classes are;

1. Metals,
2. Toxins,
3. Pesticides,
4. Dioxins (Environmental pollutant),
5. Polychlorinated biphenyls,
6. Pharmacologically active ingredients (Adulterations),
7. Industrial contaminants (Costa et al., 2019: 1125).

Even if the levels of contaminants do not exceed legal limits or are not considered to pose

a risk to human health, there is a need for more monitoring of these products for safety reasons. It is substantial to evaluate the risk associated with food supplement consumption, especially in the elderly population (Costa et al., 2019: 1113).

Safe intake may not be the same for all population groups and life stages. The size of the safe intake range for each nutrient may vary, and in some cases this range may be very small. Certain supplements, such as vitamin A and manganese, have known and potentially serious side effects at high intakes, while others, such as iron or vitamin C, may have smaller side effects that are easily reversible and may only be related to supplement intake (Mulholland & Benford, 2007: 318S).

There is an article presenting the results of studies on the potential risks associated with improper use of vitamin supplements, which until recently were considered not only highly effective but also completely safe. Special attention is paid to vitamins A, E, D and C in the research. It is emphasized that it is necessary to control the intake of vitamin supplements and to strictly control their supply, especially to high-risk patients (Marosz & Chlubek, 2014: 60).

There is a survey search investigating people's thoughts and habits about supplements during the Covid-19 pandemic. In the search; In this period (Covid-19 Pandemic), people say that there is more intense belief that the quality, composition, efficacy and safety of nutritional supplements are well controlled (Karbownik et al., 2020: S1551).

In 2015/2016 T.C. “Dietary Guidelines for Turkey (TUBER)” published by the Ministry of Health includes reference values (sufficient amounts for intake of vitamins and minerals and tolerable upper limit amounts) determined for micronutrients (T.R. Ministry of Health, 2020).

Conflict Of Interest

None of the authors has any potential financial or commercial conflict of interest associated with this research manuscript (review article).

Conclusion

Through the pandemic era, the introduction of different countermeasures such as the “lockdown”, long-term quarantine in cases of suspected or confirmed COVID-19, could generate the adoption of unhealthy eating habits, increasing the risk of non-communicable diseases in the middle-long term.

Even if several measures such as the assumption of a specific diet regimen, the use of dietary supplements, and other similar interventions are promising for the prevention, management, and recovery of COVID-19 patients, it is important to highlight that strong data from randomized clinical trials are needed to promote any such hypothesis.

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