Review

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The Importance of Vitamins A, C, and D in the Pathophysiology of SARS-CoV-2

SARS-CoV-2 Patofizyolojisinde A, C ve D Vitaminlerinin Önemi

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Abstract

The continuing pandemic of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was emerged in China, and has spread rapidly all over the whole world. Thousands of cases and deaths reported each day and it is an exceptional situation in which emergency response is required for many patients. While COVID-19 cases are seen in all age groups, death rates are high in cases of cancer that cause immunodeficiency, especially in elderly people with impaired immune systems, in those with chronic diseases.
The interaction between infections and the immune system is clear and there is a lot of relevant literature information. By keeping the immune system strong, infections can be overcome with less damage, and the harmful effects of inflammation and death rates can be reduced. Vitamins A, C and D are effective in the active functioning of the immune system, and their deficiencies have many adverse conditions, particularly susceptibility to infections. Although there is no specific treatment method, antiviral drug or vaccine with proven reliability for the treatment of COVID-19, the drugs recommended by the World Health Organization are being used. The effectiveness and efficiency of these drugs are controversial. In addition to these drugs, alternative treatment approaches are needed. In this literature review, the importance of vitamins A, C and D on the pathophysiology of SARS-CoV-2 and on the early-stage administration of high-dose intravenous (IV) C, oral A and D vitamins, which are alternative approaches, in the treatment of COVID-19 is shared.

Keywords: COVID-19, immune system, intravenous vitamin C, SARS-CoV-2, vitamin A, vitamin D

Öz

Şiddetli akut solunum sendromu koronavirüs 2'nin (SARS-CoV-2) neden olduğu devam eden koronavirüs hastalığı pandemisi (COVID-19), Çin'de ortaya çıktı ve hızla tüm dünyaya yayıldı. Her gün binlerce vaka ve ölüm rapor edilmektedir ve birçok hasta için acil müdahalenin gerekli olduğu istisnai bir durumdur. COVID-19 vakaları her yaş grubunda görülmekle birlikte ölüm oranları özellikle bağışıklık sistemi zayıflamış olan yaşlılarda, kronik hastalığa sahip olanlarda, immün yetmezliğe neden olan kanser vakalarında yüksek olmaktadır.
Enfeksiyonlar ve bağışıklık sistemi arasındaki etkileşim açıktır ve pek çok literatür bilgisi mevcuttur. Bağışıklık sistemini güçlü tutarak enfeksiyonlar daha az hasarla atlatılabilir, inflamasyonun zararlı etkileri ve ölüm oranları azaltılabilir. A, C ve D vitaminleri bağışıklık sisteminin aktif işleyişinde etkilidir ve eksiklikleri başta enfeksiyonlara yatkınlık olmak üzere birçok olumsuz duruma neden olur. COVID-19 tedavisi için spesifik bir tedavi yöntemi, antiviral ilaç veya güvenilirliği kanıtlanmış aşı bulunmamakla birlikte Dünya Sağlık Örgütü'nün önerdiği ilaçlar kullanılmaktadır. Bu ilaçların etkinliği ve verimliliği tartışmalıdır. Bu ilaçlara ek olarak alternatif tedavi yaklaşımlarına ihtiyaç vardır. Bu derlemede, A, C ve D vitaminlerinin SARS-CoV-2 patofizyolojisindeki önemi ve COVID-19 tedavisinde alternatif yaklaşımlar olan yüksek doz intravenöz (IV) C, oral A ve D vitaminlerinin erken dönemde uygulanması ile ilgili bilgiler derlenmiştir.

Anahtar kelimeler: COVID-19, immün sistem, intravenöz C vitamini, SARS-CoV-2, A vitamini, D vitamini

Introduction

COVID-19, which emerged in Wuhan Province of China in December 2019, is an easily transmissible infectious disease announced by the World Health Organization (WHO) as a pandemic on March 11, 2020.[1] According to the WHO status report, as of June 8, 2021, population of almost all countries in the world (213

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countries) have been infected, over 172 million cases and more than 3 million deaths have been reported, and these numbers continue to grow exponentially day by day.[2,3] The virus is thought to be transmitted via close contact, respiratory droplets when an infected person coughs, sneezes, or speaks, or by asymptomatic people with COVID-19.[4] It has been stated that it is taken into the cell by the angiotensin-converting enzyme-2 (ACE-2) present on the cell surface of the respiratory epithelium.[5]

Although the symptoms of coronavirus disease vary according to the age, health status etc. of the person, the infected individuals can generally show flu-like symptoms. While it is asymptomatic in some people, in others, symptoms such as cough, fever or chills, respiratory distress occur 2-14 days after the person is infected with the virus. In addition, fatigue, muscle aches, loss of taste and smell, gastrointestinal system problems such as nausea and vomiting, diarrhea and personal symptoms can also be seen.[6] The ensuing Acute Respiratory Distress Syndrome (ARDS) threatens life and causes serious lung problems. This syndrome can lead to death and thromboembolism by preventing adequate oxygen input to the lungs. In addition, coronaviruses increase oxidative stress that causes cellular damage and organ failure in later processes. The use of antioxidant agents such as high-dose IV C, oral vitamins A and D in addition to proven therapies in the control of such conditions seems promising.[7]

In this review, the importance of vitamins A, C, and D on the pathophysiology of SARS-CoV-2 and the evidence on high-dose IV vitamin C, oral A and D vitamins being a supportive agent reinforcing the immune system as well as enabling the activation of B and T lymphocytes, reducing the pro-inflammatory cytokine storm and inhibiting the increased oxidative stages induced by coronaviruses are reviewed.

Vitamin A

Vitamin A is taken into the body with food and is the source of retinoids necessary for the realization of various physiological functions from embryonal development to visual functions, from the differentiation and maturation of epithelial tissue cells to brain functions. It is obtained from vegetable sources as carotenoids such as beta-carotenoids, while from animal sources as retinol. It exists in three forms; retinol (alcohol form), retinal (aldehyde form), and retinoic acid (acid form) and the metabolically active form of vitamin A is retinoic acid.[8] All-trans retinoic acid and 9-cis retinoic acid are the two most important forms of retinoic acid (Figure 1a). In both forms, it plays an important role in the regulation of cellular proliferation and differentiation and gene expression.[8,9]

Retinoic acid has nuclear receptors as RXR (retinoid x receptor) and RAR (retinoid alpha receptor).[8] When they bind to the retinoic acid receptor, they act as transcription factors.[10] Vitamin A acts as an inhibitor or effector for T and B cell subtypes.[9] Vitamin A suppresses T-helper 1 (T_H1)- induced cellular immune response while enhancing T-helper 2 (T_H2) induced humoral immunity.[11] Transforming Growth Factor-β (TGF-β) is an important transcription factor that enables T cells to transform into different subtypes.[11] Immune system cells metabolize vitamin-A, and the resulting mini-signal molecules increase regulatory T cell (Treg) levels and decrease T_H17 levels.[12] Retinoic acid increases Mir-10a expression and Mir-10a decreases the expression of B cell lymphoma-6 protein (BCL-6), which is required for differentiation of T follicular helper (T_{FH}) cells.[13] BCL-6 also decreases T_{FH} and T_H17 levels.[13] In addition, Mir-10a induces T_H1 mediated immune system activation by stimulating the expression of T-bet, which is an immune cell-specific member of the family of T-box transcription factors.[13] Differentiation between T_H17 and Treg cells depends on the presence of transcription factors such as forkhead box P3 (FOXP3) and Retinoic acid receptor-related orphan receptor-γt (RORγt), the molecule associated with the regulatory function of Treg cells.[13] If the FOXP3 transcription factor is active, it provides immune activation in the direction of Treg, while FOXP3 binds Runt-related transcription factor 1 (RUNX1) in its nuclear localization to provide RORγt inhibition, thus T_H17 differentiation is curtailed.[13,14] Retinoic acid also inhibits the release of Interleukin-6 (IL-6) and IL-23, which are involved in T_H17 differentiation (Figure 1b). Thus, when looking at vitamin A at the molecular level, its connection with the immune system and inflammatory process would be unveiled. In patients with vitamin A support, number of Treg cells and TGF-β levels were found to be increased.[15] It has been shown that as a result of increased Treg cell differentiation IL-17 levels decreased[16] and the prognosis of patients who have severe SARS-CoV-2 infection decreased.[17] It should be considered that increased Treg differentiation in patients with Vitamin A may prevent cytokine storms.

Vitamin A has immunomodulatory effects in inflammatory diseases.[18] A current study showed that pharmacological mechanisms induced by vitamin A against SARS-CoV-2, induced cytoprotective, anti-viral, anti-inflammatory effects, and immunity-based immunomodulation.[19]

The relationship between vitamin A deficiency and the immune system has been a subject that has attracted the attention of many researchers for many years. It has been revealed that vitamin A plays a role in cellular and humoral immune processes, and its deficiency causes deterioration in immune system responses.[9] Its deficiency, may increase the likelihood of developing keratomalacia, xerophthalmia, epithelial cell dysfunction, gastrointestinal system diseases,

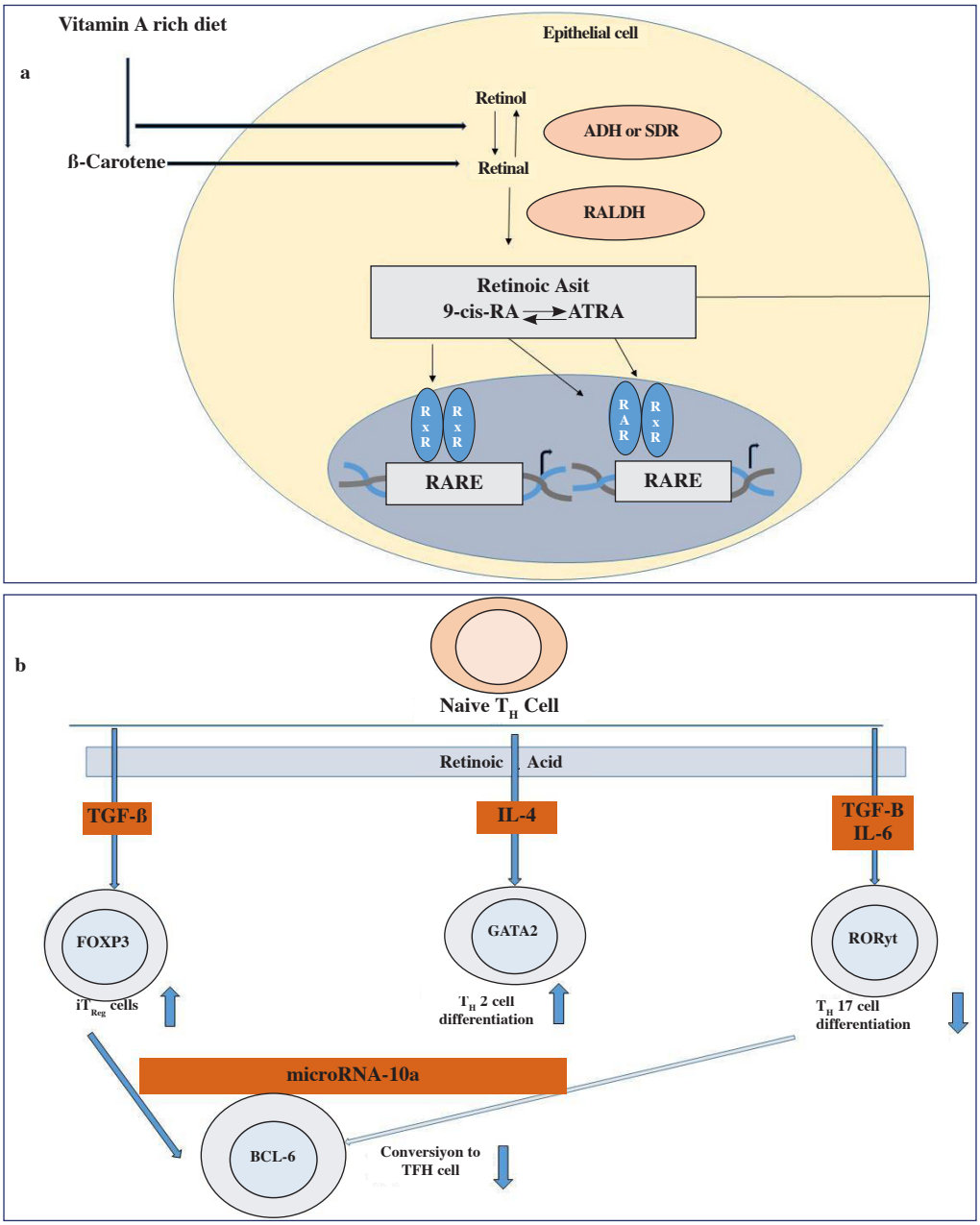

Figure 1. The metabolism of vitamin A at the cellular level and its effects on immune system cells.

(a) Dietary vitamin A and beta carotenes are metabolized into retinoic acid by enzymes from the retinoid dehydrogenase family of enzymes such as alcohol dehydrogenase (ADH) and retinal dehydrogenase (RALDHs) in immune system cells. Retinoic acid has two active isomers, 9-cis-retinoic acid (9-cis-RA) and all-trans-retinoic acid (ATRA). Active isomers of retinoic acid must bind to their receptors in order to function, and both active isomers can bind to the retinoid X receptor (RXR)- retinoid acid receptor (RAR), while the 9 cis-retinoic acid isomer can also bind to the RXR-RXR receptor. After binding to these receptors, retinoic acid response elements (RAREs) in the cell nucleus are attached.

(b) In vitro studies have shown that retinoic acid increases the expression of gut-specific homing receptors and affects T cell differentiation through direct or indirect mechanisms. Retinoic acid inhibits the transformation of these cells into TFH cells by increasing the expression of microRna-10a in induced regulatory T cells (iTReg) and TH17 cells. In vivo studies are not yet certain.

certain infections.[9] More importantly, vitamin A was reported to play a significant role against pneumonia, and It was found that when vitamin A supplementation in deficient children, both the mortality and the infection rate decreased with the strengthening of the immune system.[20] A vitamin A study conducted in 2019 on reducing the duration of stay in intensive care in patients with sepsis revealed that supplementation had no effect on the duration of weaning and

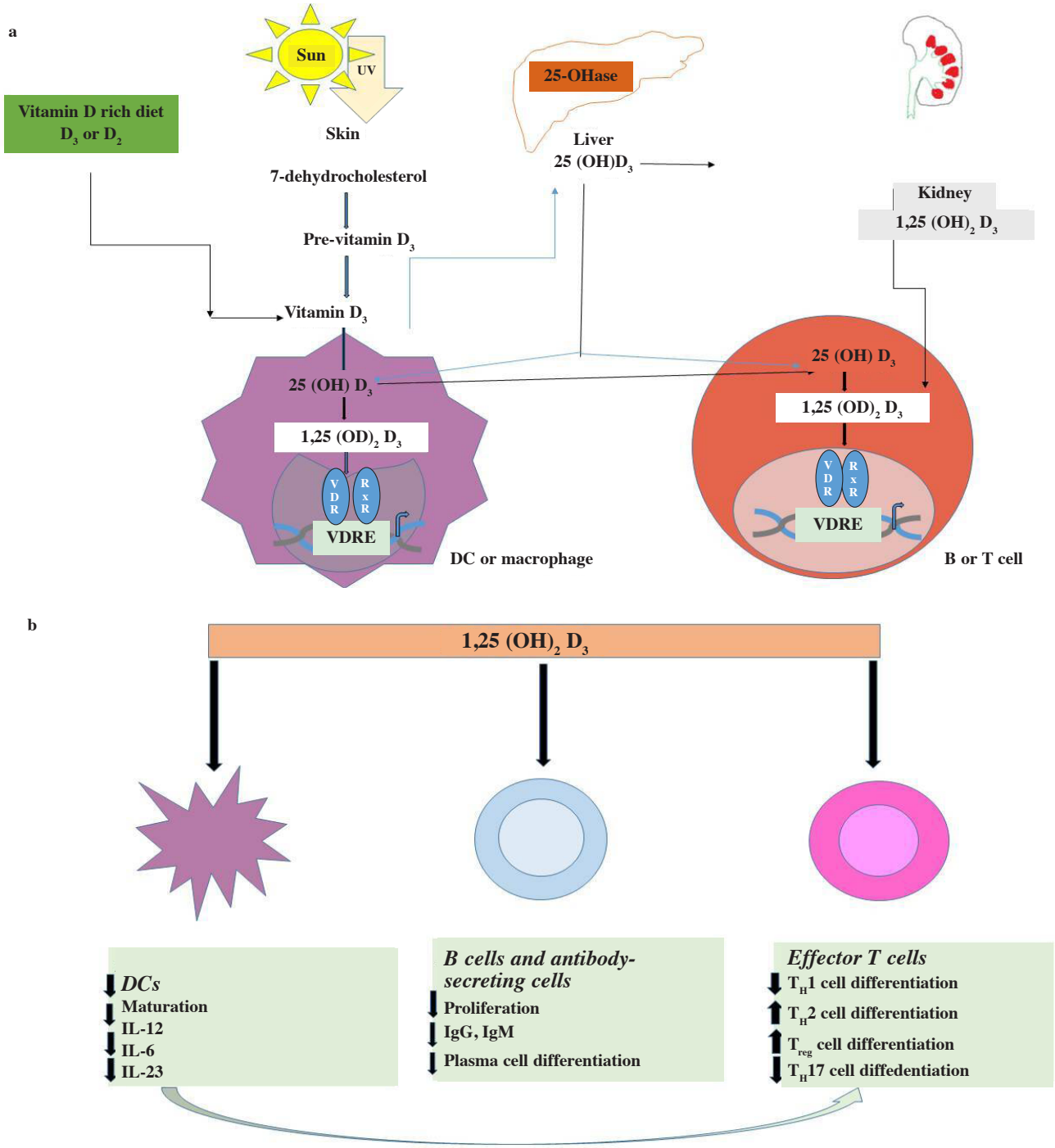

Figure 2. The metabolism of vitamin D and its effects on the cells of the immune system..

(a) Vitamin D_3 can be taken directly from the diet or synthesized from the 7-dehydrocholesterol in the skin by ultraviolet (UV) light. The 7-dehydrocholesterol is first converted to the pre-vitamin D_3 and then to the vitamin D_3 forms. In order to be converted into active metabolites, it is hydroxylated from the 25th position in the liver to 25(OH)D_3 vitamin and then hydroxylated from the 1st position in the kidney to become the most active metabolite 1,25(OH)$_2D_3$. Cells in the immune system can also hydroxylate 25(OH)D_3 to 1,25(OH)$_2D_3$ and this active form binds to the vitamin D receptor (VDR) - Retinoid X receptor (RXR). After this binding, binding occurs to the vitamin D response element (VDRE) in the nucleus.

(b) The 1,25(OH)$_2D_3$, which is formed as a result of hydroxylation in the kidney, affects some immune system cells. For example, it reduces the maturation of dendritic cells and the production of proinflammatory cytokines. In B cells and antibody secreting cells, it affects the proliferation of these cells, the differentiation of plasma cells, and the production of immunoglobulins such as IgG and IgM. It also exerts its effect on the differentiation of T cells by decreasing or increasing it. IL, interleukin.

mortality in adult population, whereas it was found to beneficial in children.[21]

According to the information obtained from the Cochrane database, clinical studies (IRCT20180520039738N2, IRCT20200405046951N1, NCT04353180, NCT04396067, IRCT20200314046774N1) are ongoing in terms of the effect of vitamin A supplementation on COVID-19 patients. In a study of 100 COVID-19 patients with mild to moderate disease severity (50 patients on placebo and 50 on treatment), patients in the treatment group received 2 doses of vitamin A (200,000 IU) for 2 days.[22] The study showed that the symptoms of the patients in the treatment group decreased after 48 hours of supplementation, while the symptoms did not decrease in the placebo group.[22] Re-infection was seen in 20.62%, and 58.03% of the cases, while symptoms persisted for 4.6, and 6.72 days, respectively.[22] In addition, in a clinical study (IRCT20210205050247N1) vitamin A was included in the treatment process of 90 patients to restore the loss of smell that occurs with the disease due to reduction in olfactory cells associated with vitamin A deficiency (https://www.irct.ir/trial/54178). Vitamin A given in pharmacological or high doses increased the formation of regulatory T cells while inhibiting the activity of T cells that might induce the development of the disease and the release of pro-inflammatory cytokines.[14,23] Further studies are needed to understand the effect of vitamins.

It should be remembered that this fat-soluble vitamin, which can be stored in the body, can cause gastrointestinal side effects, headache, vertigo, blurred vision, and neurological disorders when taken in excess.[22] Clinicians should definitely check plasma concentrations before using vitamin A for patients and it should be used in case of vitamin A deficiency.

Vitamin C

Vitamin C (also known as ascorbic acid or ascorbate) is a water-soluble vitamin with strong antioxidant property. Vitamin C cannot be synthesized by humans due to the lack of L-Gulono-gamma-lactone oxidase, a key enzyme for the biosynthetic pathway, and it must be taken as dietary element.[24]

It has been stated that the plasma levels of vitamin C begin to decrease after an infection in the body.[25] Oral intake of the vitamin cannot increase plasma concentrations to normal levels due to increased acute metabolism, limited intestinal uptake.[26,27] Absorption from the intestines is mediated via sodium-dependent transporters (SVCT-1 and SVCT-2).[24] Intravenous treatment mediates led the increase of plasma concentrations more rapidly.[28] For this reason, vitamin C has been the subject of intense researches for the treatment of cancer.[29] In addition, a phase I study conducted in patients with severe sepsis has showed that the administration of i.v. vitamin C is safe, well-tolerated, with a reduction in multiple organ damage and biomarker levels of inflammation.[30] A recent study showed that high doses of i.v. vitamin C as an adjuvant treatment for ARDS caused by viral infections (enterovirus/rhinovirus) reduced lung damage.[31]

Vitamin C has many important roles in the defense of the immune system from protecting cells against damage caused by reactive oxygen radicals[32] that led to quicker wound healing,[33] increasing phagocytosis, chemotaxis,[34] and differentiation and proliferation of B and T lymphocytes.[35] Levels of vitamin C in leukocytes are 80-fold higher than those in plasma. Laboratory studies have shown that vitamin C affects the functions of phagocytic cells, the production of interferons, the replication of viruses, and the maturation of T lymphocytes involved in cellular immunity.[36]

Vitamin C deficiency is important for the immune system, as it causes impaired immunity and higher susceptibility to infections.[34] It regulates the immune response first by inhibiting the activation of nuclear factor kappa B, known as responsible for the pro-inflammatory cytokine storm cascade, by inducing the phagocytic activities of leukocyte cells, and by reducing the production of superoxide radicals in macrophage cells.[34,37] In addition, vitamin C could suppress the cytokine storm caused by SARS-CoV-2 by reducing the secretion of IL-6, a pro-inflammatory cytokine-induced by endothelin-1 (a vasoconstrictor peptide, when its expression is increased, especially in the lungs, it has been associated with conditions such as pneumonia, lung fibrosis, and ARDS)[38]. High IL-6 levels are associated with hyper inflammation and multiorgan failure.[38] For this purpose, IL-6 antagonist drugs such as tocilizumab and sarilumab are also being evaluated in terms of efficacy in treatment (NCT04315298, NCT04332913, NCT04320615).

Vitamin C deficiency was reported to predispose to respiratory infections.[39] Vitamin C was known to be effective in reducing morbidity and mortality in children and adults with its antiviral properties.[40] With its immunomodulatory effect vitamin C was found to be effective in viral infections by increasing the production of interferon α/β or by reducing the release of pro-inflammatory cytokines.[41]

Studies on the use of high-dose i.v. vitamin C in the treatment of COVID-19 have been initiated in USA and China, and those clinical trials are presented in the International Clinical Research Registration Platform established by WHO, and also screened in *clinicaltrials.gov* database (https://www.who.int/clinical-trials-registry-platform, https://clinicaltrials.gov/). Studies evaluating the effectiveness of vitamin C on COVID-19 are still ongoing.

The data of the completed studies have not been shared yet. In the study that included 78 cases (NCT04710329); patients were administered 6 grams of vitamin C daily in 4 equal doses every 6 hours intravenously for 96 hours. Short-term mortality and length of stay in the intensive care unit, levels of vitamin C, as well as inflammatory markers such as CRP, procalcitonin, and ferritin are being evaluated in critically ill COVID-19 patients.

IV vitamin C has been reported to strengthen the immune systemís response, reduce the cytokine storm that occurs, and support increased antiviral activity through mechanisms that yet to be explained.[7] In a placebo-controlled study involving 58 patients in China, patients in the treatment group had lower IL-6 levels on the 7th day and the PaO_2/FiO_2 ratio was reported to increase.[42] In a study of 17 patients with comorbid disease(s), patients received i.v.-vitamin C (1 g/ 8 hrs for 3 days) in addition to standard therapy.[43] As a result, levels of inflammatory markers such as D-Dimer and ferritin, and the need for mechanical ventilation of the patients decreased in vitamin C group.[43]

In a study initiated in Australia also aimed to find whether patients diagnosed with active COVID-19 can prevent the progression of the disease by i.v. vitamin C in addition to their treatment.[44] National Institutes of Health in USA states that high-dose i.v. vitamin C (1.5 g/kg) is safe without any side effects.[44]

Patients with SARS-CoV-2 infection are predisposed to thrombotic events attributable to certain risk factors affecting the coagulation system, such as stasis in the blood flow due to immobility, increased inflammation, and endothelial dysfunction.[45] The increase in pro-inflammatory cytokines leads to endothelial damage.[45] Levels of D-dimer and fibrinogen/fibrin degradation products begin to rise significantly.[46] However, since a different process is experienced in SARS-CoV-2 infection from coagulopathy that develops in sepsis, this condition has been called COVID-19 associated coagulopathy.[46] While the mechanisms underlying its development are not known exactly, there were no significant changes in prothrombin time, activated partial thromboplastin time, and platelet count, but the highest increase is seen in D-dimer levels which is associated with increased mortality.[45,46] There was evidence that high doses of vitamin C reduced D-dimer levels.[47]

There have been studies investigating the role of high dose i.v. vitamin C in the early period of sepsis and infections.[48-50] Studies in experimental sepsis models have shown that i.v. vitamin C reversed the resulting organ damage and increased the likelihood of survival in septic mice.[51,52] Another study with a minimum of 800 patients with sepsis *(NCT03680274)* also investigated the effect of vitamin C on survival and persistent organ dysfunction at 28 days at high-doses (50 mg/kg /6 hrs for 96 hours).[53] One of the most comprehensive studies was also published in 2019.[54] Considering the effects vitamin C on the immune system, it seems meaningful to apply it in COVID-19, but it should not be forgotten that vitamin C has anti-oxidative effect in low doses whereas its high doses exert pro-oxidant effect.[55] The plasma concentrations of the vitamin should be assessed before any planned administration. It should be used in case of deficiency. It should be noted that this water-soluble vitamin, which is not stored in the body, can cause gastrointestinal side effects such as nausea and vomiting.[32] As there is insufficient data on the use of vitamin C in the treatment of COVID-19.

Vitamin D

Vitamin D, known for its important role in calcium and bone homeostasis, the interaction of vitamin D with the immune system has recently started to attract attention and has been the subject of research.[56] Its deficiency, which is often seen as an important public health problem, is known to predispose to diseases such as autoimmune diseases, especially infections.[57]

Vitamin D_3 is photochemically synthesized from 7-dehydrocholesterol, also known as provitamin D_3, in the skin by the effect of ultraviolet light.[58] Vitamin D receptor is expressed by most immune system cells such as macrophages and these cells metabolize the circulating 25-hydroxyvitamin D form to the active form 1,25-dihydroxyvitamin D via the 1α-hydroxylase enzyme.[58,59] This active metabolite induces immunoregulation by activating some T cell subtypes and by inactivating others).[60] Whereas its activated form is utilized directly in the kidney (Figure 2a).[60,61]

Vitamin D is connected to heterodimer nuclear-localized VDR (vitamin D receptor) and RXR (retinoid X receptor).[62] While all cells in the immune system are sensitive to $1,25(OH)_2D_3$, they also have the ability to express vitamin D receptors.[58] Vitamin D has different effects on the immune system by preventing the proliferation of B and T cells and the differentiation of B cells.[60] It enhances the T_H2-mediated immune response by suppressing the T_H1-mediated immune response.[63] It also increases the levels of Treg cells just like vitamin A.[12] Vitamin D also facilitates induction of Treg cells, resulting in reduced production of inflammatory cytokines such as IL-6, IL-12, and IL-17 and an increased production anti-inflammatory cytokines.[60,64] Interferons also have a crucial role in immune modulation by vitamin D and studies have shown that vitamin D has inhibitory effect on interferon response and it increased serum IL-10 levels.[65] It was found that vitamin D reduced T_H1 cells and the secretion

of Th17 cytokines and increased T_H2 response by affecting interferons.[66] As outlined in Figure 2b, the differentiation of T_H2 cells is induced while the differentiation of T_H1 cells diminished due to the effect of effector T cells by $1,25(OH)_2D_3$.[63] IL-12 production was also shown to be reduced by warning of antigen-presenting DCs.[67] IL-6 and IL-23 was also shown to be reduced.[67] It has been shown that IL-6 levels increased in mice with vitamin-D receptor deficiency related to to the p65-dependent nuclear factor-kappa β pathway.[68] FOXP3 was shown to be activated by activation of the VDR-RXR receptor.[69] It has been suggested that vitamin D inhibits direct T cell receptor (TCR) mediated signaling to reduce the risk of immunopathology.[70] The $1,25(OH)_2D_3$ suppressed the formation of T_H17 cells and negatively regulates the expression of the main chemotactic receptor, namely CC-chemokine receptor (CCR6) CCR6 and its ligand CC-chemokine ligand 20 (CCL20) that had a role in controlling the migration of T_H17 cells into tissues.[71,72] Interestingly, the development of CD8aa+ intraepithelial lymphocytes (IEL) was also found to be significantly dependent on TGF-β.[73] This might suggest a potential synergistic effect between TGF-β and vitamin D as it was reported with vitamin A.[73] This event was controlled via a wide variety of receptors such as RXRs, RORγt, retinoid-associated orphan receptor-α (RORα), and aryl hydrocarbon receptor (AHR).[73] These receptors are expressed in cells such as CD8aa+ IEL, T_H17, and Treg (Figure 2b).[73] Thus, vitamins A and D have the ability to change lymphocyte activation and homing, thus contributing to intestinal immune homeostasis, which is characterized by a state of tolerance to most antigens.[73]

The renin-angiotensin system is also considered to be effective in COVID-19 pathophysiology.[74] Angiotensin I is converted through angiotensin-converting enzyme (ACE) into angiotensin II, a protein that plays a role in blood pressure regulation and supports inflammation, fibrosis, and oxidase responses by driven by angiotensin II type I receptor (AT1).[75] Membrane-bound ACE-2, defined as the receptor for the SARS-CoV-1 virus that was shown to be responsible for the 2003 SARS outbreak is also the receptor for the SARS-CoV-2 virus.[76] SARS-CoV-2 penetrates epithelial cells by binding to membrane-bound ACE-2, and ACE-2 plays an important role in balancing the negative pro-inflammatory downstream effects, which are stimulated by angiotensin II binding to AT1.[77] SARS-CoV-2 also downregulated ACE-2 and caused receptors to lose function.[77] Because ACE-2 plays an important role in protecting against tissue damage, dysfunction of ACE-2 receptor could increase acute lung damage caused by angiotensin II.[77] The effect of vitamin D on this process is to play a protective role against lung damage and ARDS by increasing the decreasing ACE-2.[76] Considering these possible effects of vitamin D, it seems that it tends to reduce the damage caused by COVID-19 by targeting the impaired renin-angiotensin system and down-regulation of ACE-2 by the effect of SARS-CoV-2.[78]

When COVID-19 cases are identified in China, it has been reported that people with diabetes and hypertension are more likely to contract the disease.[44] Low plasma levels of active metabolite of vitamin D has been associated with higher blood pressure.[79] Likewise, plasma vitamin D levels were low in diabetic patients which have been associated with an increased risk of cardiovascular diseases, metabolic syndrome, and high blood pressure.[80] It has been shown that there is a relationship between seasonal influenza infection and cardiovascular diseases, and viral infections caused deterioration of endothelial function and in turn it led to secretion of pro-inflammatory agents that increase mortality[81]. In addition, vitamin D supplementation exerted, a decrease in thrombin formation.[82] Some studies have also shown the association between vitamin D deficiency and deep vein thrombosis.[83]

Viral infections including influenza, which cause damage to the respiratory system, are more common, in the winter season.[84] COVID-19, which affected all over the world as of December 2019, started to spread in the winter and caused serious consequences.[85] As it is known, people often suffer from vitamin D deficiency ((25(OH) D<20 ng/ml) due to insufficient sun exposure in winter.[86] Considering the functions of vitamin D in the body and its effects on the immune system, the question arises whether there is a link between its insufficiency and COVID-19. A possible according to a study conducted in European countries, a significant inverse relationship was found between the COVID-19 mortality rate and plasma concentrations of vitamin D.[87] It has been reported that the levels of vitamin D synthesized from skin-derived 7-dehydrocholesterol decrease with age.[88] A possible relationship could be speculated between the synthesis of vitamin D, and aging. Indeed synthesis of vitamin D decreases approximately up to 50% with aging.[88]

Since the relationship of vitamin D with infections has been on the agenda for a long time, and also associated with COVID-19, clinical studies have been initiated regarding this issue. Studies have been initiated to investigate the use of high-dose vitamin D in the treatment of COVID-19 or to determine the role of vitamin D in COVID-19 and these clinical studies are presented in the International Clinical Trial Registry Platform established by WHO and in the Cochrane library (relevant clinical studies were searched using *clinicaltrials.gov* and *covid-19.cochrane.org* databases). With the completion of ongoing clinical studies (NCT04738760, NCT04344041, NCT04733625, NCT04525820, IRCT20110726007117N11,

CTRI/2020/12/030083), more information would be obtained. The current version studies conducted/ongoing on vitamin D has been reported in a systematic review.[89] According to a study conducted in India, high-dose vitamin D (60 000 IU cholecalciferol daily for 7 days) was administered to 40 participants (control group, n=24; vitamin D treatment group, n=16) with positive COVID-19 test results, and vitamin D deficiency. The study participants were randomized to receive 25(OH)D>50 ng/ml and significant decreases were observed in the levels of inflammatory markers such as fibrinogen, D-dimer, and CRP as a result of treatment.[90]

- In an another study, which included 42 cases with acute respiratory failure in Italy, patients were divided into 4 groups as: not vitamin D deficient (≥30 ng/mL), vitamin D deficient (30< vitamin D ≥20 ng/mL), moderately vitamin D deficient (20< vitamin D ≥10 ng/mL), and severely vitamin D deficient (<10 ng/mL) cases. While inflammatory markers (CRP, D-dimer, ferritin, IL-6) were found to be high in all groups, it was reported that mortality increased as vitamin D levels decreased. The mortality rate (50%) was found to be much higher, especially in cases with severe vitamin D deficiency.[91]

- In a study that included 782 cases; 10.5% of the cases had no vitamin D deficiency, while the remaining patients had vitamin D insufficiency (76.5%) or deficiency (13.4%). In the study, the presence of factors such as age, gender, comorbid diseases, as well as the effect of vitamin D levels on hospitalization due to COVID-19 infection was analyzed, and the rate of hospitalization was found to be increased approximately 2 times in patients with insufficient levels.[92]

- In a randomized controlled study with 76 patients hospitalized for COVID-19 infection, 50 patients were treated with high-dose 25-hydroxy vitamin D in addition to standard therapy, and no patient died. Of the 26 patients who received standard treatment, 13 were admitted to the intensive care unit and there were 2 deaths. In other words, in cases treated with 25-hydroxy vitamin D, the need for intensive care decreased and the patients did better in this group.[93]

- In an another study, which included 689 cases 12.9% of the cases had vitamin D deficiency. A relationship between the length of hospital stay, the severity of the disease, admission to the intensive care unit, and vitamin D deficiency was found.[94]

- In addition, in a study investigating the effect of a single high-dose vitamin D on the duration of hospital stay in moderate and severe COVID-19 patients, it was found that any statistically significant result could not be observed compared to placebo.[95]

A relationship between vitamin D and COVID-19 was found in patients with vitamin D insufficiency (15-29.9 ng/ml) or deficiency (<15 ng/ml).[96] Therefore, clinicians should check serum concentrations before administering vitamin D to patients. Otherwise, excessive intake of this vitamin, which can be stored in the body, may result in side effects and symptoms such as hypercalcemia, hypercalciuria, hyperphosphatemia, polyuria, polydipsia, and ectopic calcifications in soft tissues such as the kidney and lung.[96]

Conclusions

Recently, the prevalence and mortality rates of SARS-CoV-2 have increased worldwide, especially in developed countries in 2020.[2,3] However, there are few existing drug treatments for COVID-19, and antiviral drugs used in clinical practice that have shown limited therapeutic effectiveness.[97] As the name suggests, vitamins are important nutrients for life. Studies have revealed that they have effective roles in both congenital and acquired immunity. Although limited number of concluded clinical studies have shown the link between COVID-19 and vitamins in the literature, clearer information will emerge as the studies have been completed. Studies have shown that mainly vitamins A, C, and D can be powerful life-savers during the intense inflammation caused by COVID-19. The inflammatory process associated with COVID-19 can lead to adverse reactions ranging from mild viral pneumonia to acute respiratory distress syndrome and multiorgan failure. ARDS, which is a life-threatening and has serious pulmonary entity, can prevent the entry of sufficient amounts of oxygen into the lungs resulting in death, and thromboembolism.[98] In addition, alternative immunomodulatory therapies will be beneficial in addition to the treatments applied. A common way to supplement vitamin C in the clinic is intravenous vitamin C application. i.v. vitamin C can be considered a safe and effective agent for ARDS. The use of antioxidant agents such as high i.v. doses of vitamin C, oral A, and D vitamins seem promising. Significant therapeutic results obtained as a result of clinical trials have also shown that there is no safety issues for vitamin C adminstration. A high-dose of i.v. vitamin C might be an approved therapeutic agent that both leaves oxidative stress and inflammation during SARS-CoV-2 infection, and suppressed viral replication, and increased antiviral immune defense. In addition, high doses of vitamin C supplementation also helps normalize both serum and leukocyte vitamin C levels. Vitamin C has many pharmacological properties: antiviral, antioxidant, anti-inflammatory and immunomodulatory effects, making it a potential therapeutic option in COVID-19 management.

Early treatment is needed to alleviate the inflammatory process, shorten hospitalization time, reduce the number of cases admitting to the intensive care unit. Numerous preclinical studies have shown that vitamins A, C, and D

could provide better removal of free oxygen radicals, limit their production and help the damaged endothelium regain its function. i.v. vitamin C, oral A, and D vitamin administrations contributed to achievement of stronger immune system response by reducing cytokine storm or enhancing antiviral effects through other unexplained mechanisms. Today, there are many experimental studies showing the importance of vitamin D in eliminating infection in the body, and strengthening especially innate immune system. It has also been clearly stated that there is a predisposition to respiratory system diseases in its deficiency. High-dose vitamin D reduces the cytokine storm caused by viral pathogens in the body by inhibiting pro-inflammatory cytokines and activating anti-inflammatory cytokines trials. Vitamin C also was shown to improve immune system by increasing the production of α, and β interferons having immunomodulatory effects, and reducing the production of pro-inflammatory cytokines supplementation could be beneficial in this pandemic.

Vitamin A supplementation contributes to reduction of clinical complications and number of hospitalizations in children with pneumonia. All this evidence suggests that vitamin A may be an optional treatment for COVID-19; however, to date, limited number of studies on vitamin A, and especially regarding its pharmacological mechanism against SARS-CoV-2 have been conducted. Adjuvant vitamin A supplement can improve the therapeutic ability of existing clinical antiviral agents and immunotherapy in an attempt to treat potentially fatal COVID-19.

Vitamin D might have a beneficial role in reducing adverse outcomes of SARS-CoV-2 infection by first regulating the renin-angiotensin system. Recent studies in which ARDS was induced, have showed that vitamin D reduced pulmonary permeability by modulating renin-angiotensin system activity as well as the expression of the ACE-2. During SARS-CoV-2 infection, downregulation of ACE-2 led to mitigated cytokine storm in the sufficient vitamin D supplementation may reduce the production of inflammatory cytokines during infection. The $1,25(OH)_2D_3$ can increase ACE-2 expression and attenuate the generation of reactive oxygen species that are induced during SARS-CoV-2 infection and the angiotensin II-induced inflammatory response. As a result, since vitamin D deficiency is frequently observed, increasing its plasma concentrations will play a role in reducing the devastating effects of this disease.

Insufficient intake of vitamins has also been associated with a variety of non-communicable diseases (diabetes, hypertension, cardiovascular diseases), and these diseases further increase the risk of COVID-19-related mortality. Therefore, attention should be paid to the plasma levels of vitamins A, C, and D during the initial and progressive stages of the disease. Thus, by intervening at an early stage, the clinical course can be changed, progression of the disease can be stopped, and the disease can be overcome with less damage. Especially based on the studies and mechanisms investigated at the molecular and cellular levels, we think that, A, D, and C vitamins will also be beneficial in this process.

In this review, the place and importance of the above-mentioned vitamins in the pathophysiology of SARS-CoV-2 has been discussed. Vitamins prevent ARDS and multiorgan damage and improve quality of life in patients with SARS-CoV-2 infection by making the immune system more effective, reducing cytokine storm and inhibiting the oxidative process. Based on the effects of these vitamins on the SARS-CoV-2 pandemic as described in the review, their role as an adjuvant agents for traditional treatments would provide great help in managing the disease. Since clinical trials are still continuing, there is no treatment protocol prepared by the competent centers (such as WHO, NIH, NHS, or Turkish Health Ministry) for the use of these vitamins. Recent NIH guidelines do not recommend the use of any vitamin in the treatment of COVID-19. It is thought that with the completion of the ongoing clinical trials and further studies on these subjects, the role of vitamin supplementations will be clarified.

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