CHAPTER 2

AN OVERVIEW OF RECENT STUDIES REGARDING THE SARS-COV-2 AND VITAMIN D LEVELS

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SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2)

It was reported that a new type of coronavirus was isolated from a patient on January 7, 2020, following the first reports of pneumonia caused by a new agent in the Wuhan region of China's Hubei province at the end of 2019. Data revealing that this new virus sequence, called 2019-nCoV, was 80-90% similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and 96% similar to a bat coronavirus (RaTG-13) (1). Besides, the disease was named COVID-19, referring to the year 2019, with the letters taken from the words "Coronavirus Disease" (2). Spike (S) protein, Envelope (E) protein, Membrane (M) protein and Nucleocapsid (N) protein are responsible for the programming of virus and emergence of infection in coronaviruses (3). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), called as 2019-nCoV, binds with the S glycoprotein to the angiotensin converting enzyme II (ACE2) receptor in eukaryotic cells (4). Although the ACE2 enzyme is highly expressed in type-II alveolar cells, it is also expressed in heart, kidney, vascular endothelium and intestinal epithelium (5).

The mean 5-6 days is incubation period for SARS-CoV-2, and fever, dry cough, fatigue, and myalgia are the most common symptoms (6). In the most of the cases, lymphopenia is detected and leukopenia or leukocytosis might be seen. Ferritin and lactate dehydrogenase levels are generally high, and aminotransferase levels may be found as increased (3). The detection of SARS-CoV-2 is made by reverse transcriptase polymerase chain reaction (RT-PCR) of samples taken from the respiratory tract (7). The corticosteroids with anti-inflammatory and immunosuppressive effects may be useful for the treatment of fever, on the other hand, ribavirin blocks the viral replicase polyprotein. The lopinavir-ritonavir formulation may support antiviral therapy in combination with ribavirin in the early stages of COVID-19 (8). Hydroxychloroquine prevents the virus from

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entering target cells by interfering with the glycosylation of the ACE2 receptor (9). In the COVID-19 adult patient treatment guide of the Republic of Turkey, Ministry of Health, General Directorate of Public Health; Favipravirin 2x600 in treatment in 'COVID-19 Cases with Asymptomatic, Uncomplicated or Mild-Moderate Pneumonia'; it is recommended to use a dose of 2x600 mg for 5 days following a 2x600 mg loading. The use of favipravir in pregnant, postpartum or breastfeeding mothers is not recommended (10). Although there is no antiviral treatment with proven safety and efficacy for SARS-CoV-2, it is recommended to start antiviral drugs in the early stages of the disease. Hydroxychloroquine and lopinavir/ritonavir were not found to be effective enough in the treatment of COVID-19 and their use was abandoned. "Remdesivir", another antiviral drug, has been continued to be used despite not having a significant benefit in severe COVID-19 patients. While randomized controlled trials showed that the use of favipiravir does not show an advantage in reducing outpatient hospitalization or death from COVID-19, its use is left to the discretion of the physician (11). On the other hand, vaccines produced from weakened or inactive parts of a particular organism are released after a long process, this process was shortened considerably with the SARS-CoV-2 that caused the pandemic. Pfizer/Biontech, Oxford/AstraZeneca, CoronaVac/Sinovac and Moderna/INH were the main vaccines produced to protect against SARS-CoV-2 infection (12).

VITAMIN D

Vitamin D might be synthesized in the skin by exposure to sunlight or taken with a diet (13). Previtamin D is produced by sunlight by the conversion of dehydrocholesterol in the skin and transported to the liver, where it is converted to the main circulating form, 25-hydroxyvitamin D (25OHD). In the kidney, the enzyme cytochrome P450 27B1 converts 25OHD to the active form, 1,25-dihydroxy vitamin D, $1,25(OH)_2D$ (14). Serum 25-hydroxy vitamin D (25OHD) with a half-life of about 3 weeks is measured to assess the vitamin D levels (15). The 25OHD is inactivated by transformation to $25,24(OH)_2D$ due to 24-hydroxylase activity (16). $1,25(OH)_2D$ binds to vitamin D receptor (VDR) with high affinity and performs its biological effects (17). With the VDR binding of $1,25(OH)_2D$, the retinoid X receptor (RXR) is also activated. With this activation process, the RXR-VDR-ligand complex passes from the cytoplasm to the nucleus and regulates gene transcription (18). The VDR protein has ligand-binding and DNA-binding regions, and vitamin D binds to the ligand-binding region. The DNA binding site binds to the vitamin D response element in the target gene (19). Vitamin D; it acts by regulating gene transcription (genomic effect) or by changing the trans-

membrane transition of Ca, chloride (Cl) ions or activating intracellular signaling pathways (non-genomic effect). It emphasizes that active vitamin D regulates 0.8-5% of the total genome and play active roles in many events such as regulation of cellular growth, membrane transport, DNA repair, cellular metabolism, apoptosis, oxidative stress and adhesion (20). The major role of vitamin D is the regulation of the calcium and phosphorus balance with parathormone. $1,25(OH)_2D$ increases phosphor absorption from the ileum and calcium absorption from the duodenum. It also prevents calcium loss in the kidneys and increases bone resorption. Furthermore, $1,25(OH)_2D$ also decreases the synthesis of parathormone and increases the production of insulin (21). Fat-soluble vitamin D is effective in all tissues which contains its receptors. Cardiovascular diseases, hypertension and various malignancies were found associated with vitamin D deficiency (22). Vitamin D attracts attention with its modulation effects such as lymphocyte activation and proliferation, production of tissue-specific lymphocyte and antibody isotypes, and regulation of immune response (23). It was detected that VDR in many regions of the brain such as the thalamus, hypothalamus and hippocampus, and the presence of 25OHD and $1,25(OH)_2D$ in the cerebrospinal fluid of adult individuals. The presence of CYP27B1 and CYP24A1 enzymes, which convert vitamin D to active and inactive metabolites, respectively, in the glial cells of the brain was also showed. Vitamin D has been reported to have autocrine and paracrine properties and has been evaluated as a neurosteroid (24).

Vitamin D Deficiency

Serum 25OHD levels are recognized as; <10 ng/mL severe deficiency, <20 ng/mL deficiency, 20-30 ng/mL insufficiency, <30 ng/mL sufficient and <150 ng/mL intoxication (25, 26).

In the study based on Istanbul, we found %49.6 of the participants had vitamin D deficiency and 29.8% of them had vitamin D insufficiency. Sufficient vitamin D levels were found in 20.5% of the subjects (27). Other studies conducted in Turkey were also found high levels of Vitamin D deficiency levels in Turkey (28-30).

Vitamin D deficiency has turned into a global pandemic, which is seen not only in our country but also in low and high income groups in almost every region of the world. Vitamin D deficiency affects individuals of all age groups; use of vitamin D supplements, age, diet, geographical latitude, culture and lifestyle, individual differences in skin pigmentation and vitamin D metabolism are effective factors for vitamin D status. The prevalence of vitamin D deficiency is quite high among immigrants living in the Middle East, Asia, and Africa, as well as in countries at higher latitudes from these regions (31). The data of 21474 sub-

jects from 23 African countries, including Egypt, Nigeria and South Africa, were analyzed in a meta-analysis study; serum 25OHD concentration was lower than 30nmol/L in 18.46% of the subjects and less than 50nmol/L in 34.22% of them for pooled prevalence of vitamin D deficiency (32). In high-income countries such as the USA, Canada and Europe, the prevalence of vitamin D deficiency (serum 25OHD< 30nmol/L) was reported as 5.9%, 7.4% and 13%, respectively, while the prevalence of vitamin D inadequacy (serum 25OHD< 50nmol/L) was reported as 24.0%, 36.8% and 40.4%, respectively (33).

THE RELATION OF SARS-COV-2 AND VITAMIN D

It is claimed that vitamin D deficiency can impair respiratory immune response function and increase the risk of disease severity and death. Considering the COVID-19 infection rates in different countries; it is reported that high infection rates positively correlated with those with high vitamin D deficiency in the population and negatively correlated with countries with higher vitamin D levels and higher dietary vitamin D intake (34). Furthermore, an association was found between increased susceptibility to respiratory infection and low vitamin D levels (35). It is thought that vitamin D may be protective against asthma, influenza, chronic obstructive pulmonary disease (COPD), bronchitis and tuberculosis and may play a role in these diseases (34).

Vitamin D increases the innate cellular immune response by increasing the expression of peptides such as defensin and cathelicidin, which have antimicrobial effects against enveloped and non-enveloped viruses. Defensins are effective in preventing the invasion of viruses by protecting the integrity of "gap junctions", "tight junctions" and "adherent junctions" between respiratory epithelial cells (36). In almost all immune cells; VDR is also expressed in antigen presenting cells such as macrophages and dendritic cells, B cells, CD4+ and CD8+ T cells. The VDR receptor modulates the adaptive and innate immunity (37). Vitamin D receptors (VDR) are present in high concentrations in active T lymphocytes. In individuals with severe respiratory disease, serum vitamin D is positively correlated with anti-inflammatory cytokines IL-10 and TGF-β, Treg cells, and maintains immune homeostasis (38). Vitamin D can increase the expression of anti-inflammatory cytokines via decreasing the expression of pro-inflammatory Th1 cytokines such as interferon γ (39).

SARS-CoV-2 down-regulates ACE2, uses for target cell entry, and this mechanism can cause lung damage and vasoconstriction. Therefore, it is thought that upregulation of ACE2 may be effective in the treatment of COVID-19 (40). It was concluded that calcitriol, the active form of vitamin D, can increase VDR and

ACE2 mRNA expressions and protein levels in rat models of acute lung injury (ALI), and may be effective in protecting against the development of ALI (41). Another study found that calcitriol modulates the expression of renin, and angiotensin II, including ACE and ACE2 from the renin-angiotensin system (RAS), and may perform protective effects on the lung (42).

It was reported that 1,25$(OH)_2$D administration reduces both in vitro and in vivo replication of rotavirus and 4000 IU/day vitamin D supplementation decreases dengue virus infection. In order to rapidly increase 25OHD concentrations to reduce the risk of infection, supplementation of 10,000 IU/day for a few weeks followed by 5000 IU/day of vitamin D to increase 25OHD concentrations to 40-60 ng/mL (100-150nmol/L) is suggested (43).

Original researches evaluating the relationship between SARS-CoV-2 and Vitamin D levels

As can be seen from the information presented, it is recommended in many publications that vitamin D is effective in respiratory infections and therefore its use in COVID-19 will also be beneficial. In this part of the article, original researches carried out in Turkey and in the world which are comparing low vitamin D levels with those with severe SARS-CoV-2 infection or the success of vitamin D in the treatment of COVID-19 will be included.

In a study conducted with 204 COVID-19 patients in Turkey, vitamin D deficiency was found in 41.7% and insufficiency in 46% (n=94). Furthermore, it was determined that for each standard deviation decrease in serum 25OHD level in the patients with vitamin D deficiency increases 38 fold the risk of severe clinical outcome (44). When the micronutrient profile and hemogram data of 310 Turkish COVID-19 patients were analyzed; low vitamin D, folate, iron and hemoglobin levels of the patients were found to be related to poor prognostic factors (45). In another study Istanbul-based, severe-critical COVID-19 patients (n=102) had significantly lower 25OHD levels compared to moderate COVID-19 (n=42) (10.1±6.2 vs. 26.3±8.4 ng/mL, respectively), vitamin D deficiency was found in 93.1% of severely critical COVID-19 patients (46).

In pediatric subjects with COVID-19(+) with a median age of 11.8 years (n=30) and COVID-19(-) with a median age of 12.7 (n=82) years, vitamin D levels were found to be quite low in patients with SARS-CoV-2 in Turkey (COVID-19 (+): 8.9 ng/ml vs COVID-19 (-): 18.5 ng/ml) (47). The rate of pediatric patients with vitamin D deficiency (mean age: 10.7±5.5 years) was significantly higher in the COVID-19 group to the controls (44% vs 17.5%), and low vitamin D group had higher C-reactive protein levels (48). It was determined that pregnant women

with 25OHD levels below 14.5 ng/ml have a 1.87-fold higher risk of having severe COVID-19 and/or poor prognostic factors (49).

Vitamin D levels were <30 ng/ml in 93.07% of 260 subjects without COVID-19 and 94.27% of 227 COVID-19 positive patients. However, severe vitamin D deficiency (<10ng/ml) was much more common in COVID-19 patients (44%). Among COVID-19 positive patients, C-reactive protein (CRP) and D-dimer levels, affected lung segments, and hospital stay were significantly lower in the group with vitamin D levels >30 ng/ml (50).

An Iran-based study showed that vitamin D deficiency was related to increase in the risk of mortality (51). In a study examining asymptomatic COVID-19 patients (n=91) and severe cases (n=63) who needed to be admitted to the intensive care unit (ICU), mean vitamin D levels (ng/mL) and vitamin D deficiency (%) were 27.89±6.21, 32.96% and 14.35±5.79, 96.82% respectively. Serum IL-6, ferritin levels, and TNFα were found to be higher in COVID-19 patients with vitamin D deficiency (52). It was determined that patients with COVID-19 had significantly decreased serum 25OHD level, total lymphocyte, TCD4+, TCD8+ and NK cell counts, while IL-12, IFN-y and TNF-α were significantly upregulated (53). Severely symptomatic COVID-19 patients (n=103) were found to have lower 25OHD levels than mildly symptomatic COVID-19 patients (n=52) (18.2± 11.4 vs 30.3 ± 8.5 ng/mL, respectively), while this value was much lower in severely symptomatic COVID-19 patients admitted to the ICU (14.4 ± 8.6 ng/mL) (54). A large observational population study (n= 41757) showed a negative correlation between vitamin D levels and the risks of SARS-CoV-2 infection and severity of disease. COVID-19 positive subjects with very low vitamin D levels (<30nmol/L) were identified as having the highest risk for severe COVID-19 (55). Vitamin D deficiency (<20 ng/mL) was more common in severe or critical patients (87.4%) than in patients with mild or moderate disease (34.3%), while those with 25OHD <20 ng/mL patients were 14 fold increased risk to have critical or severe disease than subjects with ≥40 ng/mL in another study (n=1176) (56). In a meta-analysis study, which included a total of 1,403,715 people from 54 studies, it was determined that patients with low vitamin D levels had increased susceptibility to SARS-CoV-2 infection, increased risk of Acute Respiratory Distress Syndrome (ARDS) requiring admission to the ICU, and increased mortality due to SARS-CoV-2 infection (57). Another meta-analysis has also similar result that vitamin D deficiency might increase the risk of SARS-CoV-2 infection and the likelihood of severity (58). Increased 25OHD concentrations (from 15 to 60 ng/mL) was found related to a reduction in COVID-19-related hospitalization and mortality (n=4599) (59).

According to the results based on 163 prospective COVID-19 cases who re-

ceived vitamin D supplementation and 151 retrospective COVID-19 cases with no vitamin D supplementation; the retrospective group (without comorbidity, no vitamin D therapy, 25OHD <30 ng/mL) had a 1.9 times higher risk of staying in hospital for more than 8 days compared to the prospective group (with comorbidity and vitamin D therapy). It was determined that vitamin D treatment reduced the death rate by 2.14 times. Moreover, correlation analysis of 25OHD and specific serum biomarkers found that vitamin D may be effective in regulating INOS1, IFNg, IL1B, ICAM1 and cathelicidin-LL37 levels in COVID-19 (60). Aged 65 years and older followed in the intensive care clinic, 40 COVID-19 patients who received vitamin D supplements were divided into the case group and the other 40 COVID-19 patients who did not receive vitamin D supplements were divided into the control group; On the 10th day, inflammatory markers C-reactive protein, procalcitonin, D-dimer, ferritin, interleukin-6 and lactate dehydrogenase levels were found significantly lower and lymphocyte count was significantly higher in the case group. It was concluded that vitamin-D supplementation may help reduce cytokine response in COVID-19 (61). Two groups were formed in a study in which three-month vitamin D supplements were administered to healthcare workers. Group I (n = 45) received 50,000 IU/week of water-soluble cholecalciferol for two weeks followed by 5000 IU/day for ten weeks while group II (n = 46) received a dose of 2000 IU/day for twelve weeks. The study, completed by only 78 subjects, found that neither vitamin D intake nor vitamin D deficiency/insufficiency was related to a reduction in SARS-CoV-2 morbidity. However, only asymptomatic SARS-CoV-2 was observed in 10 (26%) cases in subjects receiving high-dose vitamin D, while twice as many cases of SARS-CoV-2 with mild clinical features were observed in half of the participants receiving 2000 IU/day (62). However, there are studies that could not detect a significant relationship between Vitamin D status and COVID-19 severity (63). In a meta-analysis study found that increases in serum vitamin D were not associated with a significant reduction in the risk of COVID-19 infection or death, and that vitamin D supplementation is not significantly reduced death or the need for intensive care (64).

As a result, many studies have established consensus that the disease status of SARS-CoV-2 is related to vitamin D levels. Considering the therapeutic effects of Vitamin D in respiratory diseases such as ARDS and influenza and its relationship with immune system elements; increasing vitamin D levels above 30ng/mL and supplementation for a certain period of time seem promising in terms of protection from COVID-19 and reducing the severity of the disease.

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