

## REVIEW

# Vitamin D may protect against multiple organ damage caused by COVID-19

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**ABSTRACT**

The novel coronavirus COVID-19 outbreak quickly spread across many countries and has become a worldwide threat to health, trade and travel. In terms of clinical manifestations, although it starts as an acute respiratory disorder, it could eventually lead to death by causing damage to many organs such as: lung, liver, kidney and heart. It has been shown that COVID-19 pathology is mediated by an excessive inflammation, oxidation and an aggravated immune response. Vitamin D is an immunomodulator hormone and has receptors in many tissues and organs. In many studies, vitamin D was shown to have antimicrobial and anti-inflammatory properties. In addition, since COVID-19 infection causes a cytokine storm, vitamin D can have a protective effect on many tissues and organs by reducing the production of proinflammatory cytokines.

Vitamin D has a high safety profile, and thus could be beneficial against multiple organ damage in COVID-19 patients. This paper aims to highlight the potential benefits of vitamin D against multiple organ damage

caused by COVID-19 (Fig. 1, Ref. 109). Text in PDF [www.elis.sk](http://www.elis.sk)

KEY WORDS: COVID-19, cytokine, inflammation, vitamin D.

**Introduction**

Pneumonia outbreak caused by the novel coronavirus (COVID-19), which was firstly reported in Wuhan town in the Chinese State of Hubei, spread rapidly all over China, and despite the efforts to prevent its spread, virus has now reached a pandemic level around the world (1, 2, 3). This virus is transmitted by droplets, close contact and other means, and patients in the incubation period can potentially infect other people (4). Mild cases of COVID-19 cause symptoms of fatigue, fever, vomit, diarrhoea and dry cough. In severe cases, on the other hand, hypoxemia and respiratory distress develop about seven days after the start of the infection, followed by an acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and even death (5, 6). In the study, in which 1099 laboratory-confirmed cases were examined, common manifestation included fever (88.7 %), cough (67.8 %), sputum production (33.4 %), fatigue (38.1 %), shortness of breath (18.6 %), headache (13.6 %), sore throat (13.9 %), diarrhoea (3.8 %), and vomiting (5.0 %) (2).

Coronaviruses infect humans and other vertebrates. Novel COVID-19 is a coronavirus and is closely related to the viruses responsible for Severe Acute Respiratory Syndrome (SARS-CoV)

in 2003 and Middle East Respiratory Syndrome (MERS-CoV) in 2012, which generated severe pneumonia symptoms. These three viruses can lead to intestinal, neuronal, hepatic and respiratory diseases, and may cause the multiple organ failure, ARDS, and in severe cases even death (7, 8, 9). A small-scale autopsy study on heart, lung, spleen, liver, kidney, bone marrow, stomach, pancreas, intestine, skin and thyroid performed in three patients, who died of the novel coronavirus-related pneumonia in Chongqing, China revealed significant pathological lesions in the lungs of the patients including alveolar exudative inflammation, alveolar epithelial proliferation, interstitial inflammation and hyaline membrane formation (10). It was reported in the same study that although 2019-nCoV was mainly located in the lung, infection-related damage was also observed in blood vessels, heart, kidneys, liver and other organs. Huang et al (6) reported that about 20 % of the 41 cases had diabetes, while Chen et al (11) reported that about 40 % of 99 cases had cardio-cerebrovascular disease. Li et al (12), on the other hand, studied 1.527 novel COVID-19 cases, and reported that 17.1 % of the patients had hypertension, 16.4 % cardio-cerebrovascular disease, 9.7 % diabetes and at least 8.0 % an acute cardiac injury. In another study conducted in China with over 40,000 confirmed COVID-19 cases, fatality rate was 2.3 %, and old age > 70 years (10.2 %), diabetes (7.3 %), cardiovascular disease (10.5 %), and hypertension (6.0 %) were the most frequently reported co-morbidities (13). The incidence of liver injury was reported (14) in deaths associated with COVID-19. The recent reports pointed to a high degree of inflammation in patients diagnosed with COVID-19. Indeed, multiple organ failure and deaths were reported to be caused by a widespread inflammation.

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Vitamin D is a fat-soluble vitamin, and it is either taken in diet or synthesized in the skin by exposure to solar ultraviolet B radiation. Vitamin D is inactive, and it is metabolized twice: first in the liver and then in the kidney by cytochrome P450 enzymes to the active form 1,25 dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) (15). It plays a crucial role in phosphorous and calcium homeostasis (16). Besides, it is an immunomodulatory hormone and steroid, and regulates body's immune response (17). A high prevalence of vitamin D deficiency was demonstrated in critical diseases involving an acute respiratory failure, acute kidney failure, increased rates of infection, cardiovascular disease, sepsis (18, 19, 20, 21, 22). Beneficial effects of vitamin D supplements on blood glucose and lipid levels, body fat mass and blood pressure were reported in most studies (23). In addition, Chang and Lee (24) mentioned vitamin D deficiency as a risk factor for chronic liver and renal diseases, hyperparathyroidism, growth hormone deficiency and diabetes mellitus. Similarly, Hu et al (25) suggested that low levels of the serum 25(OH)D was indicative of the type 2 diabetes risk.

The use of approved drugs with anti-inflammatory properties and with a proven safety profiles could be useful in preventing the hyperinflammation and decreasing the mortalities caused by COVID-19.

#### **COVID-19 and inflammatory cytokine storm**

ACE2 is a homologue of angiotensin converting enzyme (ACE) with a 40 % identity and 61 % similarity (26). ACE2 is involved in the formation of angiotensin-(1-7) and angiotensin-(1-9) from angiotensin II and angiotensin I, respectively (27, 28). CoV and 2019-nCoV are known to use ACE2 as a receptor for entering the cell. ACE2 is abundantly expressed in the type II alveolar cells (AT2) in the lung (14, 29, 30), endothelial cells in liver (31), upper and stratified epithelial cells in oesophagus, absorptive enterocytes in ileum and colon (32), kidney proximal tubule cells, myocardial cells and bladder urothelial cells (29) and cholangiocytes (33). These tissues and organs are potential targets for 2019-nCoV. The recent study showed that ACE2 is abundantly expressed in mouth and tongue, facilitating the viral entrance into the host (34).

In order to enter the target cells, 2019-nCoV first should tightly bind to ACE2. Transmembrane protease serine 2 (TMPRSS2) is vital for spike glycoprotein in coronaviruses priming after binding to ACE2 (35, 36, 37). The virus damages the cell by copying itself inside the cell.

Recent studies showed that 2019-nCoV virus triggered a T-helper 1 (Th1) type cytokine response upon the infection of macrophages. Patients infected with 2019-nCoV could have plasma cytokines and chemokines such as: interleukin (IL)-1, IL-1B, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte colony stimulating factor (G-CSF), interferon- $\gamma$  inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), fibroblast growth factor (FGF), macrophage inflammatory protein 1- $\alpha$  (MIP-1 $\alpha$ ), and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), tumour necrosis fac-

tor (TNF $\alpha$ ), and gamma interferon (IFN- $\gamma$ ), (6, 38, 39, 40). Both IL-1B and TNF $\alpha$  promote TH17 responses and increase vascular permeability and leakage (41). The clinical trial with IL-6 receptor blocker tocilizumab has been approved in China for the COVID-19 patients, who developed pneumonia and had elevated IL-6 (ChiCTR2000029765). Chloroquine is a drug with immunomodulator effects suppressing production/release of the TNF- $\alpha$  and IL-6 and has long been used for the treatment of malaria (42, 43). Recently, Wang et al (44) reported that chloroquine is eminently effective in the control of 2019-nCoV infection under in vitro conditions. Clinical data collected so far revealed that inflammation is the major characteristic of COVID-19 patients. It was shown in many studies that the cytokine storm activated by an excessive inflammation contributes considerably to the pathogenesis of COVID-19. Thus, drugs that are effective in reducing inflammation appear to be beneficial.

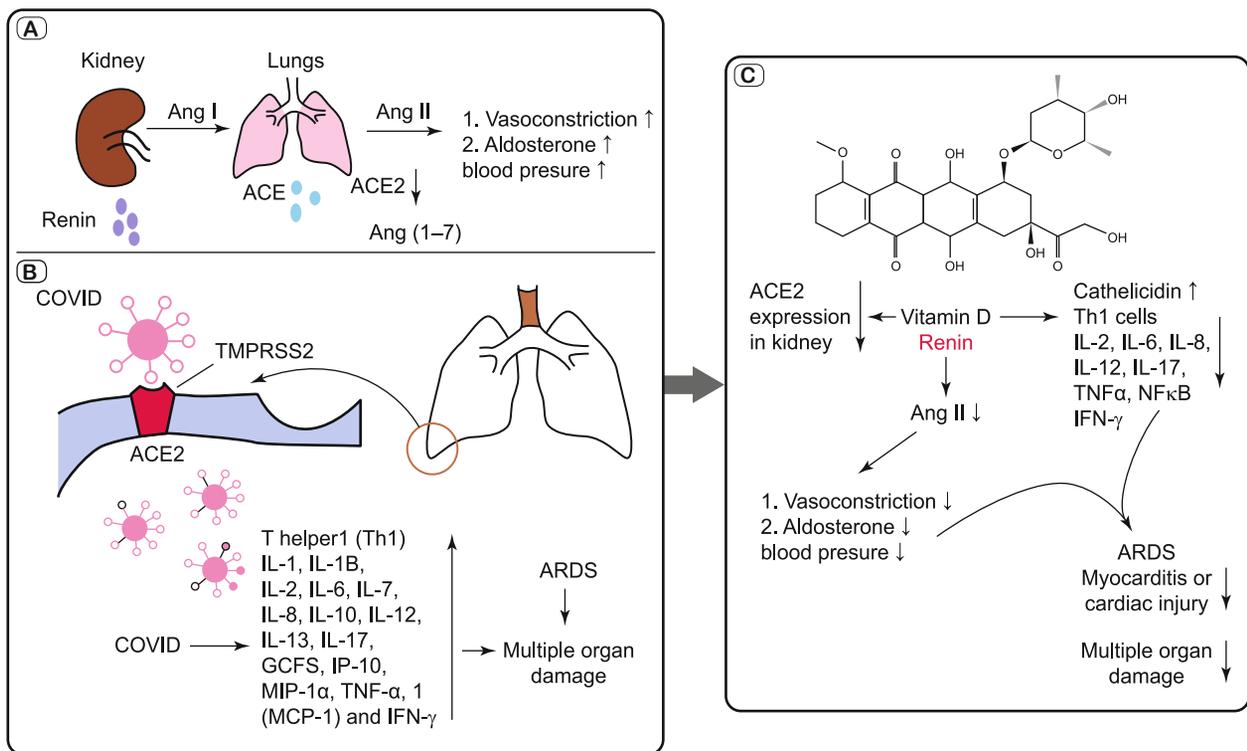
#### **Vitamin D and inflammatory cytokine storm**

Preventing hyperinflammation caused by COVID-19 using approved drugs with anti-inflammatory effects and proven safety profiles could be useful to reduce the mortality. Activation of vitamin D receptors (VDRs) needs 1,25(OH)<sub>2</sub>D<sub>3</sub>, the active form of vitamin D. Almost every organ and system of the body including immune cells have vitamin D receptor. VDRs are found in many different cell types such as: gonad, pancreas, kidney, liver, heart, lung, brain, breast cells, hematopoietic cells, and macrophages, monocytes and dendritic cells of the immune system. The activation of VDR affects both innate and adaptive immunity (45). Vitamin D is a direct and indirect modulator of Th1 cells. The production of Th1 cells is suppressed by vitamin D (46, 47, 48). Additionally, vitamin D can decrease the production of inflammatory cytokines such as: IL-6, IL-8, IL-12 and IL-17, and thus prevent inflammation from progressing and damaging to other organs (49, 50, 51). Vitamin D also reduces the production of TNF $\alpha$  and NF $\kappa$ B (52, 53). Moreover, 1,25(OH)<sub>2</sub>D directly inhibits IFN- $\gamma$  and IL-2 (54,55). Vitamin D could diminish cytokine storm caused by COVID-19 and could exert protective effects against multiple organ damage.

#### **Association of Vitamin D with COVID-19 and renin angiotensin system**

The renin angiotensin system (RAS) is of critical role in the regulation of volume, electrolyte homeostasis and blood pressure. ACE2 is the crucial counter-regulator of the RAS. ACE2 hydrolyses angiotensin II (Ang II) into Ang-(1-7) and reduces its level. Angiotensin II, the final product of RAS, is a powerful vasoconstrictor. It could lead to systemic vasoconstriction and promotes the release of aldosterone and regulates the blood pressure (56).

As in COVID-19, ACE2 is the potential receptor for SARS-CoV virus to enter the cell, and the main cause of deaths is the progression of pneumonia to ARDS, which is an acute severe lung failure (57). ACE2 expression in lungs was shown to be significantly down-regulated in the wild type mice infected with the SARS-CoV (58). In a similar way, in vivo intraperitoneal administration



**Fig. 1.** A) Physiological function of RAS and the task of ace2 enzyme in the lung. B) The COVID-19 virus binds to the ACE2 receptor in the lungs. TMPRSS2 enters the cell thanks to the serine protease enzyme and replicates itself. Then, a cytokine storm occurs, resulting in ARDS and multiple organ damage. C) Vitamin D suppresses the release of cytokines, preventing a cytokine storm caused by COVID-19. It exerts an antimicrobial effect by increasing the release of cathelicidin. Vitamin D prevents Ang II accumulation by suppressing renin release. Thus, ARDS development and multiple organ damage could be avoided. Vitamin D also reduces ACE2 expression in the kidney and provides a protective effect against COVID-19 infection in patients with diabetes and acute renal failure.

of recombinant SARS-spike protein to wild type mice or in vitro application of Vero E6 cells were reported to downregulate ACE2 expression. Similarly, Ang II peptide levels were increased and ARDS improved in mice injected with recombinant SARS-spike protein. Pharmacological inhibition of Ang II and partial remediation of ARDS symptoms were shown (58, 59). This finding indicates that a negative control of the level of Ang II by ACE2 has an important role in ARDS pathogenesis.

In COVID-19 infection, the virus binds to ACE2 receptors to enter the cell, and ACE2 cannot perform its physiological function. Thus, COVID-19 infection may downregulate ACE2, causing a toxic overaccumulation of Ang II (60, 61). Accumulated Ang II causes a pulmonary vasoconstriction through AT1 receptors and develops pulmonary oedema by increasing the pulmonary vascular permeability (62). In addition, elevated Ang II level triggers oxidative stress, causing the development of inflammation and fibrosis (60). This condition can lead to the occurrence of ARDS, which is the most severe form of the lung injury. It often induces multiple organ damage.

Vitamin D is also a negative endocrine regulator of the renin release. In many studies, vitamin D and analogues were shown to directly inhibit the renin biosynthesis (63, 64, 65). The study reported that vitamin D receptor-lacking mice had elevated levels

of renin and Ang II (63). The experimental diabetes model created by STZ, vitamin D supplementation was demonstrated to suppress the renin and Ang II levels (66). Vitamin D supplementation was shown to protect against lipopolysaccharide-induced acute lung injury by inhibiting the expression of renin, ACE and Ang II (67). Vitamin D can interfere with Ang II accumulation by suppressing the release of renin in patients infected with COVID-19, thereby preventing ARDS development and multiple organ damage.

### Vitamin D and lung diseases

Many patients with COVID-19 develop ARDS, which could eventually lead to pulmonary oedema, lung failure, heart, liver and kidney damage. These outcomes are associated with the cytokine storm, manifested with elevated serum levels of proinflammatory cytokine and chemokines.

Vitamin D was found to have major effects on primary human alveolar type II cells in in vitro conditions, and more than 600 genes were activated or inhibited by vitamin D in these cells (68). Hansdottir et al (69) showed that during a viral infection, inactive vitamin D (25(OH) D) can be converted to active vitamin D (1,25(OH)2D) by the alveolar epithelial cells, and a higher level of expression is observed in host defence gene cathelicidin. This

finding might indicate that vitamin D might have an organ-specific protective effect in lungs. Vitamin D was also reported to inhibit airway smooth muscle proliferation and to increase surfactant synthesis (70, 71). The *in vitro* study suggested that physiologically relevant doses of vitamin D had a direct protective effect on alveolar epithelium by stimulating cellular proliferation, wound repair and decreased death of human type 2 alveolar epithelial cells (68).

Miroliaee et al (72) demonstrated that a single high dose vitamin D treatment (300,000 IU) could decrease IL-6 level and reduce the mortality in patients with ventilator-associated pneumonia. Similarly, Lei et al (73) reported that vitamin D<sub>3</sub> (300 IU/kg/day) reduced the production of the proinflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , and IL-6) and inducible nitric oxide synthase (iNOS), increased the production of antimicrobial peptide cathelicidin, elevated the expression of antioxidation level (glutathione reductase and glutamate-cysteine ligase modifier subunit), and increased the autophagy in mice with pneumonia (73). Interestingly, a single high-dose preoperative vitamin D oral administration (300,000 IU, a single dose) was reported to prevent an acute respiratory distress syndrome following esophagectomy (74).

Deaths associated with influenza H1N1 pandemics during the 1918–1919 were linked to both secondary bacterial lung infections and to influenza virus itself. As in influenza pandemics, it is known that large proportion of deaths with COVID-19 occur two weeks after the onset of the symptoms. Strong correlations were found between UVB doses in July and pneumonia outcome ( $-0.77$ ,  $p = 0.005$ ) or fatality ( $r = -0.72$ ,  $p = 0.009$ ) rates of the cases (75). Similar results were obtained with wintertime UVB doses. A pneumonia rate of 9.3 % and fatality rate of 3.14 % were observed with influenza, when the UVB dose was 4.7 kJ/m<sup>2</sup>, which were 4.5 and 0.78 %, respectively, when the UVB dose reached 8.2 kJ/m<sup>2</sup> (75). It is well known that vitamin D level increases depending upon ultraviolet doses. Vitamin D was reported to upregulate increased antiendotoxin, to increase antimicrobial activities and to reduce the production of the proinflammatory cytokines, consequently, it could reduce pneumonia and mortality rates in influenza patients (75). Similarly, vitamin D prevents the lung against COVID-19 infection through reducing the production of the proinflammatory cytokines and increasing antimicrobial peptide cathelicidins.

### Vitamin D and cardiovascular diseases

According to current literature, at least 8.0 % of COVID-19 patients suffer from an acute heart damage (12). Chen et al (11) examined 99 COVID cases and found that 40 % of the patients had cardiocerebrovascular disease history. At least 8.0 % of COVID-19 patients were reported to have an acute heart damage with a strong association with mortality (12). It was even suggested that inflammation could be a potential cause of myocardial damage (76).

Cytokine accumulation directly affects vascular endothelial function and myocardial contractility. IL-6 and TNF- $\alpha$  can decrease myocyte contractility precisely through the reduction of the systolic calcium level. The experimental study with myocardial ischemia-reperfusion model in rats showed that vitamin D (500 IU/5 day) alleviated myocardial injury considerably with reduced

ST segment and inflammatory cytokine (IL-6), IL-1 $\beta$ , TNF- $\alpha$ ) levels (77). In another rat study, vitamin D prevented myocardial infarction by decreasing TNF- $\alpha$  and IL-6 level in isoprenaline-induced myocardial infarction (78). We demonstrated that vitamin D treatment (60,000/single doses) reduced myocardial damage in cardiotoxicity model in rats (79, 80). Vitamin D treatment (4,000 IU/for 5 days) was also shown to reduce serum IL-6 and IL-8 levels in patients with acute myocardial infarction (81).

The meta-analysis demonstrated that vitamin D supplement reduced the concentrations of TNF- $\alpha$  in patients with heart failure (82). Vitamin D supplement (2,000 IU oral, daily for nine months) reduced TNF- $\alpha$ , and increased IL-10 in adult patients with congestive heart failure (47). Reductions in IL-10, IL-6 and TNF- $\alpha$  levels were also reported for vitamin D supplement (1,000 IU oral, daily for three months) in infant patients with congestive heart failure (83). Reduction IL-6, TNF- $\alpha$  and elevated IL-10 levels were also reported for vitamin D supplement (1,000 IU oral, daily for three months) in infant patients with congestive heart failure (83). Witte (84) found that vitamin D supplement (4000 IU oral, daily for 12 months) has beneficial effects on left ventricular structure and function in older patients with a chronic heart failure. Levels and reduced risk of coronary heart disease mediated by decreased IL-6, C-reactive protein, interferon- $\gamma$ -inducible protein-10 and soluble intercellular adhesion molecule-1 levels (85). In individuals with any cardiovascular disease, it was shown that the increase in cytokines played a significant role in the pathogenesis and that proinflammatory cytokines could be reduced by vitamin D supplementation. Consequently, vitamin D supplementation administered in different doses was found effective especially in high doses in reducing the release of proinflammatory cytokines at all ages. It is known that the mortality rate is high in patients with a cardiovascular disease, when they contract COVID-19 infection. Vitamin D supplementation could reduce the mortality rate in cardiovascular patients infected with COVID-19 through preventing the inflammation.

### Vitamin D and kidney diseases

Following the inflammation, an increased incidence of acute renal injury was reported in patients with COVID-19 (34, 86, 87). Also, compared to other patients, Cheng et al (86) demonstrated that patients with an acute renal injury had a higher mortality rate. In the meta-analysis, severe COVID-19 infection was suggested to be associated with a chronic kidney disease (CKD) (88). Thus, CKD patients were recommended to be extremely careful against COVID-19 infection.

In chronic kidney disease, active vitamin D level was reported to be associated with a decreased mortality (89). In CKD, 1-hydroxylated vitamin D analogues were found effective for secondary hyperparathyroidism treatment (90). In vitamin D-deficient diabetic patients with the comorbid chronic kidney disease, vitamin D administrations of 1,000 or 2,000 IU/day were reported to safely increase serum 25(OH)D concentrations (91). However, significant improvements were observed for lipid profiles in higher vitamin D dose. Higher dietary vitamin D<sub>3</sub> content was reported

to improve immune function in yellow catfish through down-regulation of IFN- $\beta$  and pro-inflammatory factors TNF- $\alpha$ , IL1- $\beta$ , IL-6, IL-8 and up-regulation of anti-inflammatory factor IL-10 (92). Brito et al (93) reported that vitamin D could have protective effects against inflammation at least mediated by monocytes. They also revealed that cathelicidin was associated with the IL-6 and TNF- $\alpha$  levels, which lent further support for this hypothesis (93). Vitamin D supplementation was reported to lower fasting blood sugar, insulin, TNF- $\alpha$  and IL-6 levels (94). Lower TNF- $\alpha$  and malondialdehyde levels after vitamin D treatment were also reported by Shamardl et al (95).

Vitamin D was reported to protect against drug-induced kidney and liver injury (96). Similarly, BaSalamah et al (97) reported that vitamin D alleviated kidney inflammation and protected kidney. Accordingly, it could be stated that vitamin D supplement could ease cytokine storm caused by COVID-19 and lower mortality in COVID-19 patients with renal disease.

Abundant expression of ACE2 protein in many cell types was reported to be linked with a high probability of kidney damage (98). Increased ACE2 expression was documented in kidney damage and experimental diabetes models (99,100). Vitamin D treatment was shown to inhibit ACE2 expression (101). Thus, vitamin D supplement could lower ACE2 expression in kidney, preventing COVID-19 entry into kidneys and protecting against possible damage in kidney.

### Appropriate vitamin D doses

Despite the lack of a specific guideline from endocrinology or vitamin D societies, vitamin D concentrations of above 30  $\mu\text{g/L}$  (75 nmol/L) are recommended in many studies (102). Misra et al (103) recommended a daily dose of 400 IU for adolescents and children. Daily vitamin D supplements ranging from 200 IU to 600 IU were suggested by The Institute of Medicine (104) for adults to sustain enough vitamin D levels in the body. In vitamin D deficiency situation, however, much higher supplementation rates of 28,000 IU weekly or 50,000 IU monthly are recommended depending on the severity of the deficiency (105). No toxicity was observed in patients supplemented with vitamin D doses as high as 10,000 IU of vitamin D3 administered daily for five months (106). Differences were reported between the countries for vitamin D recommendations and their implementation to achieve the adequate vitamin D levels (107). A daily dose of up to 2,000 IU a day was suggested to maintain an adequate level of 25-hydroxyvitamin D (25OHD) (108). Chang and Lee (24) stated that people could take 2000 IU per day for 6 to 12 weeks after the first year of life, and a daily dose of 600 to 1000 IU is appropriate to maintain adequate vitamin D supply. However, for high-risk groups, this daily allowance could be as high as 6000 IU. In another study, Shirvani et al (109) mentioned that 10,000 IU daily vitamin D supplementation for six months was safe and regulated parathyroid hormone (PTH) levels. They also mentioned that this supplement regime had a considerable effect on the expression of 1200 genes and on metabolic patterns. Thus, considering the results of literature, it is seen that the safe dose range of vitamin D is high. Due to that fact it may

be beneficial to administer high doses of the vitamin D in patients with Covid 19. However, specific vitamin D supplementation recommendations should be applied for each patient individually.

### Conclusion

COVID-19 is viral agent with a very high contagion and causes mainly pneumonia. Development of the effective prevention and treatment methods for COVID-19 is an urgent need. Vitamin D is an immunomodulator hormone with a high safety profile whose anti-inflammatory, antimicrobial and antioxidant effects were proven in many studies. Vitamin D supplement could provide a protective effect against the infection of COVID-19 virus. It could be used as an agent to alleviate the inflammation in COVID-19-infected patients and to prevent multiple organ damage due to the virus.

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