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Role of vitamin D in pathogenesis and severity of COVID-19 infection

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Running title: Vitamin D deficiency and COVID-19 infection

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Role of vitamin D in pathogenesis and severity of COVID-19 infection

Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by a new virus which causes respiratory illness. Older adults and people who have previous chronic medical conditions are at higher risk for more serious complications from COVID-19.

Hypovitaminosis D is attributed to the increased risk of lung injury and acute respiratory distress syndrome (ARDS) as well as diabetes, Cardiovascular event and associated comorbidities, which are the main causes of severe clinical problem in COVID-19 patients. Considering the protective role of vitamin D through modulating the innate and adaptive *immune system* as well as inhibition of Renin Angiotensin System (RAS), vitamin D supplementation might boost the immune system of COVID-19 patients and reduce severity of the disease in vitamin D deficient individuals.

Keyword; COVID-19; Vitamin D;ACE2; Diabetes; Cardiovascular disease.

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Introduction

An increase in the incidence of infections caused by various human respiratory pathogens emerges each winter, however, the timing and magnitude of the infection are widely variable [1]. Seasonality and persistence are the two main characteristics of respiratory viruses, such as influenza, RSV and the two previously described human coronaviruses (CoV 229E and CoV OC43) [1,2].

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, Hobei province, China. SARS-CoV-2-infected individuals suffer from a variety of symptoms, ranging from tiredness, fever and cough to severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock and death[3-5]. It has been found that entry of SARS-CoV-2 into the human cells is via Angiotensin Converting Enzyme 2 (ACE 2), a membrane exopeptidase that converts Angiotensin I to the nonapeptide angiotensin [6].

The ACE2 is expressed in human airway epithelia, lung parenchyma and especially in the epithelial lining of the oral cavity, making it the portal of entry for the SARS-CoV-2 infection [6,7]. More interestingly, expression of ACE2 was also detected in lymphocytes within the oral mucosa as well as other organs of the digestive system. This expression pattern of ACE2 might be associated with the severity of the SARS-CoV-2 -induced disease, COVID-19 [6].

ACE2 and the Renin-Angiotensin System

The Renin-Angiotensin (Ang) System (RAS) regulates blood pressure through conversion of angiotensinogen to angiotensin I and ultimately angiotensing II, catalyzed by ACE2. Moreover, fluid and electrolyte balance, in addition to, systemic vascular resistance are regulated by the RAS(fig 1) [8].

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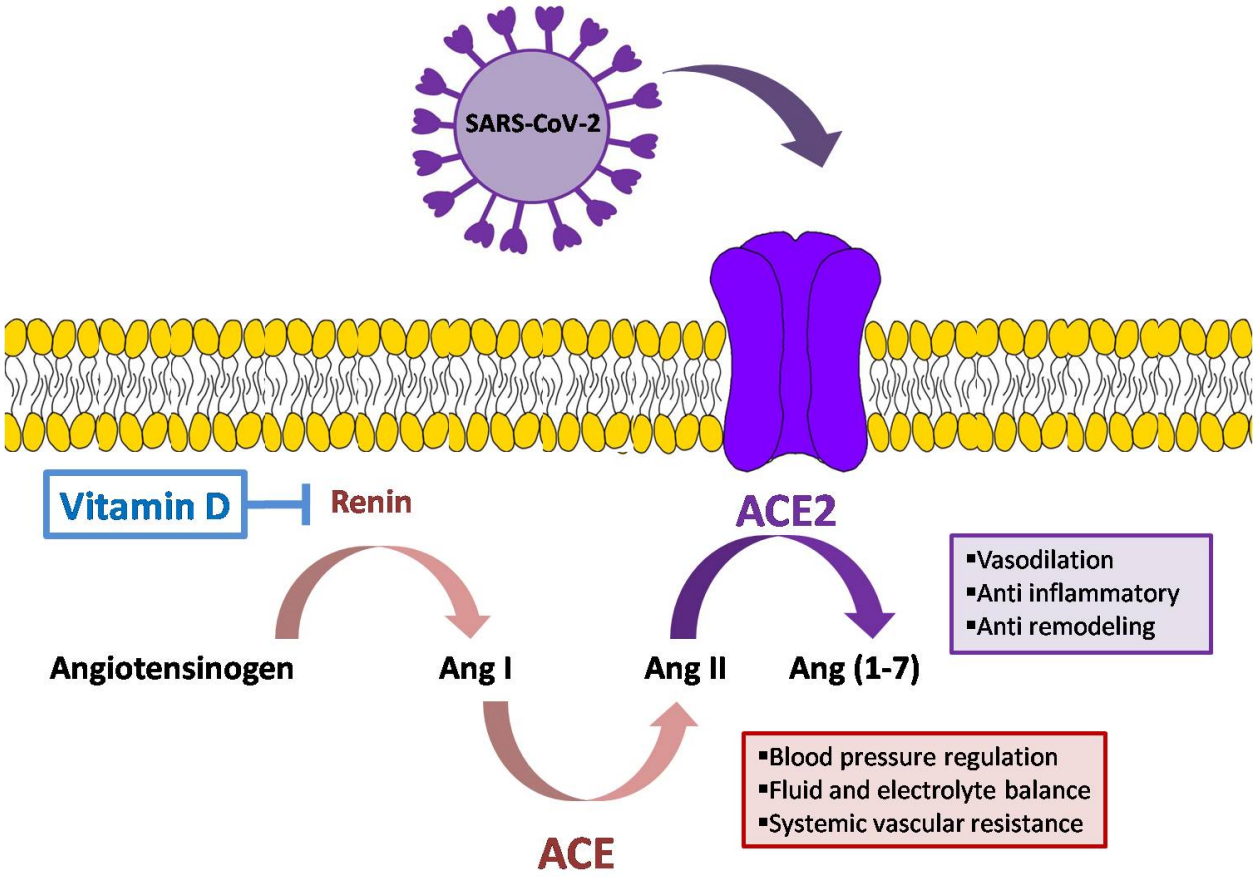

Fig 1: ACE2 , RAS and Vitamin D. Ang I and Ang II are cleaved by ACE. Binding of Ang II to the Ang II type 1 receptor results in vasoconstriction, inflammation and apoptosis. Ang-(1-7) acts against the effects of Ang II. Therefore, the endogenous ratio of Ang II: Ang-(1-7) is affected by the balance between ACE and ACE2 levels [8]. Furthermore, vitamin D may suppress RAS activity through inhibition of renin .

Vitamin D3 regulates Renin-Angiotensin System

The molecular mechanism underlying the down-regulation of the intrarenal Renin-Angiotensin System (RAS) induced by vitamin D is yet to be fully understood. It has been reported that the formation of the cyclic AMP response element-binding protein (CREB) and the related partner complex is blocked by 1,25(OH)2D3 [9]. Moreover, the other key player involved in the down-regulation of the intrarenal RAS includes the transcriptional regulatory complex, comprised of

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nuclear receptor corepressor 1 (NCOR1), CREB1, and the vitamin D receptor, which bind to the cyclic AMP response element-like domain in the renin enhancer [9]Therefore, vitamin D may suppress RAS activity through inhibition of renin and the ACE/Ang II/AT1R cascade [8] (fig 1).

Vitamin D as an immunemodulator factor

Vitamin D3, a lipophilic micronutrient, is obtained either through the conversion of 7-dehydrocholesterol by the skin when exposed to UVB radiation or via food intake [10,11]. It is involved in several cellular processes, maintenance of calcium homeostasis, and phosphorus absorption. Nevertheless, its deficiency leads to the development and progression of several chronic diseases, as well as susceptibility to infectious diseases [10,12]. The active form of vitamin D, also known as calcitriol (1,25-dihydroxycholecalciferol) is a steroid hormone that acts as an immune system modulator by down-regulating the expression of inflammatory cytokines and enhancing macrophage function [6]. Furthermore, it induces the expression of potent antimicrobial peptides (AMPs), which are present in natural killer cells, monocytes, neutrophils, as well as the epithelial cells lining the respiratory tract [13]. Vitamin D triggers development of suppressive regulatory T cells and inhibits development of pro-inflammatory Th17 cells [14]. Moreover, the pro-inflammatory peptides of the adaptive immune system are modulated by vitamin D, particularly those involved in acute inflammation cytokine storms [9,11,13,15]. It has also been found that metabolites of vitamin D induce other innate antimicrobial effector mechanisms, including autophagy and synthesis of reactive oxygen and nitrogen intermediates [11]. Some studies suggested that vitamin D is involved in a number of anti-proliferative and pro-differentiative functions via induction of growth factors (IGF-1, epidermal growth factor), cyclin-dependent kinase inhibitors, as well as mediators of apoptosis and angiogenesis [14].

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Potential mechanisms underlying anti-viral effects of vitamin D

Using vitamin D supplementation for preventing respiratory tract infection is not a common practice. Effectiveness of this intervention relies on its continuity prior to the onset of the respiratory tract infection [16].

The association between hypovitaminosis D and increased risk for serious complications from the influenza and other respiratory tract infections, especially among patients with HIV infection, has been proven by several interventional and observational epidemiological studies [17,18]. Furthermore, results of recent study revealed the potential role of vitamin D against viral respiratory infections (fig 2) [18]. The immunoregulatory functions of vitamin D in respiratory viral infections are induced via enhancing the level of virus specific CD8+ T cells (EBV and influenza) , CXCL10 and IFN-p in airway epithelium (RSV), recruitment of immune cells to the site of infection (respiratory and hepatitis viruses) and reducing viral replication (rhinovirus) [18].

The hypothesis that vitamin D directly affects viral infections, particularly infections caused by enveloped viruses, has been supported by results of several cell culture experiments [17]. These functions of vitamin D may be linked to its up-regulatory effect on the anti-microbial cathelicidin family of peptides (in the form of LL-37), as well as human beta defensin 2 and may also be induced through releasing of reactive oxygen species [17].

The anti-bacterial effect of LL-37 is linked to its ability to disrupt bacterial membranes via electrostatic interactions. It may also induce similar effect on the lipid envelopes of viruses [17,18]. It is probable that viral entry is blocked by LL-37 in a similar manner to what is observed in other antimicrobial peptides, mainly in enveloped viruses [17]. LL-37 has been demonstrated to have anti-viral effects, including inhibition of replication of herpes simplex virus type one (HSV-

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1), vaccinia virus (VACV), retroviruses, respiratory syncytial virus (RSV) and some non-enveloped viruses, such as adenovirus , rhinovirus and Human papilloma virus [17,19]. These findings support the hypothesis that the anti-viral effects of LL-37 may be partially mediated via envelope disruption [17]. Since SARS-CoV-2 is an enveloped virus, adjusting the circulating vitamin D level might help treating the newly emerged COVID-19 (Fig 2).

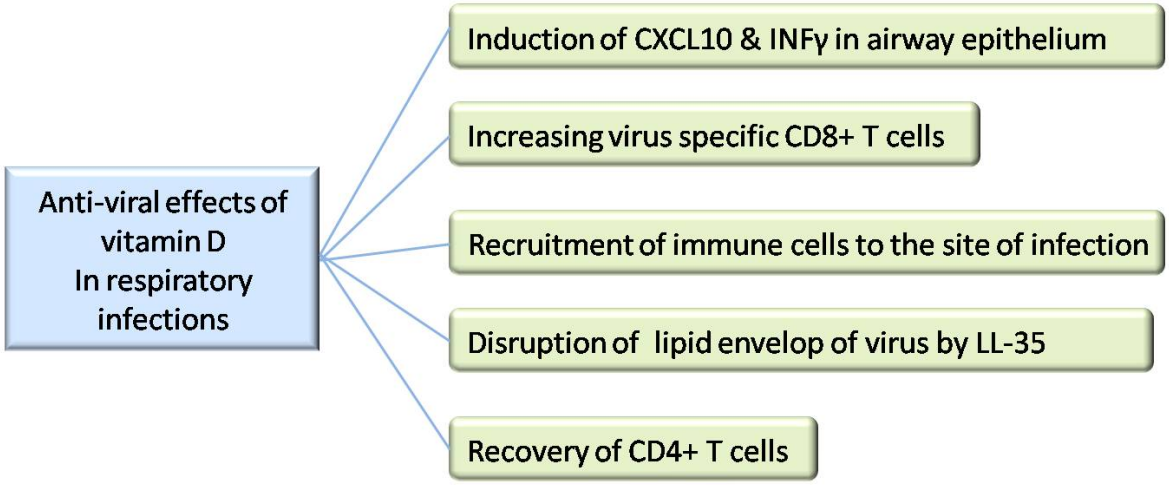

Fig 2: Immunoregulatory actions of vitamin D in respiratory viral infections

Worldwide prevalence of vitamin D deficiency

Vitamin D deficiency is a major public health problem worldwide. In 2011, the Endocrine Society considered the serum circulating 25-hydroxyvitamin D level to define vitamin D status in the population : >30 ng/mL was considered "optimal", 20–30 ng/mL was "insufficient", and <20 ng/mL as "deficient" [20]. It was estimated that the global prevalence of vitamin D deficiency is approximately 30–50% [21]. The results of a systematic review indicated that the highest prevalence of vitamin D deficiency belonged to the Middle Eastern population of all the age

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groups. In adults, the number of women who suffered hypovitaminosis D was higher than that of men. Therefore, hypovitaminosis D in the Middle East, particularly in women, is an important health issue [22,23].

Health risks of vitamin D deficiency

Several health implications are attributed to hypovitaminosis D, including respiratory disorder-related mortality**,** susceptibility to viral infections ,cardiovascular diseases (CVD) , diabetes, hypertension and osteoporosis [21,24,25]. Vitamin D deficiency induces inflammation in epithelial cells, dysregulates the expression levels of over 600 genes and contributes to the development of numerous diseases, including diabetes, cardiovascular, musculoskeletal, and respiratory systems diseases, as well as cancer [26]. Several studies indicated that people with diabetes, CVD, pulmonary disease and hypertension as well as aged people (all conditions are severe comorbidites in COVID-19) had lower vitamin D concentrations than control subjects [2,9,21,25,27-29].

Vitamin D-ACE2 interaction and respiratory illness

Acute lung injury (ALI) and Acute respiratory distress syndrome (ARDS) are the main cause of severe lung damage and respiratory failure in COVID-19 patients and vitamin D could be considered as a contributing factor [8,22].

Local RAS is present in lung tissue [15]. Enhanced expression levels of ACE/Ang II as well as decreased expression of ACE2/Ang-(1-7) are involved in ALI [15]. Dysregulated expression of ACE, ACE2, Ang II and Ang-(1-7) in the RAS pathway is a leading cause of ALI [15]. Enhanced expression levels of ACE2 and Vitamin D receptor (VDR) play a protective role against the development of ALI [14]. It has been reported that over-expression of ACE2 resulted in improvement of dysregulated expression of ACE/ACE2 and Ang II/Ang-(1-7) and alleviated

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lung injuries, whereas ACE2 knockout further attenuated the imbalance of ACE/ACE2 and Ang II/Ang-(1-7) expression levels, resulting in exacerbated lung injuries. Maintaining RAS homeostasis by enhancing the expression level of ACE2 may reduce lung injury (fig 3) [15].

Association between hypovitaminosis D and susceptibility to acute respiratory tract infections has been reported by several observational studies [11,25]. Results of an individual participant data (IPD) meta-analysis of randomized-controlled trials revealed that the risk of experiencing at least one acute respiratory tract infection is significantly reduced by taking vitamin D supplementation [11]. Furthermore, one step analyses of acute respiratory tract infection rate indicated the significant protective effects of vitamin D (adjusted incidence rate ratio 0.96, 95% confidence interval 0.92 to 0.997, P=0.04; P for heterogeneity <0.001; 10 703 participants in 25 studies). Hence, vitamin D supplementation induced a strong protective effect in patients with baseline circulating 25-hydroxyvitamin D levels less than 25 nmol/L (adjusted odds ratio 0.58, 0.40 to 0.82, NNT=8, 5 to 21; 538 participants in 14 studies; within subgroup P=0.002) [11]

Effects of vitamin D deficiency in high risk groups for COVID-19

Individuals with associated comorbidities, such as obesity, diabetes, hypertension, cardiovascular diseases, respiratory diseases and cancer, are at higher risk for severe illnesses and death [21]. It has been reported that the case fatality rate (CFR) in COVID-19 patients with no comorbidity is 1.4%, while it is 13.2%, 9.2%, 8.4% and 8.0% in those with cardiovascular disease, diabetes, hypertension and chronic respiratory disease, respectively (fig 3) [30].

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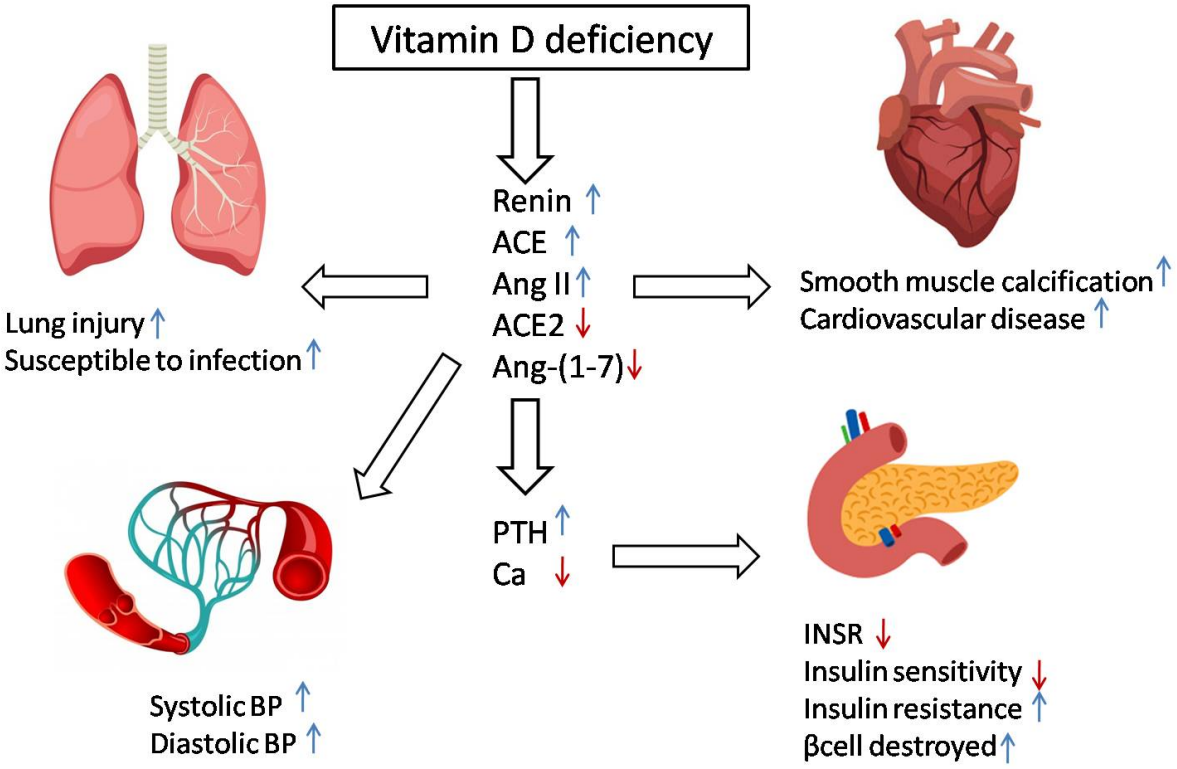

Fig3: Vitamin D deficiency and related consequences on main comorbid conditions of COVID-19 infection.

Vitamin D deficiency has been attributed to cardiovascular diseases and hypertension [21,31]. Vitamin D directly affects smooth muscle cells by inhibiting proliferation that leads to calcification leading to cardiovascular diseases (CVD) [21,28]. In an analysis of the Third National Health and Nutrition Examination Survey (NHANES III 1988–1994), low level of vitamin D was introduced as CVD risk factor along with hypertriglyceridemia, obesity and diabetes mellitus (DM). Furthermore, results of a prospective nested case-control study revealed that hypovitaminosis D enhanced the risk of myocardial infarction compared to sufficient 25(OH)D level following multivariate adjustment.

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The results of a meta-analysis of 19 prospective studies revealed a linear and inverse association between circulating vitamin D level and risk of CVD [21].

Resistant hypertension, is considered as a major risk factor for CVD [9,10,21,28]. Prolonged vitamin D3 deficiency or even short-term severe vitamin D deficiency can result in development of hypertension via modulation of the RAS system [9,31]. Using animal models, vitamin D3 has been found to down-regulate renin Ace and Agn genes, whereas it up-regulated the expression level of Ace2 wherase hypovitaminosis D3 up-regulates the expression level of Ace gene [9] [9]. Results of several human cross-sectional studies revealed an association between the lower vitamin D levels and higher RAS activity in vascular tissue, higher plasma rennin activity (PRA), higher Ang II concentrations, and altered responses to Ang II [9,21,28]. Oral vitamin D supplementation has been found to notably reduce diastolic blood pressure (BP) while it slightly, but significantly, reduces diastolic BP, in patients with preexisting cardiovascular risk [9,10].

As the other risk factors of CVD, insulin resistance and risk of diabetes are linked to vitamin D status [27,29,32]. Results of an observational study performed on 494 women undergoing serial metabolic characterization indicated that hypovitaminosis D along with increased PTH levels were independent predictors of β-cell dysfunction, insulin resistance, and hyperglycemia [29,32]. Hypovitaminosis D induces its effect on insulin secretion, insulin resistance, and β-cell dysfunction via RAS in the pancreas, so that it can enhance the production of ROS and G protein RhoA via increasing renin and angiotensin II synthesis, leading to inhibition of the pathways essential for intracellular glucose transporter and consequently the development of insulin resistance and metabolic syndrome [21,28]. Vitamin D induces its regulatory effect on insulin secretion through regulation of intracellular calcium concentration [29,33]. Moreover, vitamin D is indirectly associated with insulin synthesis and secretion in the pancreas via regulation of PTH

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concentration. Vitamin D is also attributed to insulin sensitivity (fig 3) [27,33]. It regulates insulin sensitivity by up-regulating the expression of insulin receptors [29,33]. Furthermore, inflammation, which is a main process in inducing insulin resistance, is reduced by vitamin D [29,32,33]. Vitamin D adjusts the resting levels of both Ca^{2+} and ROS, that are elevated in the β-cells during diabetes, to their normal levels [27].

Chronic kidney disease (CKD) as a complication of type 2 diabetes is associated with reduced levels of 1,25(OH)2D [29]. CKD patients with low vitamin D levels present higher risk for end stage renal disease , all-cause mortality and cardiovascular diseases [29]. However, the effectiveness of vitamin D supplementation for protection of kidney function is yet to be further investigated.

Discussion

Patients with chronic diseases have significantly higher risk of death from respiratory tract infections. On the other hand, higher vitamin D concentrations reduce the risk of many chronic diseases, including cardiovascular disease, diabetes mellitus, and hypertension [2,34]. Observational studies suggest that serum 25(OH)D concentrations are generally low in many populations, especially in the elderly [2,11].It has been shown that having comorbid conditions increase the case fatality rate significantly with increasing age. This could be explained by compromised adaptive immune response [2]. Moreover; reduced level of 1,25(OH)2Dwith aging, affects the immune system [17,18]. Therefore, it would be reasonable to postulate that the seasonality of many viral infections is associated with low 25(OH)D concentrations especially in the elderly population with associated co-morbid conditions.

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Vitamin D has diverse immunomodulatory effects to reduce viral infections. These include strengthening of epithelial cell junction integrity, up-regulatory effect on the anti-microbial cathelicid in family of peptides, recruitment of immune cells to the site of infection, and reducing the cytokine storm induced by the innate immune system as well as adaptive immune response [2]. The entry of SARS-CoV-2 into the human cells is via ACE 2, a membrane exopeptidase that converts Angiotensin I to the nonapeptide angiotensin. ACE2 negatively regulated the RAS by converting Ang II to Ang-(1–7). It is expressed in human airway epithelia. The RAS, which includes ACE and ACE2, is a complex network that has a major role in various biological functions [31]. Chronic vitamin D deficiency may induce RAS activation lung fibrosis through activation of the RAS [35]; therefore, increasing evidence indicates that 1,25(OH)2D3 may also be a negative endocrine regulator of the RAS. Inducing the expression of renin, ACE, Ang II and AT1R, and inhibiting ACE2 expression could result in acute lung injury. Vitamin D inhibits renin, ACE and Ang II expression, and induces ACE2 levels in ALI. Therefore, vitamin D may attenuate ALI by inducing ACE2/Ang-(1–7) axis and inhibiting renin and the ACE/Ang II/AT1R cascade [8,14].

In conclusion, considering the protective function of vitamin D in ALI, supplementing vitamin D deficient individuals may boost the immune system to fight COVID-19 infection and reduce its severity, especially in people with associated co-morbidities.

Compliance with Ethical Standards

These review doses not need any ethical approval and there is no potential conflict of interest.

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