European Review for Medical and Pharmacological Sciences 2021; 25: 2131-2145

The interplay between vitamin D and COVID-19: protective or bystander?

H.F. HETTA[1,2], K. MUHAMMAD[3], E.A. EL-MASRY[4,5], A.E. TAHA[4,6], E.A. AHMED[7], C. PHARES[1], H.A. KADER[3], Y. WAHEED[8], A.M. ZAHRAN[9], R. YAHIA[10], A. KH. MESHAAL[11], G. EL-SABER BATIHA[12]

[1]Department of Medical Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt
[2]Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[3]Department of Biology, College of Science, United Arab Emirates University, Al Ain, United Arab Emirates
[4]Department of Pathology, Microbiology and Immunology Unit, College of Medicine, Jouf University, Al-Jouf, Saudi Arabia
[5]Department of Medical Microbiology and Immunology, College of Medicine, Menoufia University, Menoufia, Egypt
[6]Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt
[7]Department of Pharmacology, Faculty of Medicine, Assiut University, Assiut, Egypt
[8]Foundation University Medical College, Foundation University Islamabad, Islamabad, Pakistan
[9]Department of Clinical Pathology South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[10]Department of Microbiology and Immunology, Faculty of Pharmacy, Deraya University, Minia, Egypt
[11]Department of Botany and Microbiology, Faculty of Science, Al-Azhar University, Assiut, Egypt
[12]Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicines, Damanhour University, Damanhour, Egypt

Abstract. – The world is currently facing the COVID-19 pandemic, caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Due to a lack of specific treatment and prophylaxis, protective health measures that can reduce infection severity and COVID-19 mortality are urgently required. Clinical and epidemiological studies have shown that vitamin D deficiency can be linked to an increased risk of viral infection, including COVID-19. Therefore, in this review, we looked at various possible roles of vitamin D in reducing the risk of COVID-19 infection and severity. We describe in this article that individuals at high risk of vitamin D deficiency should consider taking vitamin D supplements to keep optimal concentrations. Moreover, we discuss different possible mechanisms by which vitamin D can efficiently reduce the risk of infections through modulation of innate and adaptive immunity against various types of infections. It is advisable to perform further studies addressing the observed influence of vitamin D levels to reduce the risk of COVID-19 infection and mortality.

Key Words:
COVID-19, Vitamin D, Coronavirus, Viral infection.

Abbreviations

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2); Middle East Respiratory coronavirus syndrome (MERS-CoV); World Health Organization (WHO); Acute Respiratory Disease Syndrome (ARDS); Spike (S); Envelope (E); Membrane (M); Angiotensin Converting Enzyme 2 (ACE2); Pathogen-Associated Molecular Pattern (PAMP); Cytokine Storm Syndrome (CSS); Dendritic Cells (DCs); Fas ligand (FasL); Vitamin D Receptor (VDR); Toll-Like Receptor (TLR); Renin-Angiotensin System (RAS).

Introduction

The 2019 Coronavirus (COVID-19) is a disease caused by the novel emerging Severe Acute

Corresponding Authors: Khalid Muhammad, Ph.D; e-mail: k.muhammad@uaeu.ac.ae
Helal F. Hetta, Ph.D; e-mail: helalhetta@aun.edu.eg

Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has negatively affected the entire world. This is the third pathogenic human CoV in the last two decades. Before SARS-CoV-2 emergence, Severe Acute Respiratory Coronavirus Syndrome (SARS-CoV) emerged in Guangdong, China, in 2002, resulting in over 8000 infections and 774 deaths in 37 countries. In addition, the Middle East Respiratory Coronavirus Syndrome (MERS-CoV) was also identified in Saudi Arabia in 2012[1,2]. In March 2020, the World Health Organization (WHO) declared that SARS-CoV-2 outbreak is a pandemic[3]. As of 04 December 2020, this global outbreak has caused over 64,350,473 confirmed cases and more than 1,490,000 deaths worldwide[4]. Currently, social distancing, wearing masks, and washing hands are only the only protective measures we can take while waiting for an effective drug against COVID-19.

Vitamin D deficiency is considered a worldwide health problem that has an impact on a wide range of diseases; one of these involves viral infections[5-9]. The underlying mechanisms describing the effect of poor vitamin D status on viral infections are still not completely understood. However, some of the mechanisms could be immunomodulatory, anti-inflammatory, including some cellular and viral factors affecting viral replication[10-12]. Additionally, the protective effects of vitamin D have been shown in infections with pneumonia, cytokine storm, and Acute Respiratory Disease Syndrome (ARDS)[9]. Moreover, vitamin D has recently been a repurposed drug against influenza A H5N1[13].

Interestingly, several epidemiological scholars[14] show a potential link between vitamin D status and the risk of COVID-19 infection, severity, and mortality. Accordingly, a complete understanding of the biological effects of vitamin D could give its rationale in the management of COVID-19. In this review, we focus on the potential role of vitamin D in decreasing the risk of COVID-19 infection, severity, and death.

Coronaviruses, Epidemiology, and Transmission

Coronaviruses (CoVs) are the largest single-stranded, enveloped positive-sense RNA viruses. This family includes 4 genera: Alpha-CoV, Beta-CoV, Gamma-CoV, and Delta-CoV. Alpha-CoVs and Beta-CoVs primarily infect mammals and, until now, seven human CoVs have been identified[15-17]. Four human CoVs (HCoV 229E, NL63, OC43, and HKU1) were globally endemic and contributed to infections of the upper respiratory tract. Moreover, severe human CoVs are SARS-CoV, MERS-CoV, and SARS-CoV-2, which can be life-threatening[15,18].

SARS-CoV-2 is 30 Kb in size and is genetically similar to the 2002 CoV (SARS-CoV)[1]. A multitude of other CoVs trigger the common cold and may become infectious after reaching the animal reservoirs that provide a suitable cellular environment, where the virus can multiply and acquire a series of beneficial genetic mutations. These beneficial mutations allow the virus to cross species, infect humans, and effectively multiply[19,20]. The genome structure of SARSCoV-2 is similar to the other CoVs containing open reading frames (ORF1a/b) located at the 5`end encoding polyprotein1a and 1b (pp1a, pp1b). The other ORFs located on the 3`end encode 6 accessory proteins and four structural proteins, which are spike (S), envelope (E), membrane (M), and nucleocapsid N proteins (Figure 1)[1,13,21-27]. Spike (S) glycoprotein, which is expressed on the virus surface, consists of three S1-S2 heterodimers binding to the angiotensin-converting enzyme 2 (ACE2) type I and type II pneumocyte receptors[25-28].

Early studies showed that 49-66% of COVID-19 patients had a history of visiting the Huanan seafood market (Wuhan, China) where different types of live wild animals, including poultry, bats, and marmots, are sold[29-31]. The environmental samples taken from the Huanan seafood market have been positively checked for SARS-CoV-2, according to the WHO[32]. However, the particular animals linked to the virus were not known during early studies. We now know that bats are the host of more than 30 different CoVs, including SARS-CoV, MERS-CoV, and SARS-CoV-2; however, the intermediate host of SARS-CoV-2, which allows the virus to be spread to humans, is still unknown[33-36].

The most important mode of transmission for COVID-19 is through direct contact and droplet transmission (Figure 1). Airborne transmission is also possible due to the persistence of the virus in aerosol droplets in an infectious form[37,38]. The infected droplets can spread 1 to 2 meters and deposit on the surface[39]. Other modes of transmission were reported, including fecal, oral, conjunctiva, and fomites[40-42]. Importantly, considerations must be taken regarding the residence time of the virus on the surface; the half-life of SARS-CoV-2 in plastic aerosol, copper, cardboard, and stainless steel is 6.8 hrs, 1.5 hrs, 1 hr, 3.4 hrs, and 5.6 hrs, respectively. The virion is stabilized at lower tem-

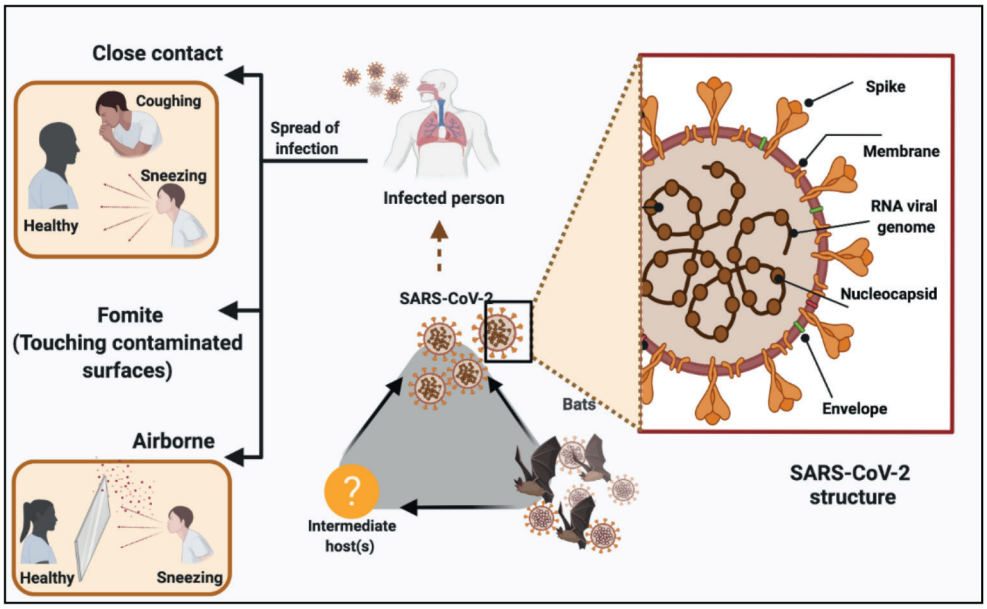

Figure 1. Coronavirus structure and modes of transmission.

peratures[39,43]. Patients infected with SARS-CoV-2 can spread the virus before and during the symptomatic course and even in the recovery time.

Symptoms and Pathogenesis of SARS-CoV-2

SARS-CoV-2 binds to angiotensin converting enzyme 2(ACE2) receptors on the surface of host cells and enters through endocytosis to multiply in the cytoplasm[44]. The ACE2 receptors are widely distributed in human organs such as the lungs, heart, kidney, and liver[34,45-48]. ACE2 Type II pneumocytes are the primary target of CoVs, because these cells have highly expressed ACE2 receptors on their surface. Additionally, Hamming et al[47] have reported that ACE2 is commonly expressed in endothelial, arterial and venous cells and smooth arterial muscle cells. Impaired type II pneumocyte function decreases the surfactant level and increases COVID-19 surface tension [50]. This provides the virus with the potential to invade and destroy blood vessels, followed by increased blood clotting and platelet accumulation, which ultimately results in thrombus formation. Accumulating data indicate coagulopathy as a major pathological mechanism in COVID-19. Extensive coagulopathy can explain the phenomenon such as ischemic skin lesions, increased risk of stroke, and hypoxemia even without breathing problems in some severely ill patients[51].

The first line of defense against viral infection is a rapid and well-coordinated innate immune response. In addition, SARS-CoV-2 RNA acts as a pathogen-associated molecular pattern (PAMP) to be recognized by receptor pattern recognition receptors such as Toll-like receptors. This results in a burst of chemokines that triggers the migration and activation of neutrophils[20]. The proinflammatory condition may result in ARDS and cytokine storm syndrome (CSS), possibly mediated by interleukin-6 (IL-6), dysregulated immune response, tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-α), interleukin-1 beta (IL-1β), and other inflammatory signaling molecules[52]. This leads to the destruction of the capillary alveolar walls, which in turn cause loss of the interface between the intra-alveolar space and the surrounding stroma at a microscopic level. Thus, the fluid leaks and fills into the alveolar sac[20].

Most of the critically ill and deceased patients in the early stages of the disease did not develop severe clinical manifestations. Some of the patients exhibited only mild fever, cough, or muscle soreness. Those patients' conditions deteriorated suddenly in the later stages of the disease or during the recovery process. ARDS and multiorgan failure occur quickly, leading to death within a short period[53].

ARDS is the number one cause of death in patients with SARS-CoV or MERS-CoV infection[54,55]. It is now known that several proinflammatory cytokines (IL-6, IL-8, IL-1β, colony-stimulating factor, granulocytes, macrophages, and reactive oxygen species) and chemokines (such as

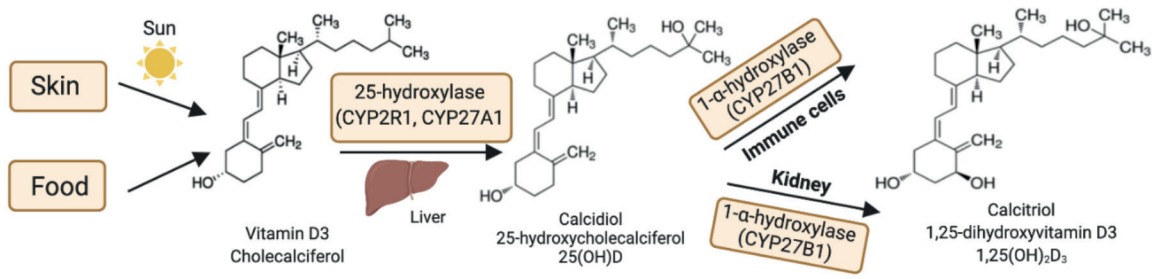

Figure 2. Vitamin D synthesis. In the layers of the skin, vitamin D3 is formed non-enzymatically by ultraviolet light. Then, vitamin D3 is enzymatically activated in the liver and kidney.

CCL-2, CCL-5, IFN α-induced protein 10 (IP-10), and CCL-3) contribute to the development of ARDS[56-58]. Cytokine storm is a major cause of ARDS and multiple organ failure[59] identified in critical COVID-19 patients and plays an important role in the disease worsening process[60]. Therefore suppressing the cytokine storm can be an important way to cure and prevent disease severity[61]. Cytokines have long been known to play a major role in immunopathology during viral infection. Dysregulated and excessive immune reactions can, however, cause damage to the human body[62-64]. *In vitro* cell experiments show that delayed cytokine and chemokine release occurs at the early stage of SARS-CoV infection in respiratory epithelial cells, dendritic cells (DCs), and macrophages. The cells then secrete low levels of IFNs and high levels of proinflammatory cytokines IL-1β, IL-6, and TNF and chemokines (C-C structure chemokine ligand (CCL)-2, CCL-3, and CCL-5)[65-67]. In animal models, it was found that the excessive inflammatory response is more relevant to the death of old nonhuman primates than the virus titer[68]. Similarly, disease severity in old mice in BALB/c mice infected with SARS-CoV is associated with an early and disproportionately strong upregulation of ARDS-related inflammatory gene signal[69]. The accumulated mononuclear macrophages receive activating signals on their surface through the IFN-α/β receptors, and produce more monocyte chemo-attractants (such as CCL-2, CCL-7, and CCL-12), resulting in further mononuclear macrophage accumulation. These mononuclear macrophages produce high levels of proinflammatory cytokines (TNF, IL-6, IL1-β, and inducible synthase of nitric oxide), thus increasing the severity of the illness. Depleting inflammatory monocyte-macrophages or neutralizing the inflammatory cytokine TNF protected mice from fatal SARS-CoV infection[62].

Induction of apoptosis in lung epithelial and endothelial cells is another consequence of rapid viral replication and vigorous proinflammatory cytokine/chemokine response. Mechanisms involving Fas-Fas ligand (FasL) or TRAIL-death receptor 5 (DR5) induce inflammatory cell infiltration and cause apoptosis of the airway and alveolar epithelial cells[70-72]. Endothelial cell and epithelial cell apoptosis damages the barriers of the pulmonary microvascular and alveolar epithelial cells, causing vascular leakage and alveolar edema, eventually leading to hypoxia in the body. Inflammatory mediators thus play a vital function in the pathogenesis of ARDS. ARDS is the number one cause of death in patients with SARS-CoV and MERS-CoV infection[54,55]. It is now known that several proinflammatory cytokines (IL-6, IL-8, IL-1β, colony-stimulating factor, granulocyte, macrophages, and reactive oxygen species) and chemokines (such as CCL-2, CCL-5, IFN α-induced protein 10 (IP-10), and CCL-3) contribute to the development of ARDS[56-58].

Vitamin D and Viral Infections

Vitamin D is a steroid hormone produced endogenously with ultraviolet B (UVB) radiation or exogenously from food and dietary supplements. During exposure to UVB radiation from the sun, vitamin D3 is synthesized non-enzymatically in the skin, followed by enzymatic activation of vitamin D3 in the liver and in the kidney using 25-hydroxylase and 1-α-hydroxylase (CYP27B1) (Figure 2).

There are three mechanisms by which vitamin D decreases the risk of infection: providing a physical barrier, cellular natural innate immunity and immunity and adaptive immunity[73]. Interestingly, the role of vitamin D in immunity was identified due to the expression of a vitamin D receptor (VDR) in immune cells (monocytes/

macrophages, T cells, B cells, natural killer cells (NK), and dendritic cells (DCs)). Immune cells are able to metabolize circulating 25-hydroxycholecalciferol (25(OH)D), producing 1,25-dihydroxycholecalciferol [1,25-dihydroxy vitamin D3, $1,25(OH)_2D_3$] (Figure 2)[74]. The binding of vitamin D to VDR is tightly linked to modulation of innate and adaptive immunity against various types of infection[75].

Epidemiological studies have shown that vitamin D deficiency is related to infections in the respiratory tract and acute lung injury[76]. Calcitriol (the active form of vitamin D) has exhibited protective effects against acute lung injury by modulating the expression of renin-angiotensin system members such as ACE2 in lung tissue[77]. Vitamin D receptors (VDRs) are distributed extensively in respiratory epithelial and immune cells (B cells, T cells, macrophages, and monocytes). 25(OH)D, the major circulating form of vitamin D in the bronchial epithelium and immune cells, is converted to the active form ($1,25(OH)_2D_3$)[78]. Diverse stimuli, including cytokines and toll-like receptor (TLR) ligands in the respiratory tract, induce the enzyme 1-α-hydroxylase (CYP27B1), which is necessary for vitamin D activation. However, sufficient serum levels of 25OHD are required to increase the levels of $1,25(OH)_2D_3$ and thus improve the immune response to respiratory virus infection[79].

Recently, Liu et al[80] indicated that a severe deficiency of vitamin D (< 25 nmol/L) is associated with progression of the disease and increased mortality in patients with autoimmune liver disease. This attribute has brought about an interest in vitamin D as a pathogenic factor that can be assessed, tracked, and manipulated[81]. Recently, Hughes and Norton[82] indicate that vitamin D deficiency is related to increased levels of IL-6 in patients with HIV infection, and there is also evidence that supplementation with vitamin D can reduce excess IL-6 levels in diabetic mice[83]. Insufficiency of vitamin D was linked to overexpression of Th1 cytokines[84].

Vitamin D is known to mitigate the immunity gained and to regenerate the endothelial lining.

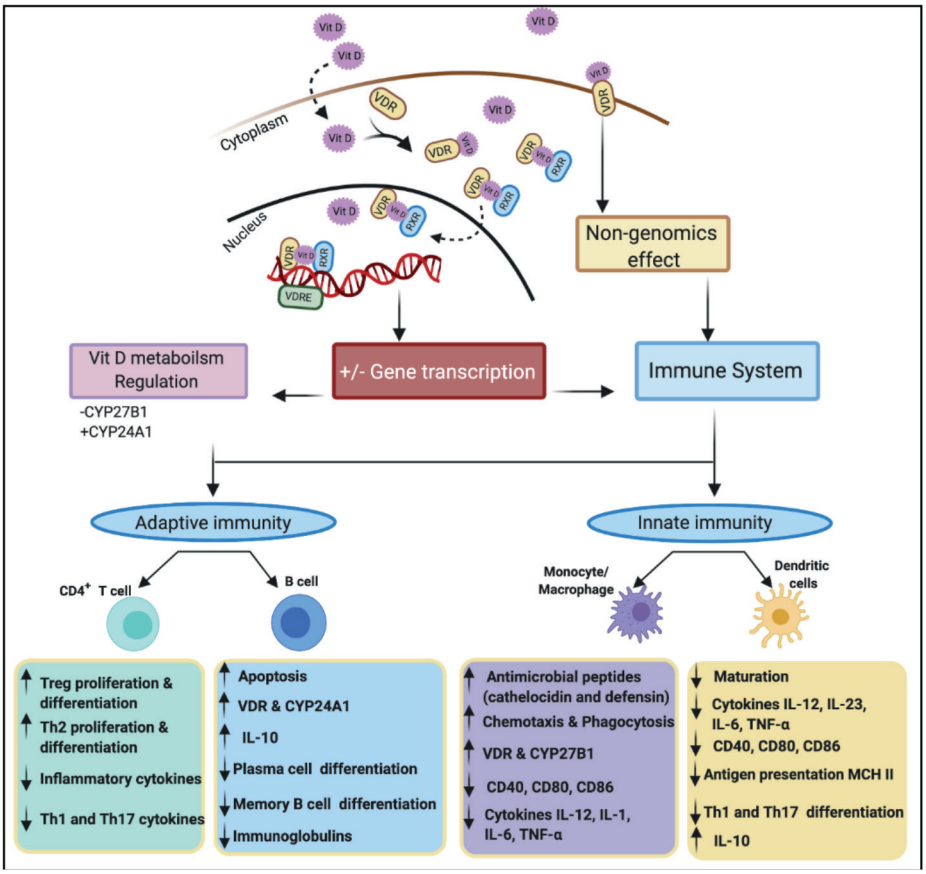

Figure 3. Schematic representation of vitamin D effects on the immune system.

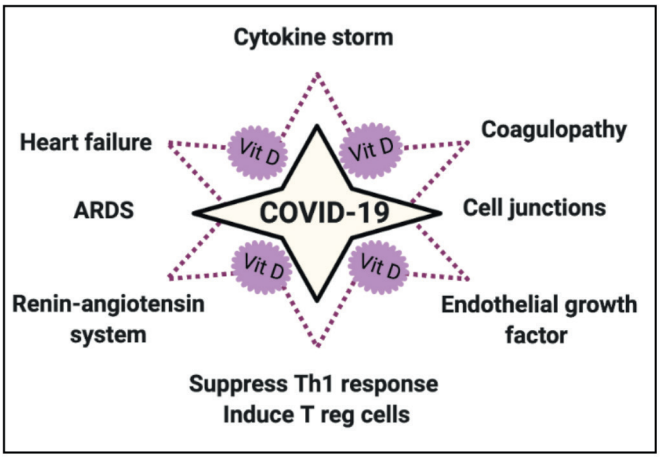

Figure 4. The different effects of vitamin D and its deficiency on COVID-19.

This may help to minimize the alveolar damage caused by ARDS. Level I evidence (N = 11,321) shows that vitamin D supplementation has a 12% overall protective impact against bacterial and viral acute respiratory tract infection (adjusted OD = 0.88, $p < 0.001$)[85]. These protective effects in those individuals increased to 19% on the daily or weekly vitamin D regimen compared to those on a monthly vitamin D bolus (adjusted OD = 0.81, $p < 0.001$). In addition, when vitamin D deficiency is treated with supplementation, there is a protective effect of 70% (adjusted OD = 0.30, $p = 0.006$)[85].

A large number of well-established data have shown antiviral effects of vitamin D that can directly interfere with viral replication but can also act in an immunomodulatory and anti-inflammatory manner[86]. The protective effect of vitamin D has been reported in many pneumonias, cytokine hyper-production and ARDS-related conditions[9,87,88] and vitamin D was recently proposed as a repurposed drug for lung injury caused by influenza A H5N1 virus[89]. Deficiency of vitamin D is a risk factor and/or driver of exaggerated and persistent inflammation[90,91]. An increased risk of respiratory infections such as respiratory syncytial virus infection, tuberculosis, and influenza was associated with vitamin D deficiency[92,93]. Winter influenza incidence is strongly associated with seasonal serum levels of vitamin D[94]. Bergman et al[93] demonstrated in a meta-analysis of randomized controlled clinical trials that prophylactic vitamin D reduced the risk of developing respiratory tract infections (OR, 0.64; 95%; CI, 0.49 to 0.84)[95]. The optimal dose used in the study was between 1,000 IU to 4,000 IU/day and the benefit in those living at latitudes greater than 40° was greatest. Grant and Giovannucci[94] reported a clear inverse association of UVB dose and case fatalities during the influenza pandemic in 1918-1919[96]. As vitamin D deficiency enhances the cytokine storm[97,98], it may be particularly lethal in patients with SARS-CoV-2 infection[99].

The high-dose treatment of 250,000–500,000 IU vitamin D was safe in mechanically ventilated, critically ill patients and was associated with decreased hospital length of stay, enhanced blood capacity to carry oxygen and increased levels of hemoglobin[100,101]. The risk of acute respiratory tract infection was twice as low if the vitamin D serum levels were equal to 0.95 nmol/L (hazard ratio 0.51; 95 % CI, 0.25 to –0.84; $p < 0.0001$) and five times less (0.80% *vs.* 3.9% , $p = 0.02$) than patients with levels < 95 nmol/L[102]. Some studies suggest the effectiveness of vitamin D as an adjuvant therapy in patients infected with HIV, along with antiretroviral agents[5]. Moreover, pretreatment with vitamin D was beneficial in animal models of ARDS, reducing lung permeability by modulation of the activity of the renin angiotensin system and ACE2 expression[77]. The findings of certain vitamin D receptor gene (VDR) alleles associated with increased susceptibility to respiratory infections also support the role of vitamin D in the context of viral infections[103], as well as in the progression of HIV infection[104].

Vitamin D and Immunity

Vitamin D affects the immune pathways through intracrine (Vitamin D acts inside a cell) and paracrine (cell-cell communication) mechanisms, with the net result of improving mucosal defense while

at the same time reducing excessive inflammation[97,98]. It has been reported that the proper function of innate immune cells is strictly associated with the synthesis of the active form of vitamin D ($1,25(OH)_2D_3$) inside monocytes[105].

After infection and stimulation of toll-like receptors (TLRs), the receptor of interferon gamma (IFN-γ) or CD40, monocytes/macrophages, and DCs upregulate the expression of genes, which code for vitamin D receptor (VDR) and 1-α-hydroxylase (CYP27B1)[105-107]. Furthermore, in monocytes/macrophages, VitD-VDR- RXR (retinoid X receptor) heterodimers translocate to the nucleus and bind to the vitamin D responsive elements (promoter DNA sequences, VDREs) of the genes for cathelocidin and defensin (antimicrobial peptides (AMPs)), resulting in subsequent transcription of these proteins (Figure 3)[108]. Furthermore, $1,25(OH)_2D_3$ increases the chemotaxis and phagocytosis ability of macrophages[109].

The intracrine activity of vitamin D inside DCs promotes an anti-inflammatory response through inhibition of its maturation and differentiation, resulting in a phenotype characterized by the downregulation of antigen-presenting molecules (MHC-class II) and costimulatory molecules (e.g., CD40, CD80, and CD86)[110]. Additionally, $1,25(OH)_2D_3$ affects the expression and secretion of cytokines and chemokines, inhibiting the secretion of IL-12, IL-23, TNF-α and IFN-γ, while increasing anti-inflammatory cytokines (IL-10) and T cell inhibitory molecule (PD-1)[111,112]. Accordingly, $1,25(OH)_2D_3$ results in a shift in the T-cell polarization from the proinflammatory Th1 and Th17 responses to a more tolerogenic Th2 response[113-115].

Similar to other immune cells, neutrophils express functional VDR and during vitamin D deficiency, neutrophils show low migration ability, confirming that 1,25(OH)2D3 improves the antimicrobial activity of neutrophils[116]. Interestingly, vitamin D can affect its synthesis through inhibition of 1-α-hydroxylase (CYP27B1) and induction of 24-hydroxylase (CYP24A1), which is responsible for its degradation[117].

Adaptive immune response depends on the highly specialized T and B lymphocytes, which have the ability to specifically identify foreign antigens. B cells independently or via T cells help terminally differentiate into plasma cells to secrete antibodies required to eliminate the invading pathogens. T cells also activate macrophages and kill infected cells. Vitamin D-related immunomodulation effect on T and B cells is through direct action on cell proliferation, differentiation, and apoptosis (Figure 3). Vitamin D-related effects like changes in $CD4^+$ T cells and decrease in cytokine secretion inhibit B cell function[118].

The expression of VDR is upregulated in B lymphocytes by activating signals, as well as $1,25(OH)_2D_3$. B cells express both 1-α-hydroxylase and 24-hydroxylase, thus the vitamin can be activated inside the B cells[110,119]. $1,25(OH)_2D_3$ inhibits the proliferation and differentiation of plasma cells (inhibiting the release of IgE), inhibits the formation of memory B cells, and enhances IL-10 production[120-123]. $1,25(OH)_2D_3$ enhances the anti-inflammatory effect by acting directly on T cells. It inhibits the proliferation of T cells by IL-2 production[124]. Moreover, $1,25(OH)_2D_3$ decreases differentiation of Th1/Th17 cells and increases Th2 differentiation[125-127]. Importantly, $1,25(OH)_2D_3$ also triggers regulatory T (Treg) cell proliferation, inhibiting the proinflammatory responses of other immune cells[128].

Vitamin D and COVID-19

Based on clinical findings, there is growing evidence that vitamin D deficiency increases the risk of COVID-19 infection severity and mortality[14,129]. Epidemiological studies showed an ethnicity link showing that COVID-19 disproportionately affects ethnic black and minority ethnic people, with the National Audit and Research Center for Intensive Care reporting that one-third of confirmed cases admitted to critical care in England are non-white[130]. This compares with the figures from the 2011 Census, which show that 14% of the general population of England and Wales identify themselves as ethnic black and minority people[131]. Similarly, African Americans have observed a pattern of higher risk of infection[132]. The relationship between ethnicity and COVID-19 has thus been identified as an urgent priority for public health research[133]. One potential mediator might be the higher prevalence of apparent deficiency of vitamin D in ethnic Black and minority populations[133]. Further, the seasonality of viral infections, the occurrence of the COVID-19 outbreak in winter, where low concentrations of 25(OH)D due to low UVB doses, is another evidence supporting the role of vitamin D in decreasing the risk of SARS-CoV-2 infection[134,135]. Furthermore, case-fatality rates increase with age and chronic diseases, which are accompanied by reduced 25(OH)D concentration[136].

Vitamin D deficiency can be lethal in COVID-19 patients[97,98] (Figure 4). COVID-19 leads to dysregulation of the immune system and the forming of a

cytokine storm, often involving IL-6, TNF-α, and IFN-γ[52]. From the perspective of the adaptive immune system, vitamin D may be able to prevent this severe complication through binding to VDRs, leading to gene transcription changes. In particular, vitamin D leads to a blunting of the Th1 immune response and favors the response of Th2 and regulatory T cells[129,137,138]. This results in a decrease in Th1-related proinflammatory cytokines, such as IL-6, TNF-α, and IFN-γ, and an increase in Th2-related anti-inflammatory cytokines, such as IL-10 and IL-2[129,137,139]. The response to Th2 also serves to further dampen the response to Th1, while the response to Treg further reduces inflammation.

On the other hand, a deficiency of vitamin D plays a role in ARDS and heart failure[129]. Importantly, vitamin D contributes to the action of other critical regulatory systems; prolonged deficiency of vitamin D triggers the renin-angiotensin system (RAS), leading to cardiovascular problems and decreased lung function. Patients with these comorbidities are significantly affected with SARS-CoV-2[140]. Another prominent feature of severe COVID-19 is coagulopathy, which is correlated with vitamin D deficiency[141]. Vitamin D receptor-knockout mice have coagulation disorders with injury[142]. Thus, the possible involvement of vitamin D in SARS-CoV-2 infection is not only due to its influence on innate and adaptive immune responses (as in the case of influenza), but also to cardiovascular system effect[143]. Several studies have shown that vitamin D deficiency was associated with endothelial dysfunction and vascular system pathological changes[144]. $1,25(OH)_2D_3$ has been reported to promote endothelial vascular repair by inducing smooth vascular muscle cells to produce endothelial growth factor (VEGF)[145]. Moreover, vitamin D can reduce the risk of infection via maintenance of tight cell junctions, preventing the virus from disturbing the junction integrity[146]. A microarray dissection indicated that 5% of the human genome and the physiological operations of 36 different cell types are either directly or indirectly regulated by vitamin D[142].

Supplementation with vitamin D also enhances antioxidant-related gene expression (glutathione reductase and glutamate – cysteine ligase modifier subunit)[147]. The increased production of glutathione spares the use of ascorbic acid (vitamin C), which has antimicrobial activity[148,149], and has been proposed for the prevention and treatment of COVID-19[150]. In addition, on 23 March 2020, a former head of the Center for Disease Control and Prevention, Dr. Tom Frieden, proposed the use of vitamin D (https://www.foxnews.com/opinion/former-cdc-chief-tomfrieden-coronavirus-risk-may-be-reduced-with-vitamin-d) to fight the COVID-19 pandemic[151]. While benefits from vitamin D may be most pronounced with longer-term supplementation, rather than large individual doses of bolus[139]. Above 30 ng/mL of 25(OH)D is required daily, especially in the winter, from food (and supplementation, if needed)[151,152]. The minimum dosage of Vitamin D reduces the risk and severity of COVID-19[148,153]. Ilie et al[14] reported that vitamin D has already been shown to be safe for acute respiratory infections. Therefore, it is advised for further studies to be performed to assess the impact of vitamin D levels on COVID-19 outcomes.

Conclusions

The COVID-19 pandemic, which is caused by the novel SARS-CoV-2, put the entire world in an unprecedented crisis. Due to the lack of available and approved treatments or vaccines, only protective measures can be applied. Vitamin D deficiency is considered as a worldwide health problem that has an impact on a range of diseases, in particular, viral infections. Epidemiological and clinical studies shed light on the beneficial role of vitamin D in viral infections, revealing that high levels of vitamin D have protective effects against COVID-19. The most vulnerable individuals for COVID-19 are the ones that have poor vitamin D status. The potential contribution of vitamin D to viral diseases may be achieved via several mechanisms including immunoregulatory mechanisms and interaction with viral and cellular factors. Several studies show that COVID-19 patients with good Vitamin D levels have reduced COVID-19 fatalities due to the effects of vitamin D on suppressing the adaptive immune system, regulating cytokine levels and thereby improving COVID-19 cases.

ORCID

Helal Hetta 0000-0001-8541-7304; Khalid Muhammad 0000-0001-6488-1722; Yasir Waheed 0000-0002-5789-4215; Gaber Batiha 0000-0002-7817-425X; A.M Zahran 0000-0001-8471-6388

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements
Biorender was used to create figures. KM's work is supported by UAE University-start up Grant # G00003347 & UAEU-UPAR-Grant#G00003458.

Author Contribution
HH, KM, CP, YW, AZ, RY, AM, HAK, VO, AB and GB contributed to Conceptualization, formal analysis, writing-original draft preparation, writing-review and editing. HH and KM lead the study. All authors have read and agreed to the publication of current version of the manuscript.

References

1) Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-574.
2) de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14: 523.
3) World Health Organization announces COVID-19 outbreak a pandemic.
4) Coronavirus disease (COVID-19): World Health Organization-Situation report. https://reliefweb.int/report/world/coronavirus-disease-covid-19-situation-report-04-December-2020.
5) Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, Rovers M, Bont L. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 2011; 127: e1513-e1520.
6) McNally JD, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol 2009; 44: 981-988.
7) Loeb M, Dang AD, Thiem VD, Thanabalan V, Wang B, Nguyen NB, Tran HTM, Luong TM, Singh P, Smieja M, Maguire J, Pullenayegum E. Effect of vitamin D supplementation to reduce respiratory infections in children and adolescents in Vietnam: a randomized controlled trial. Influenza Other Respir Viruses 2019; 13: 176-183.
8) Hong M, Xiong T, Huang J, Wu Y, Lin L, Zhang Z, Huang L, Gao D, Wang H, Kang C, Gao Q, Yang X, Yang N, Hao L. Association of vitamin D supplementation with respiratory tract infection in infants. Matern Child Nutr 2020; 16: e12987.
9) Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community-acquired pneumonia: a meta-analysis of observational studies. Medicine 2019; 98: e17252.
10) Jiménez-Sousa MÁ, Martínez I, Medrano LM, Fernández-Rodríguez A, Resino S. Vitamin D in human immunodeficiency virus infection: influence on immunity and disease. Front Immunol 2018; 9: 458.
11) Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: molecular mechanisms and therapeutic potential. Front Immunol 2017; 7: 697.
12) Teymoori-Rad M, Shokri F, Salimi V, Marashi SM. The interplay between vitamin D and viral infections. Rev Med Virol 2019; 29: e2032.
13) Huang F, Zhang C, Liu Q, Zhao Y, Zhang Y, Qin Y, Li X, Li C, Zhou C, Jin N, Jiang C. Identification of amitriptyline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. PLoS Pathog 2020; 16: e1008341.
14) Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020; 32: 1195-1198.
15) Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020; 92: 418-423.
16) Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z, Zhang Z, Wang J, Sheng J, Quan L, Xia Z, Tan W, Cheng G, Jiang T. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020; 27: 325-328.
17) Abd Ellah NH, Gad SF, Muhammad K, E Batiha G, Hetta HF. Nanomedicine as a promising approach for diagnosis, treatment and prophylaxis against COVID-19. Nanomedicine 2020; 15: 2085-2102.
18) Paules CI, Marston HD, Fauci AS. Coronavirus infections--more than just the common cold. JAMA 2020; 323: 707-708.
19) Kakodkar P, Kaka N, Baig M. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus 2020; 12: e7560.
20) Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol 2020; 79: 104212.
21) Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020; 9: 221-236.
22) Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-523.

23) Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-269.

24) Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020; 63: 457-460.

25) Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog 2018; 14: e1007236.

26) Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. J Med Virol 2020; 92: 548-551.

27) Mahmood Z, Alrefai H, Hetta HF, H AK, Munawar N, Abdul Rahman S, Elshaer S, Batiha GE, Muhammad K. Investigating virological, immunological, and pathological avenues to identify potential targets for developing COVID-19 treatment and prevention strategies. Vaccine 2020; 8: 443.

28) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

29) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

30) Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 2020; 9: 275-277.

31) Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. Viruses 2020; 12: 135.

32) Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak--an update on the status. Mil Med Res 2020; 7: 1-10.

33) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.

34) Amanat F, Krammer F. SARS-CoV-2 vaccines: status report. Immunity 2020; 52: 583-589.

35) Phan T. Novel coronavirus: from discovery to clinical diagnostics. Infect Genet Evol 2020; 79: 104211.

36) Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc Natl Acad Sci USA 2020; 117: 1091-6490.

37) Setti L, Passarini F, De Gennaro G, Barbieri P, Perrone MG, Borelli M, Palmisani J, Di Gilio A, Piscitelli P, Miani A. Airborne transmission route of COVID-19: why 2 meters/6 feet of inter-personal distance could not be enough. Int J Environ Res Public Health 2020; 17: 2932.

38) Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect 2020; 104: 246-251.

39) Zhang Y, Chen C, Zhu S, Shu C, Wang D, Song J, Song Y, Zhen W, Feng Z, Wu G. Isolation of 2019-nCoV from a stool specimen of a laboratory-confirmed case of the coronavirus disease 2019 (COVID-19). CCDC Weekly 2020; 2: 123-124.

40) Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020; 158: 1831-1833.e3.

41) Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, Marimuthu K. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 2020; 323: 1610-1612.

42) Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. J Hosp Infect 2016; 92: 235-250.

43) Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-280.e8.

44) Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, Muth D, Demmers JAA, Zaki A, Fouchier RAM, Thiel V, Drosten C, Rottier PJM, Osterhaus ADME, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495: 251-254.

45) Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426: 450-454.

46) Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med 2020; 26: 450-452.

47) Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631-637.

48) Bombardini T, Picano E. Angiotensin converting enzyme 2 as the molecular bridge between epidemiologic and clinical features of COVID-19. Can J Cardiol 2020; 36: 784.e1-784.e2.

49) Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. How does coronavirus kill. Clinicians trace a ferocious rampage through the body, from brain to toes. Science's COVID-19 reporting is supported by the Pulitzer Center, 2020.

50) Canna SW, Behrens EM. Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am 2012; 59: 329-344.

51) Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association. An update on the epidemiological characteristics of novel coronavirus pneumonia (COVID-19). Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41: 139-144.

52) Drosten C, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, Guggemos W, Kallies R, Muth D, Junglen S, Müller MA, Haas W, Guberina H, Röhnisch T, Schmid-Wendtner M, Aldabbagh S, Dittmer U, Gold H, Graf P, Bonin F, Rambaut A, Wendtner CM. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lancet Infect Dis 2013; 13: 745-751.

53) Lew TW, Kwek T-K, Tai D, Earnest A, Loo S, Singh K, Kwan KM, Chan Y, Yim CF, Bek SL, Kor AC, Yap WS, Chelliah YR, Lai YC, Goh SK. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003; 290: 374-380.

54) Jiang Y, Xu J, Zhou C, Wu Z, Zhong S, Liu J, Luo W, Chen T, Qin Q, Deng P. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am J Respir Crit Care Med 2005; 171: 850-857.

55) Reghunathan R, Jayapal M, Hsu L-Y, Chng H-H, Tai D, Leung BP, Melendez AJ. Expression profile of immune response genes in patients with severe acute respiratory syndrome. BMC Immunol 2005; 6: 2.

56) Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP, Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). Virus Res 2008; 133: 13-19.

57) Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol 2017; 39: 517-528.

58) Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. J Immunother Cancer 2018; 6: 56.

59) Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z, Qiang M, Xiang J, Zhang B, Chen Y. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv 2020. Doi: https://doi.org/10.1101/2020.02.10.20021832.

60) Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016; 19: 181-193.

61) Davidson S, Maini MK, Wack A. Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. J Interferon Cytokine Res 2015; 35: 252-264.

62) Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. Nat Rev Immunol 2013; 13: 875-887.

63) Law HK, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, Nicholls JM, Peiris JM, Lau YL. Chemokine up-regulation in sars-coronavirus–infected, monocyte-derived human dendritic cells. Blood 2005; 106: 2366-2374.

64) Cheung CY, Poon LL, Ng IH, Luk W, Sia SF, Wu MH, Chan KH, Yuen KY, Gordon S, Guan Y, Peiris JS. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J Virol 2005; 79: 7819-7826.

65) Lau SKP, Lau CCY, Chan KH, Li CPY, Chen H, Jin DY, Chan JFW, Woo PCY, Yuen KY. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol 2013; 94: 2679-2690.

66) Smits SL, de Lang A, van den Brand JM, Leijten LM, van IJcken WF, Eijkemans MJ, van Amerongen G, Kuiken T, Andeweg AC, Osterhaus AD, Haagmans BL. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog 2010; 6: e1000756.

67) Rockx B, Baas T, Zornetzer GA, Haagmans B, Sheahan T, Frieman M, Dyer MD, Teal TH, Proll S, van den Brand J, Baric R, Katze MG. Early upregulation of acute respiratory distress syndrome-associated cytokines promotes lethal disease in an aged-mouse model of severe acute respiratory syndrome coronavirus infection. J Virol 2009; 83: 7062-7074.

68) Herold S, Steinmueller M, von Wulffen W, Cakarova L, Pinto R, Pleschka S, Mack M, Kuziel WA, Corazza N, Brunner T, Seeger W, Lohmeyer J. Lung epithelial apoptosis in influenza virus pneumonia: the role of macrophage-expressed TNF-related apoptosis-inducing ligand. J Exp Med; 205: 3065-3077.

69) Högner K, Wolff T, Pleschka S, Plog S, Gruber AD, Kalinke U, Walmrath HD, Bodner J, Gattenlöhner S, Lewe-Schlosser P, Matrosovich M, Seeger W, Lohmeyer J, Herold S. Macrophage-expressed IFN-β contributes to apoptotic alveolar epithelial cell injury in severe influenza virus pneumonia. PLoS Pathog 2013; 9: e1003188.

70) Rodrigue-Gervais IG, Labbé K, Dagenais M, Dupaul-Chicoine J, Champagne C, Morizot A, Skeldon A, Brincks EL, Vidal SM, Griffith TS, Saleh M. Cellular inhibitor of apoptosis protein cIAP2

protects against pulmonary tissue necrosis during influenza virus infection to promote host survival. Cell Host Microbe 2014; 15: 23-35.

71) Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P, Faliva MA, Peroni G, Nichetti M, Perna S. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds--practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evid Based Complementary Altern Med 2018; 2018: 5813095.

72) Veldman CM, Cantorna MT, DeLuca HF. Expression of 1, 25-dihydroxyvitamin D3 receptor in the immune system. Arch Biochem Biophys 2000; 374: 334-338.

73) Rezaei R, Aslani S, Marashi M, Rezaei F, Sharif-Paghaleh E. Immunomodulatory effects of vitamin D in influenza infection. Curr Immunol Rev 2018; 14: 40-49.

74) Hansdottir S, Monick MM. Vitamin D effects on lung immunity and respiratory diseases. Vitam Horm 2011; 86: 217-237.

75) Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. Mol Med Rep 2017; 16: 7432-7438.

76) Pfeffer PE, Hawrylowicz CM. Vitamin D and lung disease. Thorax 2012; 67: 1018-1020.

77) Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7: 4240-4270.

78) Ebadi M, Bhanji RA, Mazurak VC, Lytvyak E, Mason A, Czaja AJ, Montano-Loza AJ. Severe vitamin D deficiency is a prognostic biomarker in autoimmune hepatitis. Aliment Pharmacol Ther 2019; 49: 173-182.

79) Czaja AJ, Montano-Loza AJ. Evolving role of vitamin D in immune-mediated disease and its implications in autoimmune hepatitis. Dig Dis Sci 2019; 64: 324-344.

80) Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol 2016; 13: 3-10.

81) Labudzynskyi D, Shymanskyy I, Veliky M. Role of vitamin D3 in regulation of interleukin-6 and osteopontin expression in liver of diabetic mice. Eur Rev Med Pharmacol Sci 2016; 20: 2916-2919.

82) Hughes D, Norton R. Vitamin D and respiratory health. Clin Exp Immunol 2009; 158: 20-25.

83) Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017; 356: i6583.

84) Teymoori-Rad M, Shokri F, Salimi V, Marashi SM. The interplay between vitamin D and viral infections. J Med Virol 2019; 29: e2032.

85) Hong M, Xiong T, Huang J, Wu Y, Lin L, Zhang Z, Huang L, Gao D, Wang H, Kang C, Gao Q, Yang X, Yang N, Hao L. Association of vitamin D supplementation with respiratory tract infection in infants. Matern Child Nutr 2020; 16: e12987.

86) Tsujino I, Ushikoshi-Nakayama R, Yamazaki T, Matsumoto N, Saito I. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. J Clin Biochem Nutr 2019; 65: 245-251.

87) Huang F, Zhang C, Liu Q, Zhao Y, Zhang Y, Qin Y, Li X, Li C, Zhou C, Jin N, Jiang C. Identification of amitriptyline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. PLoS Pathog 2020; 16: e1008341.

88) Dancer RC, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, Park D, Bartis DG, Mahida R, Turner AM, Sapey E, Wei W, Naidu B, Stewart PM, Fraser WD, Christopher KB, Cooper MS, Gao F, Sansom DM, Martineau AR, Perkins GD, Thickett DR. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015; 70: 617-624.

89) Parekh D, R Thickett D, M Turner A. Vitamin D deficiency and acute lung injury. Inflamm Allergy Drug Targets 2013; 12: 253-261.

90) Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. Br J Nutr 2011; 106: 1433-1440.

91) Cannell J, Vieth R, Umhau J, Holick M, Grant W, Madronich S, Garland C, Giovannucci E. Epidemic influenza and vitamin D. Epidemiol Infect 2006; 134: 1129-1140.

92) Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Int Arch Intern Med 2009; 169: 384-390.

93) Bergman P, Lindh ÅU, Björkhem-Bergman L, Lindh JD. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2013; 8: e65835.

94) Grant WB, Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918–1919 influenza pandemic in the United States. Dermatoendocrinol 2009; 1: 215-219.

95) Khare D, Godbole NM, Pawar SD, Mohan V, Pandey G, Gupta S, Kumar D, Dhole TN, Godbole MM. Calcitriol [1, 25 [OH] 2 D3] pre-and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. Eur J Nutr 2013; 52: 1405-1415.

96) Parlak E, Ertürk A, Çağ Y, Sebin E, Gümüşdere M. The effect of inflammatory cytokines and the level of vitamin D on prognosis in Crimean-Congo hemorrhagic fever. Int J Clin Exp Med 2015; 8: 18302.

97) Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? Medicine in Drug Discovery 2020; 6: 100041.

98) Han JE, Jones JL, Tangpricha V, Brown MA, Brown LAS, Hao L, Hebbar G, Lee MJ, Liu S, Ziegler TR, Martin GS. High dose vitamin D administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial. J Clin Transl Endocrinol 2016; 4: 59-65.

99) Smith EM, Jones JL, Han JE, Alvarez JA, Sloan JH, Konrad RJ, Zughaier SM, Martin GS, Ziegler TR, Tangpricha V. High-dose vitamin D3 administration is associated with increases in hemoglobin concentrations in mechanically ventilated critically ill adults: a pilot double-blind, randomized, placebo-controlled trial. J Parenter Enteral Nutr 2018; 42: 87-94.

100) Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One 2010; 5: e11088.

101) Jolliffe DA, Greiller CL, Mein CA, Hoti M, Bakhsoliani E, Telcian AG, Simpson A, Barnes NC, Curtin JA, Custovic A, Johnston SL, Griffiths CJ, Walton RT, Martineau AR. Vitamin D receptor genotype influences risk of upper respiratory infection. Br J Nutr 2018; 120: 891-900.

102) Jiménez-Sousa MA, Jiménez JL, Fernández-Rodríguez A, Brochado-Kith O, Bellón JM, Gutierrez F, Díez C, Bernal-Morell E, Viciana P, Muñoz-Fernández MA, Resino S. VDR rs2228570 polymorphism Is related to non-progression to AIDS in antiretroviral therapy naive HIV-infected patients. J Clin Med 2019; 8: 311.

103) Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311: 1770-1773.

104) Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, Borregaard N, Modlin RL, Hewison M. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J Immunol 2009; 182: 4289-4295.

105) Kroner JDC, Sommer A, Fabri M. Vitamin D every day to keep the infection away? Nutrients 2015; 7: 4170-4188.

106) Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH. Cutting edge: 1, 25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004; 173: 2909-2912.

107) Taylor AE, Finney-Hayward TK, Quint JK, Thomas CM, Tudhope SJ, Wedzicha JA, Barnes PJ, Donnelly LE. Defective macrophage phagocytosis of bacteria in COPD. Eur Respir J 2010; 35: 1039-1047.

108) Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, Eliopoulos AG, Kilby MD, Moss PA, Chakraverty R. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol 2003; 170: 5382-5390.

109) Penna G, Amuchastegui S, Giarratana N, Daniel KC, Vulcano M, Sozzani S, Adorini L. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. J Immunol 2007; 178: 145-153.

110) Willheim M, Thien R, Schrattbauer K, Bajna E, Holub M, Gruber R, Baier K, Pietschmann P, Reinisch W, Scheiner O, Peterlik M. Regulatory effects of 1α, 25-dihydroxyvitamin D3 on the cytokine production of human peripheral blood lymphocytes. J Clin Endocrinol Metab 1999; 84: 3739-3744.

111) Ferreira GB, van Etten E, Verstuyf A, Waer M, Overbergh L, Gysemans C, Mathieu C. 1,25-Dihydroxyvitamin D3 alters murine dendritic cell behaviour in vitro and in vivo. Diabetes Metab Res Rev 2011; 27: 933-941.

112) Penna G, Adorini L. 1α, 25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000; 164: 2405-2411.

113) Ferreira GB, Gysemans CA, Demengeot J, da Cunha JP, Vanherwegen AS, Overbergh L, Van Belle TL, Pauwels F, Verstuyf A, Korf H, Mathieu C. 1,25-Dihydroxyvitamin D3 promotes tolerogenic dendritic cells with functional migratory properties in NOD mice. J Immunol 2014; 192: 4210-4220.

114) Hoe E, Nathanielsz J, Toh ZQ, Spry L, Marimla R, Balloch A, Mulholland K, Licciardi PV. Anti-inflammatory effects of vitamin D on human immune cells in the context of bacterial infection. Nutrients 2016; 8: 806.

115) Pike JW, Meyer MB. The vitamin D receptor: new paradigms for the regulation of gene expression by 1, 25-dihydroxyvitamin D3. Rheum Dis Clin North Am 2012; 38: 13-27.

116) Müller K, Heilmann C, Poulsen LK, Barington T, Bendtzen K. The role of monocytes and T cells in 1,25-dihydroxyvitamin D3 mediated inhibition of B cell function in vitro. Immunopharmacology 1991; 21: 121-128.

117) Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J, Rutgeerts O, Saint-Arnaud R, Bouillon R, Mathieu C. Identification and immune regulation of 25-hydroxyvitamin D-1-α-hydroxylase in murine macrophages. Clin Exp Immunol 2000; 120: 139-146.

118) Heine G, Anton K, Henz BM, Worm M. 1α,25-dihydroxyvitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. Eur J Immunol 2002; 32: 3395-3404.

119) Terrier B, Derian N, Schoindre Y, Chaara W, Geri G, Zahr N, Mariampillai K, Rosenzwajg M, Carpentier W, Musset L, Piette JC, Six A, Klatzmann D, Saadoun D, Patrice C, Costedoat-Chalumeau N. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. Arthritis Res Ther 2012; 14: R221.

120) Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007; 179: 1634-1647.

121) Chen W, Vayuvegula B, Gupta S. 1,25-Dihydroxyvitamin D3-mediated inhibition of human B cell differentiation. Clin Exp Immunol 1987; 69: 639.

122) Rigby W, Stacy T, Fanger MW. Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). J Clin Invest 1984; 74: 1451-1455.

123) Chang SH, Chung Y, Dong C. Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression. J Biol Chem 2010; 285: 38751-38755.

124) Palmer MT, Lee YK, Maynard CL, Oliver JR, Bikle DD, Jetten AM, Weaver CT. Lineage-specific effects of 1, 25-dihydroxyvitamin D3 on the development of effector CD4 T cells. J Biol Chem 2011; 286: 997-1004.

125) Ikeda U, Wakita D, Ohkuri T, Chamoto K, Kitamura H, Iwakura Y, Nishimura T. 1α,25-Dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentiation and expansion of Th17 cells. Immunol Lett 2010; 134: 7-16.

126) Kalicki B, Wawrzyniak A, Lipińska-Opałka A, Lewicki S, Zdanowski R. Influence of vitamin D and cotinine on T-regulatory cells and asthma severity in children. Adv Exp Med Biol 2017; 1021: 27-36.

127) Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12: 988.

128) Pareek M, Bangash MN, Pareek N, Pan D, Sze S, Minhas JS, Hanif W, Khunti K. Ethnicity and COVID-19: an urgent public health research priority. Lancet 2020; 395: 1421-1422.

129) Statistics OfN. 2011 Census. Office for National Statistics London; 2011.

130) Hopkins J. Corona virus resource center. (2020): https://coronavirus jhu edu/data. 2020.

131) UK G. Ethnicity facts and figures. 2017. https://www.ethnicity-facts-figures.service.gov.uk/

132) Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ 2019; 366: l5021.

133) Grant WB, Fakhoury HMA, Karras SN, Al Anouti F, Bhattoa HP. Variations in 25-Hydroxyvitamin D in Countries from the Middle East and Europe: The Roles of UVB Exposure and Diet. Nutrients 2019; 11: 2065.

134) Daneshkhah A, Eshein A, Subramanian H, Roy HK, Backman V. The role of vitamin D in suppressing cytokine storm in COVID-19 patients and associated mortality. medRxiv 2020.

135) Gruber-Bzura BM. Vitamin D and influenza--prevention or therapy? Int J Mol Sci 2018; 19: 2419.

136) Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. J Clin Virol 2011; 50: 194-200.

137) Boucher BJ. The problems of vitamin d insufficiency in older people. Aging Dis 2012; 3: 313.

138) Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, Xue X. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. Sci Rep 2017; 7: 1-10.

139) Mohammad S, Mishra A, Ashraf MZ. Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. Biomolecules 2019; 9: 649.

140) Aihara K, Azuma H, Akaike M, Ikeda Y, Yamashita M, Sudo T, Hayashi H, Yamada Y, Endoh F, Fujimura M, Yoshida T, Yamaguchi H, Hashizume S, Kato M, Yoshimura K, Yamamoto Y, Kato S, Matsumoto T. Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem 2004; 279: 35798-35802.

141) Tian Y, Rong L. Letter: does vitamin D have a potential role against COVID-19? Authors' reply. Aliment Pharmacol Ther 2020; 52: 410-411.

142) Kim HA, Perrelli A, Ragni A, Retta F, De Silva TM, Sobey CG, Retta SF. Vitamin D Deficiency and the risk of cerebrovascular disease. Antioxidants (Basel) 2020; 9: 327.

143) Norman P, Powell J. Vitamin D and cardiovascular disease. Circ Res 2014; 114: 379-393.

144) Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res 2011; 55: 96-108.

145) Lei GS, Zhang C, Cheng BH, Lee CH. Mechanisms of action of vitamin D as supplemental therapy for Pneumocystis pneumonia. Antimicrob Agents Chemother 2017; 61: e01226-17.

146) Mousavi S, Bereswill S, Heimesaat MM. Immunomodulatory and antimicrobial effects of vitamin C. Eur J Microbiol Immunol (Bp) 2019; 9: 73-79.

147) Colunga Biancatelli RML, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Rev Anti Infect Ther 2020; 18: 99-101.

148) Wimalawansa SJ. Global epidemic of Coronavirus--Covid-19: what can we do to minimize risks. Eur J Biomed Pharm Sci 2020; 7: 432-438.

149) Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12: 988.

150) Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, Povoroznyuk V, Balatska N, Barbosa AP, Karonova T, Rudenka E, Misiorowski W, Zakharova I, Rudenka A, Łukaszkiewicz J, Marcinowska-Suchowierska E, Łaszcz N, Abramowicz P, Bhattoa HP, Wimal-

awansa SJ. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol 2018; 175: 125-135.

151) Pilz S, März W, Cashman KD, Kiely ME, Whiting SJ, Holick MF, Grant WB, Pludowski P, Hiligsmann M, Trummer C, Schwetz V, Lerchbaum E, Pandis M, Tomaschitz A, Grübler MR, Gaksch M, Verheyen N, Hollis BW, Rejnmark L, Karras SN, Hahn A, Bischoff-Ferrari HA, Reichrath J, Jorde R, Elmadfa I, Vieth R, Scragg R, Calvo MS, van Schoor NM, Bouillon R, Lips P, Itkonen ST, Martineau AR, Lamberg-Allardt C, Zittermann A. Rationale and plan for vitamin D food fortification: a review and guidance paper. Front Endocrinol 2018; 9: 373.

152) Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, Povoroznyuk V, Balatska N, Barbosa AP, Karonova T, Rudenka E, Misiorowski W, Zakharova I, Rudenka A, Łukaszkiewicz J, Marcinowska-Suchowierska E, Łaszcz N, Abramowicz P, Bhattoa HP, Wimalawansa SJ. Vitamin D supplementation guidelines. 2018/01/01/ 2018;175:125-135. doi:https://doi.org/10.1016/j.jsbmb.2017.01.021

153) Orrù B, Szekeres-Bartho J, Bizzarri M, Spiga AM, Unfer V. Inhibitory effects of Vitamin D on inflammation and IL-6 release. A further support for COVID-19 management? Eur Rev Med Pharmacol Sci 2020; 24: 8187-8193.