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HEALTH SCIENCES

Vitamin D: a potentially important secosteroid for coping with COVID-19

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Abstract: COVID-19 is a disease that has caused a high number of deaths in the world, and despite being controlled, it requires attention and the search for new quick and economical therapeutic strategies. In this sense, vitamin D stands out, an immunomodulator that has shown beneficial effects in decreasing the risk and severity of acute respiratory tract infections, including COVID-19. Therefore, this review presents a number of experimental, observational and clinical studies on the importance of vitamin D against viral infections with an emphasis on COVID-19, highlighting the relationship between vitamin D, Renin-Angiotensin System and cytokine storms with decreased inflammatory lesions in patients with COVID-19. In addition, aspects of pathophysiology, metabolism, risk factors, sources and recommendations of vitamin D are described. We conclude that vitamin D plays a protective role against inflammatory lesions and can decrease the risk of infections and the severity of COVID-19. Therefore, it is essential to maintain adequate levels of vitamin D to avoid complications related to its deficiency.

Key words: COVID-19, fat-soluble vitamin, Renin-Angiotensin System, SARS-CoV-2.

INTRODUCTION

In the past five decades, several infectious diseases, including herpes and legionnaires in 1970, AIDS, Ebola, Zika, Severe Acute Respiratory Syndrome (SARS), and, recently, COVID-19, continue to threaten humans (Huremović 2019, Jones 2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), popularly known as COVID-19, started in Wuhan province in China in December 2019 and is a disease caused by the SARS-CoV-2 virus, a new member of the Coronaviridae family (Lu et al. 2020). However, only on March 11, 2020, did the World Health Organization (WHO) declared COVID-19 a global pandemic (WHO 2020). This is the third-largest epidemic of coronavirus (CoV) infections. Previous CoV epidemics include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), started in China in 2002 (Zhong et al. 2003), and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), first reported in 2012 in the Middle East (Assiri et al. 2013).

The spread of the new SARS-CoV-2 virus and COVID-19 disease continues at an accelerated pace. According to WHO data, 521,920,560 cases and 6,274,323 deaths were confirmed (WHO 2022). Given these numbers, saving lives, and reducing the world pandemic are of extreme importance for the general population.

The characteristics of this disease include fever, dry cough, dyspnea, myalgia, and fatigue. A small number of patients also experience sputum, headaches, hemoptysis, and diarrhea. In addition, patients commonly have leukopenia and lymphopenia (Huang et al. 2020a). These symptoms can gradually progress to severe

manifestations, such as lethal Acute Respiratory Distress Syndrome (ARDS).

Therefore, alternative solutions to prevent progression, and severity of this disease are important. The focus on the use of existing drugs in an attempt to obtain a faster therapeutic option may be an alternative to mitigate the harmful effects of COVID-19. Different drugs have been reported, including: Lopinavir-Ritonavir (Cao et al. 2020), Remdesivir (Wang et al. 2020b), Hydroxychloroquine (Horby et al. 2020a), Tocilizumab (Guaraldi et al. 2020), Arbidol (Zhu et al. 2020), Ivermectin (Caly et al. 2020) e Dexamethasone (Horby et al. 2020b). However, contraindications have been reported and the use of these drugs is not a definitive therapy.

In addition to these attempts, vitamin D supplementation in patients with COVID-19 was associated with lower disease severe and improved clinical status of hospitalized patients (Annweiler et al. 2020, Castillo et al. 2020). However, little is known about the definitive role of vitamin D in preventing COVID-19 infection and fatality. In this sense, this article proposes a review of the general aspects of vitamin D, highlighting its possible role against the COVID-19.

Vitamin D: fundamental concepts, pathophysiology, and importance for the organism

Vitamin D is a fat-soluble secosteroid that exists in two main forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). These structures differ chemically only in the side chain, where vitamin D2 has a double bond between carbon atoms C-22 and C-23, in addition to a methyl group (CH_3) on carbon C-24, unlike vitamin D3 (Figure 1). Vitamin D3 is produced in the skin from the cholesterol derivative 7-Dehydrocholesterol (7-DHC) during exposure to sunlight (UVB radiation 285-315 nm) (Lehmann et al. 2001), whereas the

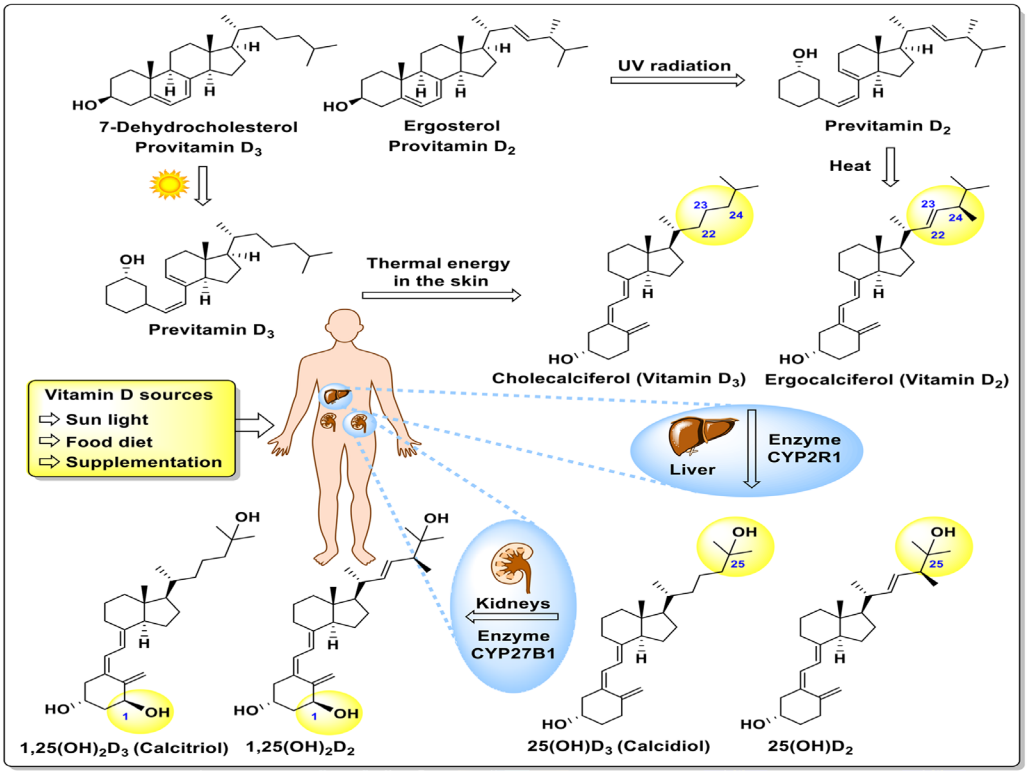

Figure 1. Metabolism of vitamin D2 and vitamin D3.

vitamin D2 isomer is produced by UVB radiation in plants and fungi from ergosterol (Boland et al. 2003).

Humans obtain vitamin D from three sources: from UVB radiation, from the diet, or through supplementation (Holick 2007). The D2 and D3 forms of vitamin D are inactive in a biological environment and their active forms are formed from a sequence of enzymatic hydroxylation reactions. Initially, vitamin D (D2 and D3) is transported in the blood mainly by a vitamin D binding glycoprotein (DBP) until it reaches the liver, where the enzyme CYP2R1 promotes a hydroxylation at C-25 carbon atoms, giving rise to the pre-hormones 25-hydroxyvitamin D2 (25(OH)D2) and 25-hydroxyvitamin D3 [25(OH) D3 (calcidiol)], respectively. Subsequently, when these prehormones reach the kidney, they undergo a second hydroxylation at C-1 carbon atoms through the enzyme CYP27B1, leading to the biologically active hormones 1α,25-dihydroxyvitamin D2 (1,25(OH)2D2) and 1α,25-dihydroxyvitamin D3 [1,25(OH)2D3 (calcitriol)], respectively (Figure 1) (Bikle & Christakos 2020). It is important to highlight that in the blood of normal individuals, about 85% of circulating vitamin D metabolites are bound to DBP. Albumin binds about 15% of these metabolites and does so with much lower affinity. Approximately 0.4% of total 1,25(OH)2D3 and 0.03% of total 25OHD3 are free in serum from normal individuals (Bikle & Schwartz 2019).

Free vitamin D diffuses through the plasma membrane and binds to the vitamin D receptor (VDR) in the cell nucleus, where the complex formed between vitamin D and VDR interacts with the vitamin D response elements in the genome. Vitamin D, through its active metabolites, affects the transcription of several genes, including the genes responsible for cell proliferation, differentiation, and apoptosis (Pike et al. 2016).

The active compounds of vitamin D, mainly calcitriol, are best known for their effects on calcium and phosphate absorption, activation of osteoclasts, and, therefore, on bone calcification and muscle strength (Bikle 2012). However, vitamin D receptors are widely expressed and the tissues with the highest VDR content are the intestine, kidney, parathyroid gland, and bone, all associated with the maintenance of calcium homeostasis (Wang et al. 2012). Vitamin D receptors are also expressed by immune cells, where inactive forms of vitamin D are metabolized to their active forms, indicating a regulatory role for vitamin D in the innate immune system (immediate "nonspecific" response to pathogens) and adaptive (response specific to the antigen that follows the innate immune response) (Di Rosa et al. 2011).

Vitamin D is a known regulator of innate immunity modulating the function of monocytes/macrophages and dendritic cells in response to infections. Therefore, vitamin D leads to the expression of several genes, mainly including the microbial proteins cathelicidin (CAMP) and β-defensin 2 (DEFB4) (Gombart et al. 2005, Wang et al. 2005). It increases the chemotaxis and the phagocytic capabilities of innate immune cells. (Gauzzi et al. 2005, Xu et al. 1993). Additionally, vitamin D promotes an anti-inflammatory response by inhibiting the maturation of dendritic cells, negatively regulating antigen-presenting molecules (MHC-class II), co-stimulatory molecules (CD1a, CD14, CD40, CD80 and CD86) and pro-inflammatory cytokines (IL-12 and IL-23, IL-6 TNFα), while increasing the production of anti-inflammatory cytokine (IL-10 and TGFβ) and regulatory T cells (Treg) (Almerighi et al. 2009, Pedersen et al. 2009, Quraishi et al. 2015, Unger et al. 2009). Vitamin D also acts on the adaptive immune system by modulating the function of CD4 + T cell and B cell in response to infections. Thus, vitamin D

reduces the proliferation of auxiliary T cells of the Th1/Th17 type, inhibiting the production of inflammatory cytokines including IL-2, IFNγ, IL-17 and IL-22, in addition to increasing the anti-inflammatory cytokines associated with Th2 cells (IL-5, IL-10, IL-4, IL-13) (Alroy et al. 1995, Jeffery et al. 2009, Joshi et al. 2011, Lemire et al. 1985). Vitamin D also acts on B cells, causing apoptosis, differentiation of impaired plasma cells, inhibition of the formation of memory B cells and increased production of IL-10 (Terrier et al. 2012). Figure 2 summarizes the main effects of vitamin D on the innate and adaptive immune system. Additional details can be found in the works of Chirumbolo et al. (2017), Chun et al. (2014), Sassi et al. (2018) and Jiménez-Sousa et al. (2018).

The discovery of the expression of nuclear vitamin D receptors and metabolic vitamin D enzymes in immune cells provides a scientific explanation for the potential role of vitamin D in maintaining immune homeostasis and preventing the development of autoimmune processes (Vanherwegen et al. 2017). Although vitamin D has been recognized mainly for bone metabolism, growing evidence indicates its proper function for almost all tissues in the body, including the brain, heart, lung, muscle, immune system, and skin (Mostafa & Hegazy 2015). Therefore, vitamin D hormones have important functions, including immunomodulating, anti-inflammatory, and anti-infectious roles, performing important role in the immune system that are highly relevant to response to different pathogens.

Risks associated with vitamin D deficiency

The most accurate way to quantify vitamin D in the body is through biochemical tests that measure the levels of prehormones 25(HO)D2 and 25(HO)D3 produced by liver hydroxylation of vitamin D from the skin or intestine by ingestion of oral food or supplementation. The clinical advantages of these metabolic forms as

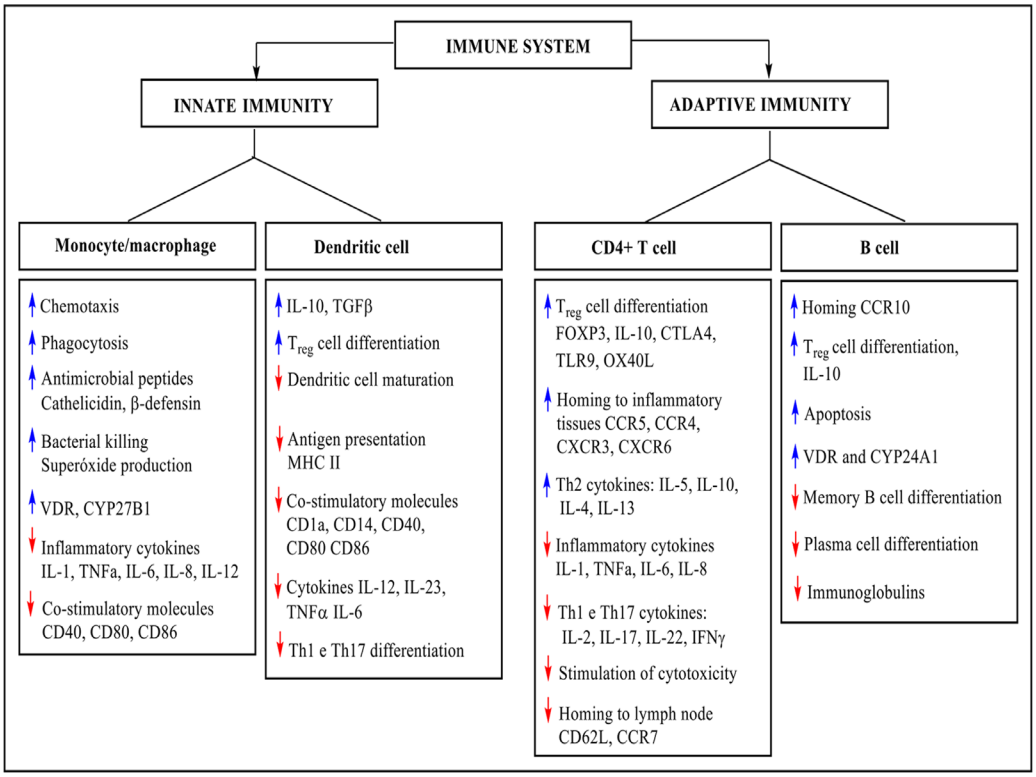

Figure 2. Summary of the main effects of vitamin D on the innate and adaptive system. Adapted from Jiménez-Sousa et al. (2018).

markers of vitamin D status can be attributed to these metabolites being in higher concentration than all other vitamin D metabolites, their levels remaining stable for almost two weeks and, in addition, it is believed that vitamin D toxicity is a function of these pre-hormones (Rajasree et al. 2001).

It is important to note that there are at least three biological limitations impeding the achievement of a robust result in for determining vitamin D; these are represented by the hydrophobic nature of the compound with the tight binding to its carrier (vitamin D binding protein (DBP)), the different forms circulating in blood, and the issue of standardization. Furthermore, endogenous lipids may affect binding and chromatographic separation, as they co-extract from plasma and serum (Romagnoli et al. 2013). Despite these limitations, the measurement of vitamin D levels is mainly carried out using two methodologies: i) competitive immunoassays, such as competitive protein-binding assays or radioimmunoassay (RIA), which do not differentiate between the 25(OH)D2 prehormones and 25(OH)D3; and ii) tests using high-performance liquid chromatography (HPLC) and direct detection with liquid chromatography coupled with mass spectrometry (LC/MS) which are highly sensitive and allow independent quantification of 25(OH) D2 and 25(OH)D3 (Holick 2009, Hollis 2010).

Different studies classify vitamin D levels, which are usually expressed in nanograms per milliliter (ng/mL) or nanomole per liter (nmol/L). Although there are some variations in these quantities and their classifications in different studies in the literature (Chang & Lee 2019, Holick & Chen 2008, Holick et al. 2011, Lips et al. 2019, Norman & Bouillon 2010), the classification found in Table I is the most common (Alshahrani & Aljohani 2013). Thus, we consider that a value less than 20 ng/mL of 25[OH]D corresponds to vitamin D deficiency.

Table I. Classification of vitamin D levels in the body.

Level 25[OH]D (ng/mL)	Level 25[OH]D (nmol/mL)	Classification
<20	<50	Deficiency
20-32	50-80	Insufficiency
54-90	135-225	Normal in sunny countries
>100	>250	Excess
>150	>325	Intoxication

Several risk factors contribute to vitamin D deficiency, including lack of adequate sun exposure (UVB) (Van der Mei et al. 2007), dark skin (Clemens et al. 1982), smoking (Brot et al. 1999), living with air pollution (Agarwal et al. 2002), winter, living in higher latitudes (Huotari & Herzig 2008), and malabsorption syndromes (Dedeoglu et al. 2014). Also, some pharmaceutical drugs activate the pregnane X receptor (PXR), reducing serum concentrations of vitamin D in the prehormonal form (Pascussi et al. 2005, Gröber 2020).

Since vitamin D has receptors in most types of tissue cells, regulating various biological pathways, vitamin D deficiency is associated with an increased risk of chronic diseases, including autoimmune diseases (Dankers et al. 2017), various types of cancers (Weinstein et al. 2015), cardiovascular diseases (Wang et al. 2008), infectious diseases (Gois et al. 2017), dementia and Alzheimer's (Chai et al. 2019), schizophrenia (Yüksel et al. 2014), myopia (Yazar et al. 2014), osteoporosis (Shahnazari et al. 2019), rickets (Thacher et al. 2006) and type 2 diabetes (Mattila et al. 2007).

It is important to mention that vitamin D deficiency (<20 ng/mL) is a public health problem that affects more than one billion people worldwide, with 50% of the population

having vitamin D insufficiency (<30 ng/mL) (Holick 2010). Therefore, maintaining adequate levels of vitamin D in the body, either through exposure to solar radiation, a balanced diet, or through supplementation is essential to maintain the proper functioning of the body.

Sources of vitamin D and daily needs

The daily requirement for vitamin D is estimated between 5 and 20 micrograms, depending on age and physiological status. Ultraviolet radiation (UVB) is the main source of vitamin D, providing about 80% in the form of vitamin D3 (cholecalciferol) in healthy individuals up to 65 years of age. The rest is obtained from the diet or supplementation (Biesalski 2020). However, with increasing age, the production of vitamin D in the skin, and the serum concentrations of 1α,25-dihydroxyvitamin D decrease considerably (McLaughlin & Holick 1985).

Several government agencies have established recommendations on the daily requirement for vitamin D based on different target populations. A detailed list involving recommendations in different countries was published by Bouillon (2017). An update of these recommendations was made available by Roth et al. (2018) involving the main organizations. Table II summarizes the recommendations for vitamin D intake by age group.

It is not easy to get daily necessities from diet alone, as few foods contain vitamin D. Foods like salmon and other oily fish, cod liver oil, egg yolk, milk, and sun-dried mushrooms are the main natural sources of vitamin D (Schmid & Walther 2013). The concentration in these foods is low and generally does not meet the daily requirement. However, the enrichment or fortification of staple foods with vitamin D, including mainly dairy products and flour products, can significantly increase their concentration (Pilz et al. 2018). Figure 3 shows the main sources of vitamin D and their quantities in international units (IU).

Evidence that vitamin D may be associated with a lower risk and severity of viral infections

In addition to the benefits of vitamin D for homeostasis, several *in vitro* and *in vivo* studies, including clinical trials of vitamin D supplementation, have extensively shown the characteristics of vitamin D against different respiratory viruses, such as respiratory

Table II. Recommendations for vitamin D intake by age group. Adapted from Roth et al. (2018).

Organization	Recommended [25(OH)D] level	Babies (<1 year)	Children	Teenagers	Adults	Pregnancy and lactation	Seniors
(WHO), 2016	27 nmol/L	5 µg/day[a]	5 µg/day[a]	5 µg/day[a]	5 µg/day[a]	5 µg/day[a]	10 µg/day[a] (51-65 years)15 µg/day[a] (+65 years)
(IOM), 2011	50 nmol/L	10 µg/day[b]	15 µg/day[c]	15 µg/day[c]	15 µg/day[c]	15 µg/day[c]	20 µg/day[c]
(SACN), 2016	25 nmol/L	8,5-10 µg/day[d]	10 µg/day[a]	10 µg/day[a]	10 µg/day[a]	10 µg/day[a]	10 µg/day[a]
(EFSA), 2016	50 nmol/L	10 µg/day[b]	15 µg/day[b]	15 µg/day[b]	15 µg/day[b]	15 µg/day[b]	15 µg/day[b]

[a]Recommended Nutrient Intake (RNI); [b]Adequate Intake (AI); [c]Recommended Dietary Allowance (RDA); [d]Safe Intakes (SI); WHO (World Health Organization); IOM (Institute of Medicine); SACN (Scientific Advisory Committee on Nutrition); EFSA (European Food Safety Authority).

syncytial virus (RSV) (Halasa et al. 2015), human metapneumovirus (hMPV) (Hurwitz et al. 2017), human rhinovirus (HRV) (Schögler et al. 2015), influenza A (Urashima et al. 2010), influenza H9N2 (Gui et al. 2017), influenza H5N1 (Huang et al. 2020b), and COVID-19 (Annweiler et al. 2020, Castillo et al. 2020), in addition hepatitis C (Gal-Tanamy et al. 2011), rotavirus (Zhao et al. 2019), human immunodeficiency virus (HIV) and *M. tuberculosis* (Campbell & Spector 2012), herpesvirus (Kumar et al. 2018) and dengue virus (Martinez-Moreno et al. 2020).

Although vitamin D has beneficial effects on various viral infections, Lee (2020) highlights, in his extensive review about the role of vitamin D in the progression of viral diseases, that there are some inconsistent and, in some cases, contradictory results. In the case of acute respiratory tract infections, some studies have suggested that vitamin D supplementation does not prevent respiratory tract infection and can be harmful, especially for those who are not vitamin D deficient and/or those receiving bolus doses (Lehouck et al. 2012, Manaseki-Holland et al. 2012, Remmelts et al. 2013).

On the other hand, population-based studies show positive associations between circulating vitamin D concentrations and lung function (Craveiro et al. 2018). In addition, a recent meta-analysis concluded that serum vitamin D levels are inversely associated with the risk and severity of acute respiratory infections,

Natural sources	Portion	Vitamin D content
Bovine liver	(1 kg)	32-344 UI (D_2 and/or D_3)
Beef[a]	(1 kg)	20-920 UI (D_2 and/or D_3)
Pig meat[a]	(1 kg)	20-2760 UI (D_2 and/or D_3)
Swine liver	(1 kg)	160-500 UI (D_2 and/or D_3)
Lamb meat[a]	(1 kg)	12-480 UI (D_2 and/or D_3)
Chicken	(1 kg)	80-120 UI (D_2 and/or D_3)
Turkey	(1 kg)	40 UI (D_2 and/or D_3)
Domestic duck	(1 kg)	930 UI (D_2 and/or D_3)
Fresh wild salmon	(99,2 g)	600-1000 UI (D_3)
Fresh farmed salmon	(99,2 g)	100-250 UI (D_2 ou D_3)
Canned salmon	(99,2 g)	300-600 UI (D_3)
Canned sardines	(99,2 g)	300 UI (D_3)
Canned mackerel	(99,2 g)	250 UI (D_3)
Canned tuna	(102,1 g)	230 UI (D_3)
Cod liver oil	(5 mL)	400-1000 UI (D_3)
Fresh shitake mushrooms	(99,2 g)	100 UI (D_2)
Sun dried shitake mushrooms	(99,2 g)	1600 UI (D_2)
Egg yolk	1 unity	20 UI (D_2 or D_3)
Sun light[b]	5-10 min.	3000 UI (D_3)

Fortified foods	Portion	Vitamin D content
Milk	(250 mL)	100-200 UI (D_3)
Orange juice	(226,8 g)	100 UI (D_3)
Infant formulas	(226,8 g)	100 UI (D_3)
Yogurt	(226,8 g)	100 UI (D_3)
Butter	(99,2 g)	50 UI (D_3)
Margarine	(99,2 g)	430 UI (D_3)
Cheese	(85 g)	100 UI (D_3)
Cereals	(100-150 g)	40-100 UI (D_3)
Milk (soy, oats or almonds)	(250 mL)	60-120 UI (D_3)
Bread	(250 g)	90 UI (D_3)

Supplements	Portion	Vitamin D content
Vitamin D_2	(1 capsule)	50.000 UI
Drisdol	(1mL)	8.000 UI (D_2)
Multivitamin	(1 capsule)	400 UI (D_2 or D_3)
Vitamin D_3	-	400 - 50.000 IU

Note: If the product label indicates calciferol, it refers to vitamin D_2; if it indicates cholecalciferol it indicates that the product contains vitamin D_3.

[a]It varies according to the type of meat (Schmid & Walther 2013).

[b]It depends on the time of day, season, latitude, pigmentation and skin sensitivity, space of skin exposed directly to direct sunlight (Holick 2007).

Figure 3. Main sources of vitamin D. Adapted from Holick (2007) and Schmid & Walther (2013).

indicating that hypovitaminosis D is a risk factor for respiratory infections (Pham et al. 2019). Another meta-analysis included randomized, double-blind, placebo-controlled clinical trials in which patients were supplemented with vitamin D3 or D2, and the effectiveness of the incidence of acute respiratory infections was verified. The study gathered 25 clinical trials with a total of 11,321 patients from 0 to 95 years of age. It was concluded that the administration of vitamin D daily or weekly was able to reduce the risk of acute respiratory infections among all patients. In addition, the authors concluded that the protective effects of vitamin D have better effects in patients who had precisely baseline levels of vitamin D <10 ng/mL (Martineau et al. 2017).

Vitamin D can reduce the risk of respiratory infections in three main ways: physical barrier, natural cellular immunity and adaptive immunity (Rondanelli et al. 2018). In this way, studies have shown that immunomodulatory properties, which include negative regulation of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines, are the main route to mitigate the risk and severity of acute respiratory tract infections (Kong et al. 2013, Tsujino et al. 2019).

The active vitamin D-generating enzyme, 1α-hydroxylase (CYP27B1), is expressed by the airway epithelium, alveolar macrophages, dendritic cells, and lymphocytes, indicating that active vitamin D can be produced locally within the lungs. The effects of vitamin D in the lungs include increased secretion of the antimicrobial peptide cathelicidin, decreased production of chemokines (pro-inflammatory cytokines), inhibition of dendritic cell activation, and alteration of T cell activation (Hansdottir & Monick 2011). These cellular effects are important for the host's responses to infections. The secretion of cathelicidins is one of the most important pathophysiological events, as these peptides have a direct antimicrobial effect against gram-positive and gram-negative bacteria, fungi, non-enveloped and enveloped viruses, such as the coronavirus (Herr et al. 2007).

Vitamin D can also reduce viral transmission and decrease lung damage by modulating the Renin-Angiotensin System (Yuan et al. 2007). In this sense, recent studies involving the administration of calcitriol in rats have shown that the clinical characteristics and the pathological changes of the lung tissues were notably lighter than the controls. It was noted that calcitriol in rats with lung injury decreased the concentration of angiotensin-converting enzyme (ACE) and the ACE/ACE2 ratio, in addition to increasing the concentration of angiotensin-converting enzyme II (ACE2) (Lin et al. 2016, Yang et al. 2016). An important study reported by Xu et al. (2017) demonstrated that, in animal models with an acute respiratory syndrome, pretreatment with vitamin D reduced the transmission of the virus to the lungs by modulating the activity of the Renin-Angiotensin System and expression of ACE2. In that study, rats supplemented with vitamin D exhibited milder symptoms of the acute respiratory syndrome and moderate lung changes compared to controls. Cui et al. (2019) reported that calcitriol suppressed the angiotensin II receptor type 1 (AT1) and ACE and reduced the formation of angiotensin II in spontaneously hypertensive rats. According to these authors, ACE2 protects against acute lung injury and calcitriol has marked impacts on the ACE2/Ang-(1-7)/MAS axis with enhanced expression of ACE2.

Additionally, low serum vitamin D levels have been associated with acute respiratory tract infections (Ginde et al. 2009, Kuwabara et al. 2020). Other trials have shown that treatment with high doses of vitamin D (250,000

to 500,000 IU) is safe in adult patients on mechanical ventilation and in critical condition. This treatment was associated with a shorter hospital stay, improved blood capacity to carry oxygen, and increased hemoglobin levels (Han et al. 2016, Smith et al. 2018).

Structure of SARS-CoV-2 and its relationship to the Renin-Angiotensin System

Phylogenetic analyses of the coronavirus genomes revealed that SARS-CoV-2 belongs to the family Coronaviridae and is a member of the genus betacoronavirus. It is a single-stranded RNA virus, positive polarity, enveloped, and basically consisting of four structural proteins that perform different functions. The name coronavirus derives from the crown of tips, seen in electron microscopy images, consisting of a glycoprotein called spike, which has two domains. The S1 domain or receptor-binding domain (RBD) is responsible for recognizing the virus at the transmembrane ACE2 receptor, while the S2 domain is responsible for fusing the virus with cell membranes (Lu et al. 2020) (Figure 4). It is important to mention that SARS-CoV-2 enters the cell only when this virus binds to the transmembrane ACE2. The presence of soluble ACE2 can prevent the virus from binding to the transmembrane ACE2, preventing its entry into

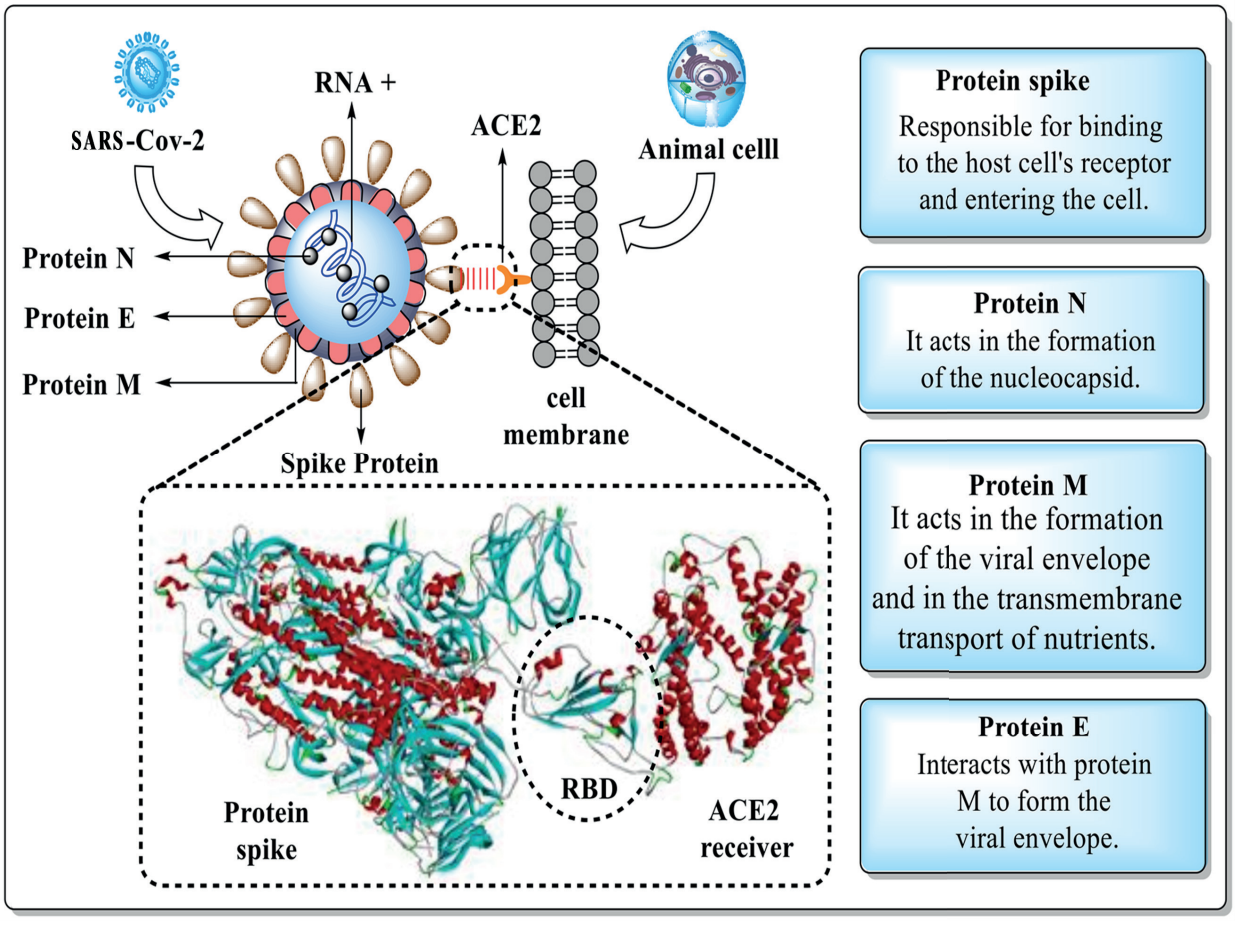

Figure 4. General structure of SARS-CoV-2 and its interaction with ACE2. The structure of the complex formed between the spike protein and its RBD domain with the ACE2 receptor was obtained from the protein database (PDB 2020), determined by Kirchdoerfer et al. (2018).

the cell and can also activate antibodies against this virus (Kruse 2020).

Angiotensin-converting enzyme 2 (ACE2) is part of the renin-angiotensin-aldosterone system, which is a regulatory system for body fluid homeostasis and inflammatory responses (Ocaranza et al. 2019). Briefly, the functioning of this system begins with the secretion of renin by renal juxtaglomerular cells. Renin converts angiotensinogen to angiotensin I (ang I), which is inactive, and by the action of the angiotensin-converting enzyme (ACE) is converted to angiotensin II (ang II). Angiotensin I can be converted to angiotensin 1-9 [(ang-(1-9)] via the enzyme ACE2. In turn, angiotensin 1-9 can be converted to angiotensin 1-7 [(ang-(1-7)] by the action of ACE enzymes and neutral endopeptidase (NEP). Also, angiotensin I can be converted directly into angiotensin 1-7 using the enzymes NEP and prolyl endopeptidase (PEP). Besides, angiotensin II can also be converted to angiotensin 1-7 by the action of ACE2 (Figure 5). When angiotensin II binds to its AT1-type receptor, in addition to vasoconstriction, a series of inflammatory effects occur, damaging tissues, including kidney, heart, and lung damage. On the other hand, when angiotensin 1-7 binds to its MAS receptor, it triggers opposite effects, such as vasodilation, anti-inflammatory, antifibrogenic, cardioprotective, nephroprotective, and protection against lung injuries (Gheblawi 2020, Kai & Kai 2020, Silva & Flynn 2012, Verdecchia et al. 2020).

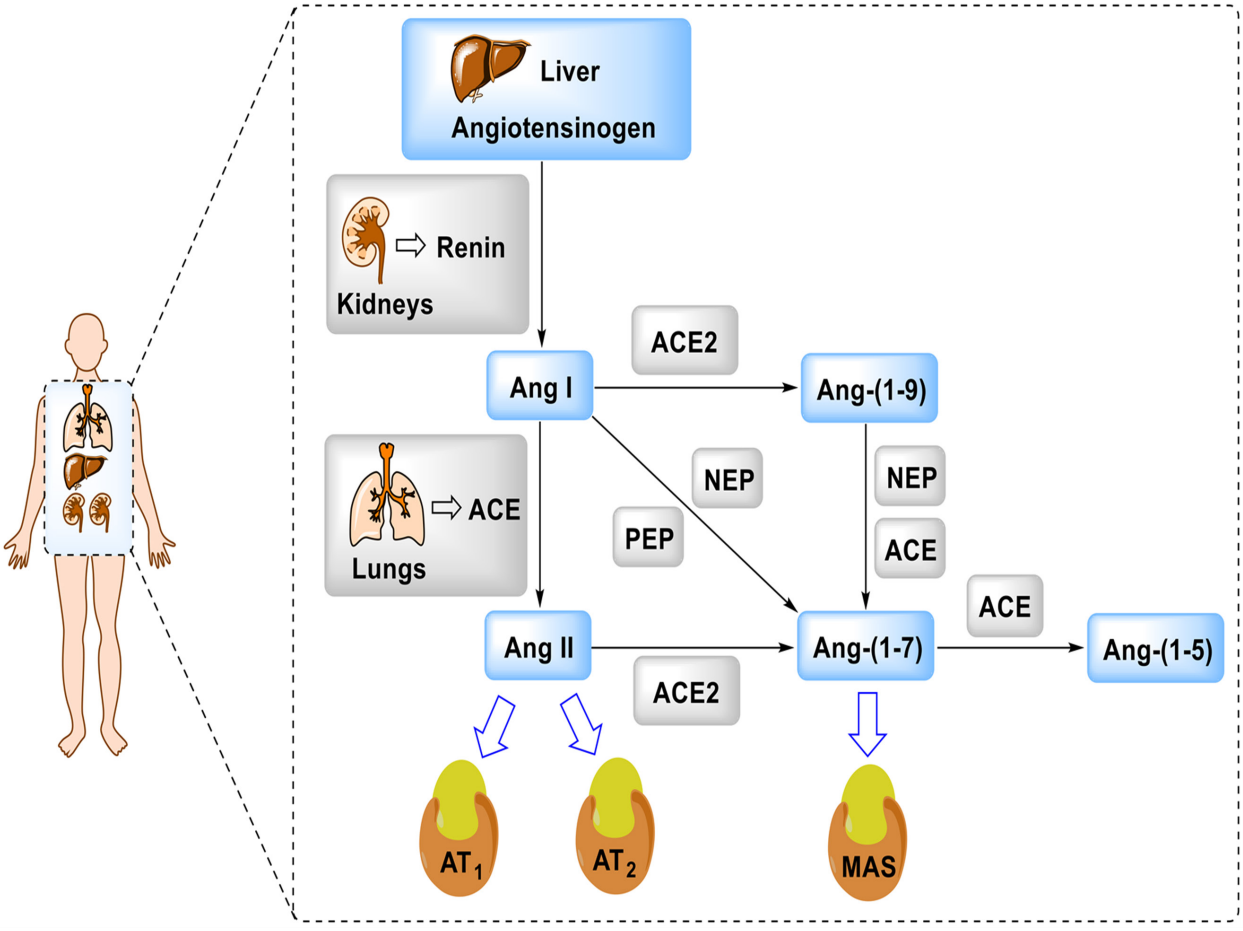

Figure 5. General overview of the renin-angiotensin system.

Once the virus binds to transmembrane ACE2, there is a decrease in the expression of this enzyme, including soluble ACE2, which is derived from transmembrane ACE2. Therefore, there is less conversion of angiotensin II to angiotensin 1-7, increasing lesions in various tissues/organs, and leading to greater severity of COVID-19 (Vaduganathan et al. 2020). In addition, as ACE2 is expressed in various tissues, including the epithelial cells of the lungs, intestines, kidneys, and blood vessels, therefore, these tissues/organs are vulnerable to infection by the new SARS-CoV-2 (Sungnak et al. 2020, Zou et al. 2020). Thus, the new coronavirus can be considered a systemic virus, leading to multiple organ dysfunction and not just a cause of respiratory diseases.

A potential adjuvant is vitamin D, since supplementation of hospitalized patients with COVID-19 has been associated and less disease severity (Annweiler et al. 2020, Castillo et al. 2020).

Possible action of vitamin D against SARS-CoV-2 and COVID-19

In general, when the SARS-CoV-2 virus is inhaled, it binds to the transmembrane ACE2 through its spike protein, forming a complex that is the target of transmembrane serine protease 2 (TMPRSS2). TMPRSS2 is responsible for activating the spike protein, resulting in the fusion of the virus with the cell membrane for entry of the viral RNA into the host cell, initiating its processes of replication, injury, and contamination of other cells (Hoffmann et al. 2020, Rabi et al. 2020).

In the early stages of viral infection, the protective immune response is responsible for eliminating the virus and, in most cases, patients recover without further complications. However, as the disease progresses and reaches the pulmonary alveoli, causing alveolar damage due to the release of proinflammatory cytokines, immune system cells are recruited to these sites, creating a fluid with a high content of serum proteins and leukocytes. At this stage, gas exchange is compromised, as well as all dependent processes. At this stage of inflammation, a dysfunctional immune response occurs that triggers the release of several cytokines, a process known as a "cytokine storm" (Tang et al. 2020).

Several studies have shown that the severity of COVID-19 is determined by the presence of pneumonia, severe acute respiratory distress syndrome, myocarditis, microvascular thrombosis, and/or cytokine storms. All involving underlying inflammation due to increased generation of pro-inflammatory cytokines (Wang et al. 2020a). In view of these lesions, the main defense against uncontrolled inflammation and viral infection, in general, is provided by the action of regulatory T lymphocytes (Tregs), but in patients with COVID-19, a common feature is a lymphopenia, making patients still most vulnerable (Chen & Wherry 2020, Yang et al. 2020). In addition, during the cytokine storm, patients infected with COVID-19 showed high concentrations of 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-γ inducible protein 10 (IP-10), macrophage inflammatory protein 1-α (MIP-1α), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and IFN-γ (Conti et al. 2020, Huang et al. 2020a).

A potentially important alternative pathway that can mitigate the severity of COVID-19 is vitamin D supplementation since studies have shown that vitamin D supplementation can increase Treg levels (Fisher et al. 2019, Prietl et al. 2014) and also mitigate the cytokine storm in patients with the respiratory syndrome (Khoo et al. 2011). Recently, vitamin D has been shown to regulate the response of auxiliary

CD4+ T lymphocytes to suppress the gene expression of pro-inflammatory cytokines, such as IFN-γ and IL-17, and in addition to inducing anti-inflammatory cytokines, such as IL-10, suppresses Th1 type cytokines and Th3 type cytokines, such as IL17A, IL17F, IL22 and IL26. (R. McGregor et al. unpublished data) Additionally, vitamin D decreases the generation of TNFα and nuclear factor-κB (NFκB) (Peterson & Heffernan 2008, Talmor et al. 2008), in addition to inhibiting the action of the inflammatory cytokine IL-2 (Provvedini et al. 1983, Tsoukas et al. 1984). Thus, vitamin D can mitigate the deleterious effects of the cytokine storm in patients with COVID-19.

It is also important to highlight that the Renin-Angiotensin System (RAS) is involved in the pathogenesis of COVID-19 and that vitamin D can play an important role against inflammatory lesions caused by hyperactivation of the Renin-Angiotensin System. Under normal RAS conditions, ACE2 is highly expressed in the lungs, in order to balance the higher levels of angiotensin II produced by ACE. Coronavirus studies have shown that viral replication can down-regulate ACE2 (Dijkman et al. 2012). A gradual depletion of ACE2 during the progression of SARS-CoV-2 infection can unbalance RAS and lead to its activation. It is important to note that RAS activation in pulmonary fibrosis can be induced by chronic vitamin D deficiency (Shi et al. 2017).

Low levels of vitamin D cause increased plasma renin activity, higher concentrations of angiotensin II and higher RAS activity, increasing inflammation, and damage to various organs (Forman et al. 2010). On the other hand, it has been shown that vitamin D suppresses renin activity, reduces the expression of ACE, reduces the production of angiotensin II, in addition to increasing the production of soluble ACE2, reducing inflammatory lesions (Lin et al. 2016, Xu et al. 2017). Therefore, vitamin D acts by negatively regulating RAS, modulating the expression of its components: renin, ACE, and ACE2. Vitamin D suppresses the transcription of the renin gene, blocking the activity of the cyclic AMP response element in the promoter of the renin gene and in the cascade ACE/Ang II/AT1 (Kong et al. 2013, Yuan et al. 2007), in addition to inducing activity of the axis ACE2/Ang-(1-7)/MAS (Xu et al. 2017). This leads, for example, to a decrease in pro-inflammatory cytokines and an increase in antiviral and antibacterial peptides, such as defensin β2 and cathelicidin (Mahdavi 2020). A graphical overview of these events can be seen in Figure 6. Therefore, a adjuvant therapeutic approach to address COVID-19 and induced ARDS is to target the unbalanced negative regulation of RAS and ACE2 with vitamin D in SARS-CoV-2 infection.

Aygun (2020) gathered important evidence that guides a possible role of vitamin D in coping with COVID-19 (Figure 7).

Evidence that vitamin D helps to combat COVID-19

A series of studies reported below indicate that vitamin D deficiency may be associated with greater severity of COVID-19 and that supplementation with vitamin D may mitigate the severity of this disease.

A study conducted at the Medical University of Chicago, from March 3 to April 10, 2020, sought to analyze whether deficiency and vitamin D treatment were associated with a positive test for COVID-19. That study included 489 patients with an average age of 49.2 ± 18.4 years and with vitamin D levels measured within 1 year before being tested for COVID-19. The relative risk of a positive test for COVID-19 was 1.77 times higher for patients with probable vitamin D deficiency (<20 ng/mL) compared to non-deficient patients (>20 ng/mL) of vitamin D (Meltzer et al. 2020).

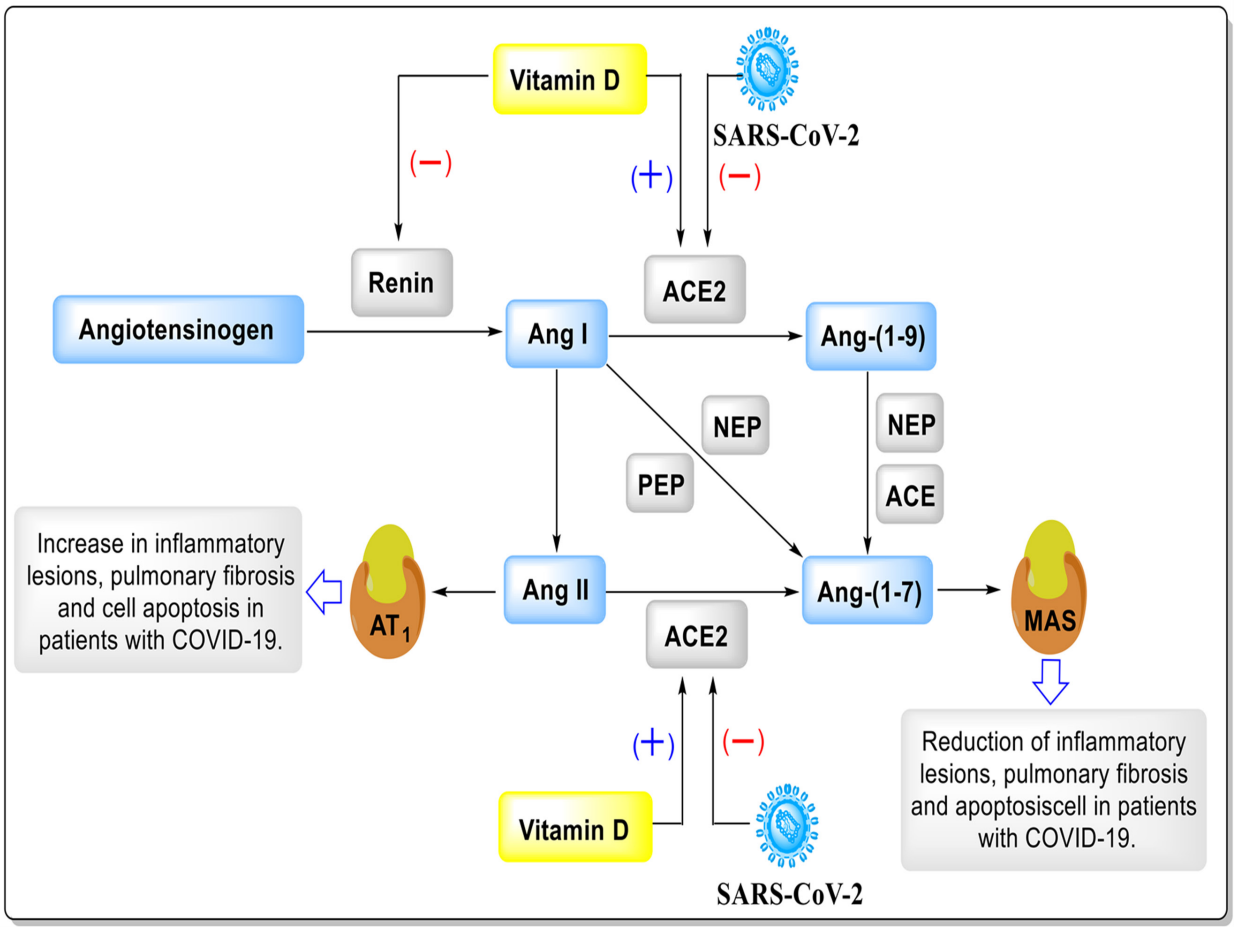

Figure 6. Possible action of vitamin D on RAS and COVID-19. Adapted from Mahdavi (2020).

In the study by F.H. Lau et al. (unpublished data), the medical records of patients with COVID-19 between March 27 to April 21, 2020, were reviewed retrospectively. 20 patients with identified serum vitamin D levels were included in the study, 13 of whom were admitted to the ICU. The prevalence of vitamin D insufficiency in patients in the ICU was 84.6%, against 57.1% in patients not admitted to the ICU. In addition, 100% of ICU patients under 75 years of age had insufficient vitamin D; 62.5% had coagulopathy and 92.3% were lymphocytopenic.

A Swiss retrospective study conducted by D'Avolio et al. (2020), between March 1 and April 14, 2020, assessed serum vitamin D levels in 107 patients with the acute respiratory syndrome and aged 63 to 81 years. Among these patients, those who tested positive for COVID-19 (27 patients) had low average levels of vitamin D (11.1 ng/mL), while patients who tested negative for COVID-19 (80 patients) had average vitamin D levels of 24.6 ng/mL.

Abrishami et al. (2020) evaluated the possible existence of an interaction between serum 25(OH)D concentrations and the extent of pulmonary involvement and clinical evolution in patients with COVID-19. Demographic and clinical data, serum levels of 25(OH)D and chest computed tomography were evaluated in 73 individuals with confirmed diagnosis of COVID-19. The average age of patients was 55.18 ± 14.98 years, where 46.4% were male. It was found

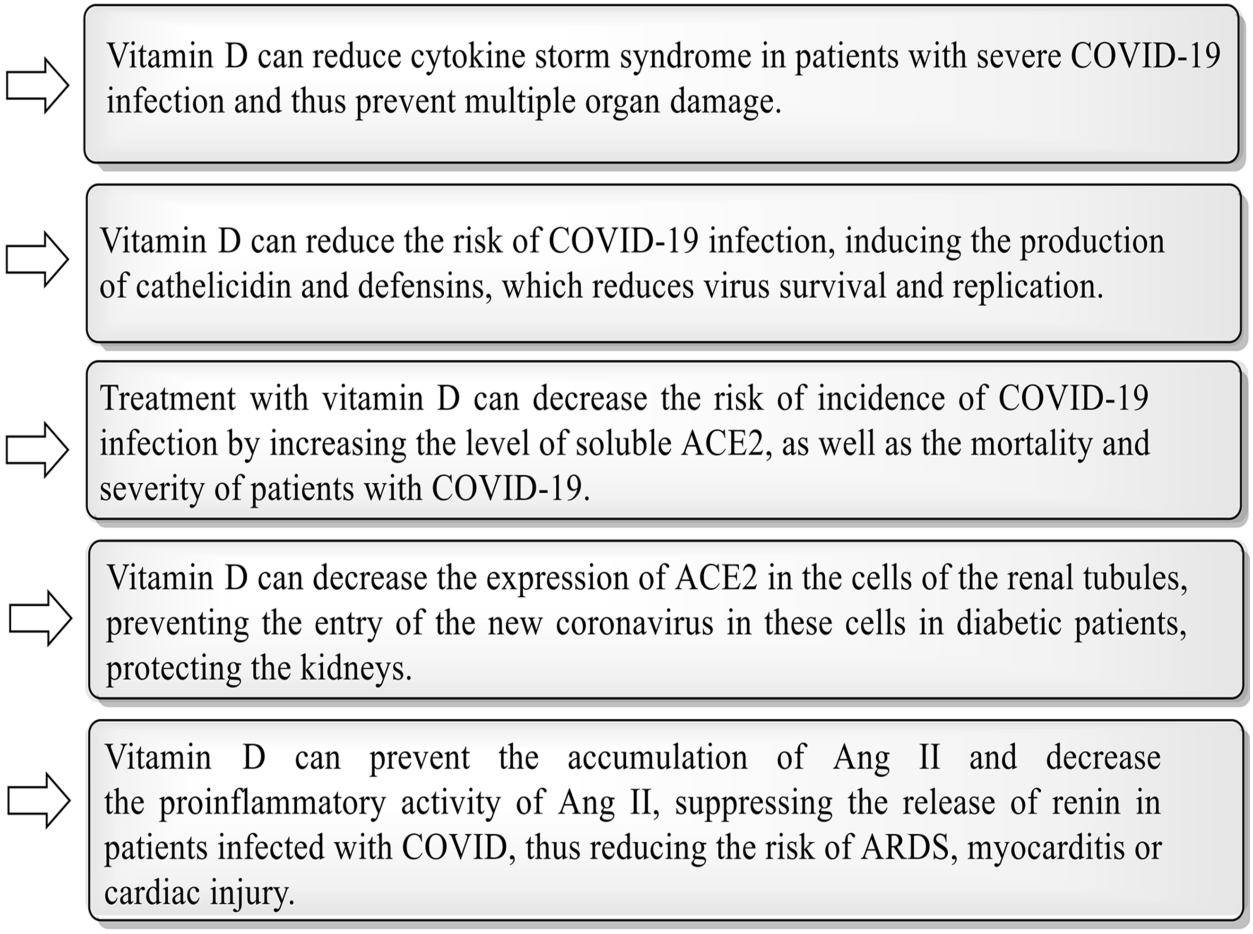

Figure 7. Possible role of vitamin D in face of COVID-19.

that the mean serum concentration of 25(OH)D was lower in patients who died (13.83 ± 12.53 ng/mL) compared to patients who were discharged (38.41 ± 18.51 ng/mL). In addition, higher levels of 25(OH)D were associated with less extent of lung involvement and less risk of death.

Ferrari & Locatelli (2020) retrospectively analyzed vitamin D levels in 347 patients admitted to a hospital in northern Italy with suspected COVID-19, with 128 positive and 219 negative for COVID-19. The average age of patients was 62.28 ± 17.40 years, where 57.7% were male. It was found that there was no significant difference in the average levels of vitamin D in the two groups: 21.8 ± 16.1 ng/mL and 22.8 ± 14.0 ng/mL for the positive and negative groups, respectively. Since most patients had vitamin D insufficiency (<30 ng/mL), it was concluded that vitamin D supplementation, restoring normal levels, could be beneficial in reducing the risk of infection.

In a population-based Israeli study conducted between February 1 to April 30, 2020, the association of plasma vitamin D level with the likelihood of coronavirus infection and hospitalization for COVID-19 was assessed. The study included 14,832 people, of whom 7,807 were tested positive for COVID-19. It was concluded that plasma levels of vitamin D below ideal (30 ng/mL) may be a potential risk factor for COVID-19 infection, particularly for the high risks of hospitalization (Merzon et al. 2020). However, in a similar study conducted in the United

Kingdom, no evidence was found to support a potential link between vitamin D concentrations and the risk of COVID-19 infection (Hastie et al. 2020). But, this latest study is limited by the use of historical vitamin D measurements from 2006 to 2010 and may not reflect vitamin D concentrations in the current pandemic. In addition, two ecological studies have reported inverse correlations between estimates of vitamin D level with COVID-19 incidence and mortality in a total of 21 countries in Europe (Ilie et al. 2019, Laird et al. 2020). Besides that, several recent reports have found an inverse correlation between vitamin D levels and COVID-19 severity and mortality (A. Daneshkhah et al. unpublished data, Darling et al. 2021, Jolliffe et al. 2021, Kara et al. 2020).

A systematic review and meta-analysis, described by Pereira et al. (2020), analyzed the association between vitamin D deficiency and COVID-19 severity, through an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease. Inclusion criteria were observational studies measuring serum vitamin D in adults and the elderly with COVID-19, with 27 studies selected. It was concluded that vitamin D deficiency was not associated with an increased chance of COVID-19 infection, but in severe cases of the disease, vitamin D levels were 64% lower compared to mild cases. In addition, an insufficiency of vitamin D concentration increased COVID-19 hospitalization and mortality.

No large well-designed randomized controlled trial (RCT) has tested the effect of vitamin D supplements on COVID-19 outcomes yet. However, in hospital-based quasi-experimental study described by Annweiler et al. (2020) 77 patients diagnosed with COVID-19 were divided into three groups: group 1 (29 patients, supplemented with vitamin D3 in the previous year); group 2 (16 patients, supplemented with vitamin D3 a few hours after the diagnosis of COVID-19) and group 3 (32 patients, not supplemented). In group 1, 93.1% of COVID-19 participants survived on the 14th day, compared with 81.2% of survivors in group 2 and 68.7% of survivors in group 3. It was concluded that vitamin D supplementation associated with COVID-19 decreased severity and increased survival in the elderly.

A pilot study was conducted to assess the clinical effectiveness of treating patients hospitalized for COVID-19 with calcifediol (25-hydroxyvitamin D3) in early stages of the disease. 76 patients were included in the study, 26 without treatment with calcifediol and 50 received treatment with calcifediol. Among the 26 patients not treated with calcifediol, 13 required admission to the ICU (50%), while of the 50 patients treated with calcifediol only 1 requested admission to the ICU, while the other patients remained in conventional admission. Of the patients treated with calcifediol, none died and all were discharged without complications, while of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged. It was concluded that the administration of calcifediol can improve the clinical outcome of individuals who require hospitalization for COVID-19 (Castillo et al. 2020).

It is important to highlight that, at the present moment, 45 clinical studies are underway in different regions of the world on the relationship between vitamin D and COVID-19. Such studies were recorded in the ClinicalTrials.gov (2020) database, where different aspects of vitamin D in coping with COVID-19 are being analyzed.

Despite these advances, Martineau & Forouhi (2020) highlight that vitamin D supplementation can be challenge in critically ill patients with COVID-19 for two reasons. The first is that patients tend to come to the hospital

in the hyperinflammatory stage of the disease. Therefore, it may be too late for them to benefit from any antiviral effects induced by vitamin D supplementation. The other reason is that it may be difficult to show anti-inflammatory effects of vitamin D superior to dexamethasone, a glucocorticoid that has potent anti-inflammatory effects against severe cases of COVID-19.

Recommendations

Vitamin D deficiency and insufficiency are recognized as a public health problem, affecting many people around the world. In the current COVID-19 pandemic, social isolation measures have led people to adopt a new lifestyle, spending most of their time indoors with limited access to sunlight, which is the main natural source of vitamin D. Thus, due to the importance of vitamin D to the body and its role in helping viral diseases, especially in respiratory infections and possibly in the current COVID-19, it is essential to maintain adequate levels of vitamin D to avoid complications related to its deficiency.

Thus, safe exposure to sunlight is one of the first steps to increase vitamin D levels through dermal synthesis. In pandemic times, this can be done without leaving the house, in the garden, or on the balcony, with short and daily exposures. In order for the dermal synthesis to be efficient, the radiation must directly affect the skin (Webb & Engelsen 2006, Webb 2006). A nutritionally balanced diet is also important, including foods rich in vitamin D (Figure 3).

Adequate supplementation is an important option for rapidly increasing vitamin D levels and possibly mitigating the risk of infection and the severity of COVID-19 in the general population, especially in individuals positive for SARS-CoV-2 and professionals in the front line, who live in hospital environments with a high risk of infection. In this sense Grant et al. (2020) emphasize that hospitals are potentially infectious environments and recommend that during the COVID-19 epidemic, everyone in the hospital environment, including patients and staff, should take vitamin D supplements to increase its concentrations [40-50 ng/mL (100-125 nmol/L)] as an important step in preventing infection and spread. Recently, a pragmatic protocol performed in an Italian hospital on patients with COVID-19, suggested that patients with a vitamin D deficit <20 ng/mL should receive 50,000 IU/weekly, while patients with a deficit between 20 to <30 ng/mL should take 25,000 IU/weekly (Caccialanza et al. 2020).

It is important to mention that magnesium supplementation is recommended when taking vitamin D supplements. Magnesium helps to activate vitamin D since all enzymes that metabolize vitamin D seem to require magnesium, which acts as a cofactor in enzymatic reactions in the liver and kidneys. The recommended daily allowance of magnesium for adults is 310 to 420 mg/d (Uwitonze & Razzaque 2018).

Lanham-New et al. (2020) report that the UK Scientific Advisory Committee (SACN), the US Institute of Medicine (IOM), and the European Union's European Food Safety Authority (EFSA) recommend that intake of vitamin D (total sum of food and supplements) should be limited to 4000 IU/day (100 µg/day) for adults. The authors also emphasize that there is a broad international consensus that the general public should avoid high-dose supplementation. Likewise, Hedlund et al. (2020) suggest that vitamin D supplementation (400-4000 IU) is a safe intervention with great potential to reduce morbidity during the flu season and in the current COVID-9 pandemic. In addition, a meta-analysis study concluded that the effectiveness of vitamin D supplements in preventing acute respiratory tract infections was best demonstrated with the ingestion of low doses, to the detriment of the

administration of large doses (Martineau et al. 2017). However, a clinical study reported that taking vitamin D supplementation from 4,000 to 10,000 IU/day for 6 weeks increases the baseline serum vitamin D concentration by 2 to 3 times, respectively, without adverse health effects (Charoenngam et al. 2020). Similarly, clinical studies of vitamin D supplementation in high doses, including 4,000-10,000 IU/day and 5,000-10,000 IU/day (McCullough et al. 2019) have shown no adverse effects. However, these last two studies were carried out in patients who did not have infection with the new coronavirus.

Liu et al. (2020) speculate that in patients with vitamin D deficiency or insufficiency, a single dose of 300,000 IU of vitamin D may play a role in the prevention and treatment of COVID-19. According to the authors, four weeks after administration, the serum concentration of 25(OH)D can be increased to about 60 ng/mL, and all patients have normal blood calcium levels.

However, while more data related to the effectiveness of vitamin D on COVID-19 is available, Trovas & Tournis (2020) recommend that the general population should take a daily supplement containing 800 to 1000 IU, which can confer a benefit and certainly cause no harm.

CONCLUSIONS

In this review we gathered an extensive set of information about vitamin D, highlighting its possible role against COVID-19. Several studies indicate that there is solid evidence that vitamin D acts in the regulation of the immune system and that hypovitaminosis D has an inverse relationship with acute respiratory infections and its greater severity. Besides, most of the studies indicate that the serum deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) of vitamin D are associated with an increased risk of acute respiratory tract infections, including COVID-19 and supplementation for those with deficiency/insufficiency can improve the clinical picture of these diseases.

Vitamin D can reduce cytokine storm syndrome in patients with severe COVID-19 infection; induces the production of cathelicidin and defensins, which reduces the survival and replication of the virus; increases the level of soluble ACE2, reducing the virus from entering the cells; prevents the accumulation of angiotensin II and decrease its pro-inflammatory activity, suppressing the release of renin. Therefore, vitamin D can reduce the risk of injury to various tissues/organs, as well as the mortality and severity of patients with COVID-19.

In this sense, prophylaxis with vitamin D can reasonably serve as a highly accessible, natural, and economical adjuvant therapy to improve the immune response of patients, decrease the risk of infection by SARS-CoV-2 and improve the inflammatory lesions associated with COVID-19. Therefore, vitamin D prophylaxis can mitigate dependence on the use of antivirals, reduce hospitalizations and health costs, in addition to significantly improving quality of life, since hypovitaminosis D is associated with several pathologies. However, there is still no consensus on the adequate dose of vitamin D that can mitigate the severity of this disease. This may be associated with the heterogeneity of the affected populations and the risk factors that lead to greater vitamin D deficiency.

Although vitamin D's role on COVID-19 is not yet fully understood and clinical studies are scarce, we believe that vitamin D supplementation, without overdosing, as part of standard nutrition can be effective in providing clinical benefit. In addition, it is essential to maintain adequate levels of vitamin D in the general population.

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