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MINI-REVIEW ARTICLE

Vitamin D and its Possible Relationship to Neuroprotection in COVID-19: Evidence in the Literature

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Abstract: Vitamin D is a hormone involved in the regulation of important biological processes such as signal transduction, immune response, metabolic regulation and also in the nervous and vascular systems. To date, coronavirus disease 2019 (COVID-19) infection does not have a specific treatment. However, various drugs have been proposed, including those that attenuate the intense inflammatory response, and recently, the use of vitamin D, in clinical trials, as part of the treatment of COVID-19 has provided promising results. It has been observed in some clinical studies that the use of cholecalciferol (vitamin D3) and its two metabolites the circulating form, calcidiol or calcifediol (25-hydroxycalciferol, 25-(OH)-D), and the active form, calcitriol (1,25-(OH)2-D), in different doses, improve the clinical manifestations, prognosis, and survival of patients infected with COVID-19 probably because of its anti-inflammatory, antiviral and lung-protective action. In relation to the central nervous system (CNS) it has been shown, in clinical studies, that vitamin D is beneficial in some neurological and psychiatric conditions because of its anti-inflammatory and antioxidant properties, modulation of neurotransmitters actions, and regulation of calcium homeostasis between other mechanisms. It has been shown that COVID-19 infection induces CNS complications such as headache, anosmia, ageusia, neuropathy, encephalitis, stroke, thrombosis, cerebral hemorrhages, cytotoxic lesions, and psychiatric conditions and it has been proposed that the use of dietary supplements, as vitamin and minerals, can be adjuvants in this disease. In this review, the evidence of the possible role of vitamin D, and its metabolites, as a protector against the neurological manifestations of COVID-19 was summarized.

Keywords: Vitamin D, COVID-19, SARS-CoV-2, Neuroprotection, Neurological manifestations, Clinical studies.

1. INTRODUCTION

Currently, there is great interest in vitamin D supplementation, not only for its effects on mineral and bone metabolism but also because of the high prevalence of hypovitaminosis in some populations and its effects on the immune system [1]. Vitamin D modulates multiples processes such as host defense, inflammation, immunity and epithelial repair [2, 3]. In humans, the main source is skin synthesis induced by solar radiation and, to a lesser extent food [2]; the bioavailable forms are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), vitamin D2 or D3 after being absorbed through the digestive tract and passing into the bloodstream are hydroxylated by a 25-hydroxylase enzyme in liver originating 25-hydroxy cholecalciferol (25-(OH)-D), later in the kidney and secondarily in other tissues this com-

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pound is hydroxylated by 1-α-hydroxylase to generate 1α,25-dihydroxy vitamin D (1,25-$(OH)_2$D) the active compound of this hormonal system, then, even though, it is called a vitamin it is a hormone that together with parathyroid hormone regulates the concentration of calcium in the blood [4].

At the cellular level, the nuclear receptor for vitamin D predominates in the enterocyte and the osteoblast. However, its presence has been identified in almost every cell in the body, including the brain, heart, skin, beta cells of the pancreas, gonads, prostate, breast, colon, and cells of the immune system [5]. 1,25-$(OH)_2$D has been shown to intervene in cell growth and maturation, stimulate insulin secretion, inhibit renin production and modulate the function of B, T and macrophage lymphocytes. Different chronic diseases have been linked directly to vitamin D deficiency, especially type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Crohn's disease, psoriasis, prostate, breast, ovarian and colon cancer, and metabolic disease bone [1, 2].

The most common method to determine the body status of vitamin D is to measure the serum concentration of 25-(OH)-D and less common is to measure the concentration of 1,25-$(OH)_2$D. Serum 25-(OH)-D concentration allows assessment of whether deposits are sufficient, insufficient or there is intoxication [5], sufficient vitamin D concentration in adults is >30 ng/mL and the insufficiency and deficiency values are 21-29.9 ng/mL and <20 ng/mL, respectively [4, 6, 7]. One disease associated with low vitamin D concentration is hypertension, it is now well known that lower levels of 25-(OH)-D is strongly associated with an increased risk of developing high blood pressure [8], this may be explained in part because vitamin D deficiency may increase renin-angiotensin system (RAS) activity in the kidneys. Vitamin D-deficient subjects have also been shown to have a significantly reduced renal plasma flow response to Angiotensin II (Ang II) infusion [6, 9].

Regarding the role of vitamin D in relation to viral infections, clinical and epidemiological studies provide evidence of enhanced immune protection by this vitamin against hepatitis, human immunodeficiency virus and respiratory diseases [10]. In Vitamin D-antiviral effects are involved various mechanisms related to the promotion of innate immunity through the induction of the cationic polypeptides cathelicidin and β-defensins, and through the promotion of autophagy [11, 12] by activation of Toll-like receptors and consequent complement system activation [13]. Several observational studies have reported that vitamin D deficiency is a factor independently associated with the increased risk of acute respiratory viral diseases [14]. In a study, 25-(OH)-D levels greater than 38 ng/mL in adults were associated with a statistically significant decrease in the risk of developing acute respiratory infections during autumn and winter [15].

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has generated until now approximately 4 million deaths and more than 186 million confirmed cases in the world [16]. The pandemic caused by the SARS-CoV-2 coronavirus has generated high morbidity, mortality and expenses related to the measures taken for its control and mitigation [17]. For this reason, many studies have recently been published investigating potential treatments to improve the prognosis of this disease, as those currently on the market do not succeed in positively impacting the survival of all cases. Among them, trials related to vitamin D have also been published due to its anti-inflammatory, antiviral and pulmonary protective potential. However, the evidence they show is weak due to the fact that they are studies with small samples with heterogeneous populations, different administration regimens and many of them are retrospective [18-21]. However, vitamin D deficiency in SARS-CoV-2 infected patients has been observed to be associated with increased immune and respiratory impairment, severity and mortality from the disease [20, 22, 23]. The RAS, and its main product Angiotensin 1-7 (Ang 1-7), is the major regulator within the pathophysiological mechanisms of COVID-19, and sufficient levels of vitamin D are required to increase angiotensin-converting enzyme 2 (ACE2) concentrations in acute lung injury to induce the ACE2/Angiotensin 1-7 suppressing the renin axis and the ACE/AngII/AT1R axis [24]. The RAS imbalance causes the activation of ACE/Ang II/AT1R axis, which in turn causes a hyperinflammatory state and pulmonary injury, inducing the activation of various signaling pathways, including extracellular signal-regulated kinase (ERK), Jun-N-terminal kinase/mitogen-activated protein kinase (JNK/MAPK) as well as protein kinase C (PKC) and also suppresses the anti-inflammatory ACE2/Ang-(1-7)/Mas Receptor (MasR) axis, this being the paradoxical action of ACE2 in COVID-19 [25, 26]. In addition, vitamin D sufficiency can decrease RAS activity through several pathways, including transcriptional suppression of renin, ACE, and Ang II expression [27]. In Fig. (**1**), we showed the effects of vitamin D on ACE2 and RAS.

To date, clinical scientific evidence indicates that vitamin D administration in the early stages of the disease has potential utility as an adjuvant to treatment and, to a lesser extent, to prevent SARS-CoV-2 infection [28]. The role of hypovitaminosis in diseases that increase the risk of death by COVID-19, such as diabetes, hypertension, obesity, and cardiovascular diseases, is well established; all of these diseases have in common vascular inflammation and endothelial dysfunction and are more prevalent in the risk group of older adults. Fortunately, several studies are underway in order to determine and establish specific aspects (prehospital or hospital administration, dosage of vitamin D or its metabolites) of vitamin D possible beneficial effect on SARS-CoV-2 [29]. In a review based on data from observational studies, it is proposed that patients with a risk for COVID-19 should take 10,000 UI/day of vitamin D3 for a few weeks to increase 25-(OH)-D levels by at least 40-60 ng/mL, this is because in most populations low serum vitamin D levels are more common than previously thought, especially due to the current lifestyle characterized by few hours of sun exposure per week and little consumption of foods high in vitamin D such as some types of fish, fortified milk and cereals [30, 31]. In relation to the neuroprotective

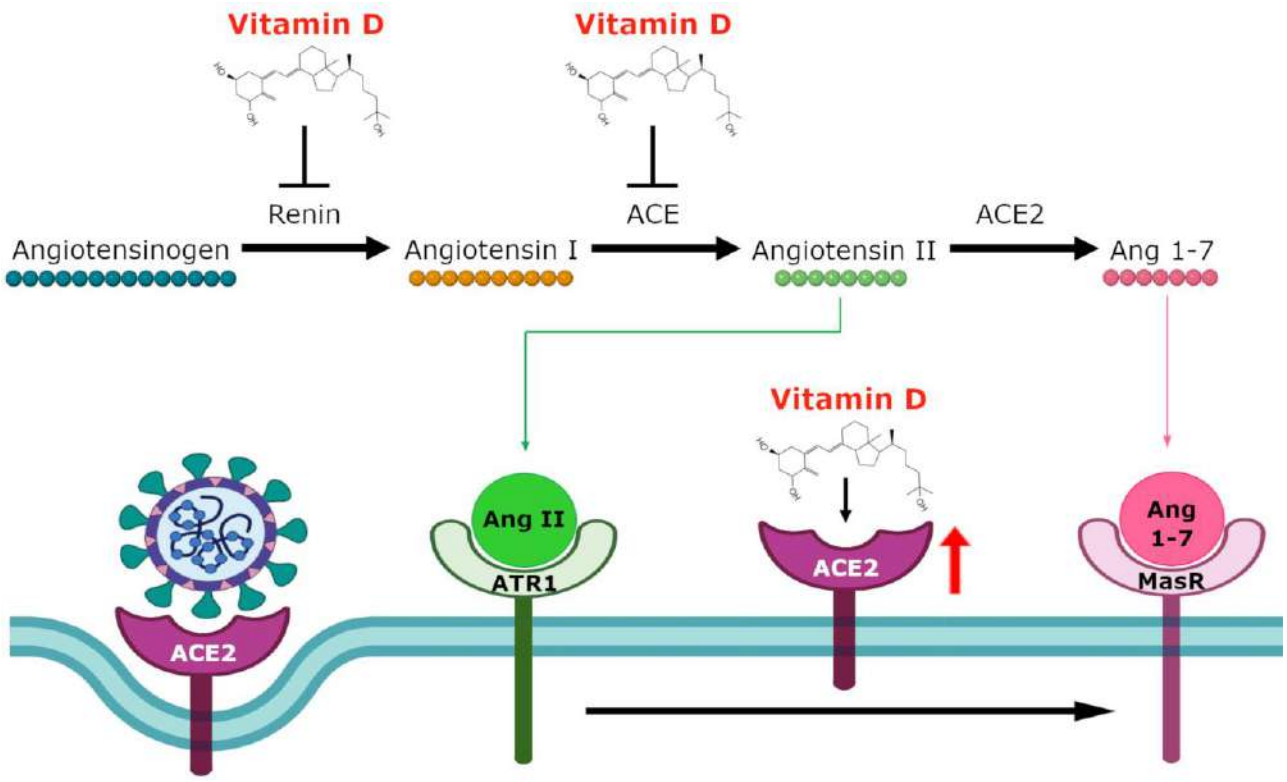

Fig. (1). Effects of vitamin D on the angiotensin-converting enzyme 2 (ACE2) and renin-angiotensin-aldosterone system (RAS). Under physiological conditions, angiotensinogen is converted to angiotensin I (Ang I) by renin, then Ang I is transformed to angiotensin II (Ang II) by the angiotensin I convertase enzyme (ACE). Ang II interacts with its two receptors ATR1 and ATR2. During COVID-19 infection, RAS over-activation leads to inflammation and tissue damage by activating several signaling pathways. Vitamin D decreases Ang II levels and the interaction with its receptors by reducing the expression of renin and ACE, resulting in decreased tissue damage. Vitamin D also increases the expression of ACE2, which besides being a SARS-CoV-2 receptor, reduces the activity of the renin-angiotensin axis by converting Ang I and Ang II into Ang 1-9 and Ang 1-7, respectively. Ang I-7 binds with the Mas receptor (MasR) receptor, counteracting the inflammatory effects of the ACE/Ang II/ATR1 axis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

effect of vitamin D, evidence exists where vitamin D showed protective effects in neurological conditions in clinical studies such as benign paroxysmal positional vertigo, multiple sclerosis, fibromyalgia syndrome, migraine headache, neurocognitive function, as an auxiliary in rehabilitation therapy in cerebral palsy, in autism spectrum disorders, in the quality of sleep, in Alzheimer´s and Parkinson diseases and in the pain control [32-42] but poor information of its vitamin related to the neurological conditions induced by SARS-CoV-2. Tacking all of the above into account, the objective of the present study is to summarize the evidence of the possible role of vitamin D as a protector against the neurological manifestations of COVID-19 infection.

2. MOLECULAR MECHANISMS OF VITAMIN D

2.1. Role of Vitamin D (Cholecalciferol)

Vitamin D was identified in the 1920s [43]. It is a lipophilic hormone whose classic role has been regulating calcium transport processes in many different tissues [44].

The term "vitamin D" refers to its production from 7-dehydrocholesterol in the skin by direct exposure to sunlight or by obtaining it from food and dietary supplements. There are two circulating vitamin D metabolites: 25-hydroxy vitamin D (25-(OH)-D), known as calcifediol or calcidiol, and the 1,25-$(OH)_2$D, known as calcitriol, the active form of vitamin D [44, 45].

Beyond the fact that in higher vertebrates, the 1,25-$(OH)_2$D plays an important evolutionary role in facilitating intestinal absorption of dietary calcium and skeletal mineralization [45], as well as in modulating plasma calcium and phosphate concentrations [46] 1,25-$(OH)_2$D also regulates many other cellular processes such as transduction of extracellular signals to various intracellular sites [45, 47], cell proliferation and differentiation [48-50], immune response [51-53], and cell metabolism [54, 55], as well as functions of the nervous and vascular systems [56-59].

2.2. Vitamin D Pathways

In humans, endogenous synthesis of the active form of vitamin D begins in the skin by direct exposure to UV-B radiation, which makes it the main source of vitamin D [60]. Through a series of reactions, the metabolite 7-dehydrocholesterol is converted to provitamin D (dehydrocholesterol) and rapidly isomerized to cholecalciferol (vitamin D), as a result of the influence of thermal energy [61]. The newly formed vitamin D is transported from the skin to the liver through the vitamin D-binding protein (DBP) [62].

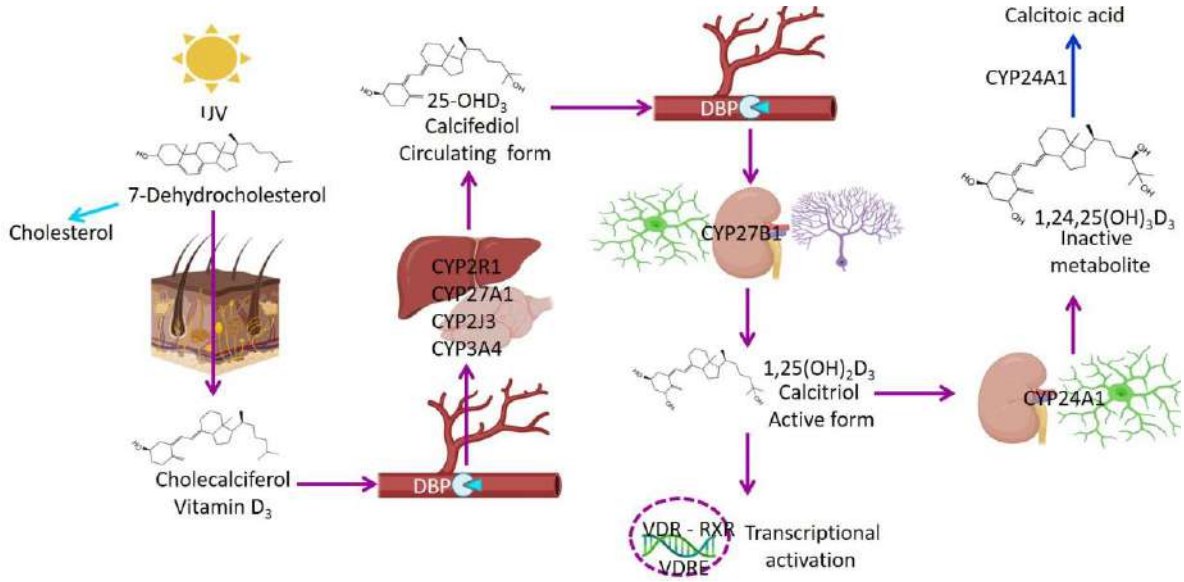

Fig. (2). Classical synthesis and catabolism of Vitamin D. The precursor vitamin 7-dehydrocholesterol is converted in the skin by ultraviolet radiation to pre-vitamin D3 and vitamin D3. Subsequently, vitamin D3 binds in circulation to D-binding protein (DBP) to be transported to the liver/brain where the first hydroxylation occurs and the formation of 25-(OH)-D is carried out by the set of mitochondrial enzymes encoded by CYP2R1, CYP27A1, CYP2J3, CYP3A4 genes. Then, 1,25-$(OH)_2$D is formed primarily in the kidney/glia/neuron by 25-hydroxyvitamin D-1α hydroxylase (CYP27B1), next is released into the circulation to exert its actions in a variety of cell types through its receptor the VDR. Its degradation occurs in the kidney *via* CYP24. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In the liver, vitamin D is the substrate of the vitamin D-25-hydroxylases of the cytochrome family P450 (CYP): CYP2R1, CYP3A4, CYP27A1 and CYP2J3 [63-66], which exhibits 25-hydroxylation activity on the vitamin D, that results in a first hydroxylation at carbon 25 of the molecule, producing the 25-hydroxycholecalciferol (25-(OH)-D). It is then released into the bloodstream as the major metabolite of vitamin D, which is commonly measured in serum to assess the status of the vitamin in circulation [4]. The next step for the synthesis of the active form of vitamin D occurs mainly in the proximal tubular epithelial cell in the kidney and consists of a second hydroxylation facilitated by 25-hydroxyvitamin D-1α hydroxylase (CYP27B1), which produce the 1,25-$(OH)_2$D [67]. The 1,25-$(OH)_2$D acts as a steroid hormone system in the cell cytoplasm through the vitamin D receptor (VDR), also called nuclear receptor subfamily 1, group I, member 1 (NR1I1) a ligand-activated transcription factor and member of the superfamily of nuclear receptors. Its genomic effects are mediated by the binding to specific DNA sequence elements. The VDR heterodimerizes with related retinoid X receptors (RXR) partners, which allows high-affinity binding to specific DNA motifs called vitamin D responsive elements (VDREs), in vitamin D responsive genes and ultimately influences their RNA polymerase II-mediated transcription rate [68] in multiple cellular tissues [51, 56, 59], while a series of additional hydroxylation negatively regulate its production in tubular epithelial cell [61, 67] conducted by mitochondrial 1,25-dihydroxyvitamin D-3 24-hydroxylase (CYP24A1) [69] a target gen of fibroblast growth factor 23 (FGF23) and low levels of parathyroid hormone (PTH), which produces an increase in serum of 24,25-$(OH)_2$D as a product of the catabolism of the 1,25-$(OH)_2$D [4, 69, 70]. In Fig. (**2**) it is showed the classical synthesis and catabolism of vitamin D.

2.3. Mechanism of Action of Vitamin D

2.3.1. Immunological Role

As mentioned before, the serum 25-(OH)-D is considered to be the best biomarker for assessing vitamin D status, moreover, it reflects the other free fractions and metabolites of vitamin D [71]. A consensus on the serum/plasma 25-(OH) account of vitamin D is still a controversial [72]. However, the Institute of Medicine (IOM) referrer the vitamin D deficiency 25-(OH)-D <50 nmol/L (20 ng/mL) and severe vitamin D deficiency <30 nmol/L (12 ng/mL), which compromises the health of the individual increases the risk of excess mortality [4, 7].

Recently, the impact of vitamin D on the immune system has been widely referred to in the context of respiratory infections and especially has gained relevance in COVID-19. Studies conducted in the 2000s highlighted the immunomodulatory role of vitamin D in cardiovascular disease, common cancers and chronic inflammatory autoimmune disorders; through regulation of T helper 17 (Th17) cell activity and decreased production of interleukin 17A (IL-17A), interleukin-22 (IL-22), and interferon γ (IFNγ) as well as a decreased production of interleukin-6 (IL-6), interleukin-8 (IL-8), matrix metalloproteinase-1 (MMP-1) and prostaglandin E2 (PGE2) [73]. In type 1 diabetes, dysregulation of cytokines balance occurs, and Th1 cells play an important role in this pathogenesis. Some studies have shown the immunoregulatory effect of vitamin D as a reduction in the production of interleukin-12 (IL-12), a cytokine involved in

the development of Th1 cells, which in turn promotes a Th2 phenotype, stimulating Th2 cytokines and inducing regulatory T cells (Treg) [74]. Furthermore, transcriptional-level inhibition of IL-12 by 1,25-$(OH)_2$D occurs by down-regulation of NF-κB in both activated macrophages and dendritic cells [75].

Interestingly, in myeloid dendritic cells (M-DCs), the most efficient antigen-presenting cells (APCs), 1,25-$(OH)_2$D induces tolerogenic properties through C-C motif chemokine ligand 17 (CCL17) and IL-12 depletion by down-regulating the expression of co-stimulatory molecules such as the cluster of differentiation 40 (CD40) and up-regulation C-C motif chemokine ligand 22 (CCL22) as well as down-regulating C-C chemokine receptor 7 (CCR7), which would promote the activity of the CD4+ lymphocyte suppressor T cell subset [68].

Another cell population of importance in the regulation of the immune response is the ones called myeloid-derived suppressor cells (MDSCs), which can suppress T cells responses, down-regulate T cell receptors, and recruit Treg well as inhibiting the antitumor activity of T cells. In recent *in vitro* work, MDSCs were shown to be targets of 1,25-$(OH)_2$D activity through reduced nitric oxide (NO) production; vitamin D decreased the immunosuppressive capacity of these cells, and increased VDR expression, which facilitates cell differentiation [76].

Furthermore, in an NK-cell granular lymphocyte leukemia (NK-LGLL) model, up-regulation of VDR with 1,25-$(OH)_2$D treatment and a significant decrease in phosphorylation of signal transducer and activator of transcription 1 (STAT1) and signal transducer and activator of transcription 3 (STAT3) were demonstrated, as well as decreased intracellular interleukin-10 (IL-10), which may influence the decrease in inflammatory cytokine load at the systemic level [77]. On the other hand, although the synthesis of 1,25-$(OH)_2$D in tubular epithelial cells is widely recognized, the immune system cells have the necessary machinery for its production. In recent years, the number of related studies has increased.

In innate immune responses, immune cells express the enzyme for the synthesis of the active form of vitamin D. The vitamin D-activating enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) catalyzes the conversion of 25-OH-D to 1,25-$(OH)_2$D in Toll-like receptor (TLR2/1)-sensitized monocytes, which promotes autocrine and paracrine vitamin D activity in cells and tissues by modulation of gene expression including those coding the antimicrobial peptides in response to microbial infection [78] In turn, in dendritic cells (DCs) the synthesis endogenous of 1,25-$(OH)_2$D through the CYP27B1 mediates the inhibition of DC maturation *in vivo* and *in vitro* [79, 80].

Thus, due to the relevance and current role of vitamin D in the immune response to viral infection, such as in SARS-CoV-2 infection, generates a rapid hyperinflammation in various epithelia and organs, followed by a dysregulated and excessive immune response involving the entire immune system, vitamin D supplementation as an adjuvant treatment is nowadays considered a potential powerful alternative for COVID-19 disease, because it has been shown to have immunomodulatory response through modulation of specific target gene expression as well as repression of transcription of others.

2.3.2. Metabolic Role

Despite the increasing importance placed on vitamin D supplementation for cellular and tissue function, there is a marked deficiency of 25-(OH)-D in populations that, due to their geographical location, is expected to be high, for example for European populations the prevalence was of 40.4% [81] while a similar percentage was reported in U.S. population [82]. Clinical consequences of vitamin D deficiency could play a notable role in cardiovascular disease, cancer and diabetes [82].

In the endocrine system, the active form 1,25-$(OH)_2$D has many targets, including adipose tissue, where the VDR and three cytochrome P450 enzymes to synthesize 1,25-Dihydroxyvitamin D3 are expressed: CYP2R1, CYP2J2 and CYP27A1 in addition to CYP27B1 hydroxylase. Notably, in adipose tissue, the CYP27B1 is not regulated by dietary calcium and vitamin D as in the renal case [83].

Interestingly, early studies in this area, demonstrated, in a rodent model, that adipose tissue is the main storage site for vitamin D3 in its various forms [84]. Whereas in humans, a small amount of vitamin D is stored in body fat after administration of a dose of 50,000 IU/week [85]. Moreover, in mice, the active form of vitamin D increases the expression of adipogenic genes and decreases the expression of uncoupling proteins [86]. While in human adipocyte cultures 1,25-$(OH)_2$D facilitates inhibition of basal lipolysis and in the WNT/β-catenin pathway, 1,25-$(OH)_2$D suppresses adipogenesis in 3T3-L1 adipocytes [87].

Likewise, it has been described that poor vitamin D status, in humans is strongly associated with obesity [86]. In rodents have shown that 1,25-$(OH)_2$D regulates in adipocytes the secretion of adipokines; proteins implicated in the development of tumors such as breast cancer [83], while in models of obesity, the effect of vitamin D supplementation reduced the expression of inflammatory genes in inguinal adipose tissue, an important site of metabolic homeostasis, as well as the accumulation of lipid droplets and of triglyceride in the liver, which is related to a decreased expression of genes encoding key enzymes involved in hepatic *de novo* lipogenesis and fatty acid oxidation [88, 89]. Therefore, it is in the interest of metabolic health to develop strategies to harness the potential benefic effects of vitamin D.

2.3.3. Antioxidant Function

Oxidative stress (OS) in the cell is the result of an imbalance between the production and accumulation of reactive oxygen species and the insufficiency or failure of the cell's antioxidant system to maintain redox balance, allowing alterations in biomolecules and association with a wide variety of diseases and disorders [90, 91]. In this regard, the antioxidant function of vitamin D has been well document-

ed; it was previously demonstrated to act by stabilizing the membrane against lipid peroxidation through the interaction between its hydrophobic rings [92]. In addition, 1,25-$(OH)_2$D activity was related to OS reduction by inhibiting antiprotease activity and acting on nuclear factor erythroid 2-related factor 2 (Nrf2), a transcriptional regulator of most antioxidant genes [71]. In preeclampsia, 1,25-$(OH)_2$D was shown to exert an antioxidant effect through downregulation of cyclooxygenase 2 (COX-2) expression [93] and by inhibiting the production of thromboxane, a potent vasoconstrictor in placental trophoblasts [94]. In a diabetic animal model, vitamin D activates antioxidant activity through the Nrf2/erythroid cell-derived protein with the CNC homology (ECH) (Keap1) pathway and attenuates the progression of nephropathy [95].

In skeletal muscle, vitamin D deficiency may impair muscle antioxidative capacity, which was demonstrated *in vitro* [96], thus, showing the role of both VDR and vitamin D in regulating mitochondrial respiration in muscle. In diabetic subjects, the 25-(OH)-D deficiency is associated with inflammation and OS [97]. However, an analysis published by Tagliaferri *et al.* has revealed numerous inconsistencies in the results obtained in studies using vitamin D supplementation as an antioxidant in healthy subject and diabetics patients due to a great variability and heterogeneity in the types of supplementations, different doses, different parameters, among others, used for the diagnosis of vitamin D deficiency, which prevents obtaining solid and reliable conclusions on this subject. Furthermore, regarding clinical trials, the results of the antioxidant effect of vitamin D, are even more controversial due to the lack of information related to patient characteristics, specific molecule, dose, duration and type of vitamin D administration [98]. Therefore, all those findings highlight the importance and care that should be taken into account for the study design and the need to expand and provide information about variables to acquire a better understanding of the antioxidant role of vitamin D.

3. EFFECT OF VITAMIN D IN PATIENTS WITH COVID-19

The entry of SARS-CoV-2 into human cells has been identified to be mediated mainly by the ACE2 receptor [99]. ACE2 is a cell membrane-localized carboxypeptidase and is expressed on type I and II alveolar cells, epithelial cells, fibroblasts, endothelial cells, and macrophages; it is involved in the cleavage of angiotensin I and angiotensin II [100]. Like other coronaviruses, during viral entry into host cells the SARS-CoV-2 envelope spike proteins are cleaved into S1 and S2 subunits (formed by heptad repeat 1, HR1 and heptad repeat 2, HR2 domains), with the S1/receptor protein being determinant for infection in the host species, S1 contains the ACE2 peptidase domain-binding domain for entry into cells [101]. S1 cleavage is mainly dependent on transmembrane protease serine protease 2 (TMPRSS2) principally [102]. The HR1 and HR2 domains of the SARS-CoV-2 S2 protein interact with ACE2 receptors inducing the formation of six-helix fusion structures. The binding of S1 to the ACE2 receptor cleaves ACE2 by the metallopeptidase domain 17 (ADAM17). Cleavage by ADAM17 and TMPRSS2 facilitates effective virus entry [103].

Once the structural and functional characteristics of SARS-CoV-2 were identified and the glycoprotein spike was recognized as the main antigenic protein responsible for viral binding to ACE2 and infection of host cells, scientists were hard at work, proposing, analyzing, and validating a high-priority list of potential candidates that could mitigate SARS-CoV-2 invasion of human cells. A group of candidate molecules for activating or repressing the targets ACE2 and ubiquitous endoprotease FURIN (necessary for cleaving both SARS-CoV-2 spike protein) have been studied, among which vitamin D is highlighted [104]; as mentioned above, it has been reported to influence several immune pathways [105-107] and induces protection against acute respiratory tract infection [15, 108], consequently, a vitamin D deficiency may increase the risk of bacterial and viral infection [109]. This has been ascertained in mid-2020 in COVID-19 patients who required admission to the Intensive Care Unit (ICU), which a higher prevalence of vitamin D deficiency compared to patients treated in medical wards who did not require ICU admission [110].

Recently a study suggests that vitamin D deficiency may be associated with worse clinical biomarker profiles (high levels of IL-6 and D-dimer) and increased mortality in hospitalized COVID-19 patients [111]. However, a two-sample Mendelian randomization analysis to assess the causal effect of the 25-(OH)-D levels on COVID-19 susceptibility, severity and hospitalization traits using GWAS data (summary-level) found a lack of strong evidence to associate serum 25-(OH)-D concentration and these parameters [112]. A pilot study was shown that 25-(OH)-D may improve the clinical outcome of subjects requiring hospitalization for COVID-19, as patients treated with 25-(OH)-D required fewer ICU admission *vs* patients without vitamin D treatment [113]; a likely explication for it is that once the virus spread and migrates through the respiratory tract, it reaches the alveoli, O_2 and CO_2 exchange units of the lung, infects alveolar epithelial cells type II and causes severe injury, inflammatory changes, and subsequently respiratory failure [114, 115]. However, treatment with 25-(OH)-D can induce in alveolar epithelial cells type II the expression and activity of enzymes that produce 1,25-$(OH)_2$D, the active form of vitamin D, which act on themselves and on the immune system cells at the site, regulating gene expression and consequently preventing tissue damage by hyperinflammation [113]. Furthermore, the role of vitamin D/VDR signaling in regulating epithelial barrier function and integrity through increased expression of the intercellular junctions in various epithelia tissues [116-118], as well as on up-regulating of the antimicrobial peptide cathelicidin in airway epithelial cells [106] which, stimulates the local innate immune response and promotes the control of viral infections by its pleiotropic immunomodulatory properties.

Importantly, serum 25-(OH)-D concentrations (<38 ng/mL) were correlated to the incidence of viral respiratory in adults [15] and <50 nmol/L (20 ng/mL) vitamin D was associated

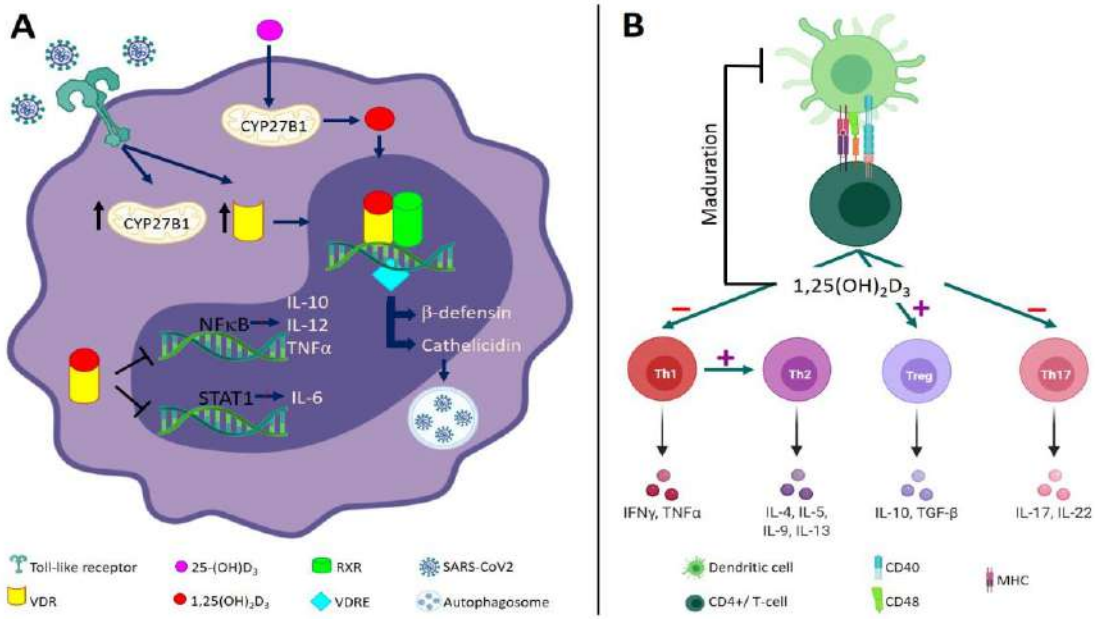

Fig. (3). Putative vitamin D mechanism against coronavirus disease 2019 (COVID-19). Vitamin D exerts multiple mechanisms against COVID-19 infection. An adequate supplementation of this vitamin may strengthen innate and adaptative immunity. A) Related to innate immunity, the activation of toll-like receptors (TLR1/TLR2) by coronavirus increases the expression of both vitamin D receptor (VDR) and mitochondrial CYP27B1. Circulating 25-hydroxyvitamin D 25-(OH)D_3 bounds to serum vitamin D-binding protein and enters macrophages in its free form by passive diffusion, then is converted to its active form 1,25-dihydroxyvitamin D (1,25-$(OH)_2D_3$) by mitochondrial CYP27B1. In turn, it binds to VDR, which elicits transcriptional effects together with the retinoid X receptor (RXR). The VDR/RXR complex binds to the promoter region of vitamin D responsive genes (Vitamin D response element; VDRE), increasing the expression of antimicrobial peptide synthesis: cathelicidin and β-defensin. Vitamin D promotes macrophage differentiation and autophagy through autophagosome formation, increasing viral clearance. Additionally, the complex VDR-vitamin D blocks the activity of NF-κB and STAT1 reducing the formation of pro-inflammatory molecules, avoiding the cytokine storm characteristic of COVID-19 infection. B) Regarding adaptative immunity, vitamin D acts through intracrine, paracrine, and endocrine pathways. Vitamin D inhibits the maturation of dendritic cells, modulating CD4+ function, reducing antigen-presentation and dendritic cell proteins CD40 and CD48 (blue and green respectively). It inhibits the activation of type 1 and type 17 helper T cells (Th1 and Th17) and hinders immune responses related to tissue damage. Vitamin D upregulates T regulatory cells (Treg) and the shift from a Th1 to Th2 response. This results in suppressed release of pro-inflammatory cytokines. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

with COVID-19 infection, hospitalization and death [119, 120]. Moreover, vitamin D deficiency status was considered as a risk factor for acute respiratory distress syndrome (ARDS) [109]. ARDS is a serious lung condition that results in low blood oxygen levels due to alveolar damage and disruption of the alveolar epithelial barrier, also to an inflammatory cell infiltration and an extensive inflammatory process [109, 116]. Interestingly data on ARDS show that ARDS patients who died in the ICU had deficient 25-(OH)-D levels (35.5 pmol/L) compared to survivors whose levels remained, on average, above 50 pmol/L [109]. Moreover, ARDS is a common complication in severe COVID-19 patients [121, 122], so the use of vitamin D as a treatment or prophylaxis for COVID-19 and ARDS could provide benefits by modulating the inflammatory immune response: suppressing Th1 cells activation, modulating Th2 cells, Treg and Th17 cells activity, as well as the proinflammatory cytokines synthesis and secretion, in addition to improving cellular and innate immunity and the physiological barrier function, which could reduce hospitalization and/or mortality rates in those diagnosed with COVID-19 [107]. In Fig. (**3**) we showed the putative vitamin D mechanism against COVID-19.

In these settings, trying to demonstrate the potential therapeutic of vitamin D against COVID-19, numerous evidence has been collected in clinical trials, which is summarized in Table **1**. However, a recent publication about the German national treatment guidance for hospitalized COVID-19 patients Key pharmacologic recommendations urges in one of its 11 key recommendations, not to use vitamin D in hospitalized patients and either in routine care of COVID-19 because it is considered that there is insufficient evidence to recommend its use, this based on an analysis of the literature (reviews and/or meta-analysis), as well as on expert consensus opinion [123]. However, contrasting evidence is analyzed and presented in this review. Several working groups support the therapeutic and prophylactic effects of vitamin D in patients and animal models, while the *in vitro* results clearly show the mechanisms involved in the effect at the systemic level. On the other hand, the authors of that paper argue that the use of vitamin D would not be entirely justified due to the lack of evidence and randomized controlled trials, as well as uncertain data on patient benefit and weak or non-existent clinical cause and effect (duration of hospitalization, mortality, ICU admission and initiation of ventilation). Individually all these parameters

Table 1. Therapeutic effects of vitamin D in COVID-19 in clinical trials.

Clinical Characteristics, (n=)/ Country, Age	Dose and Time	Study	Effects/Outcome	References
Men and women, patients in ICU with COVID-19 infection (Mean age was 53 ± 10), Spain (N=76)	Group 1: oral 25-(OH)-D in soft capsules (0.532 mg) on the day of admission. They continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. Group 2: no 25-(OH)-D	A parallel pilot randomized open-label, double-masked clinical trial.	Only 1 % required ICU admission in the Group 1, in comparison with the 50% in Group 2. Multivariate Risk Estimate Odds Ratio (OR) for ICU in patients with Calcifediol treatment *vs* Without treatment ICU (adjusting by Hypertension and type 2 diabetes): 0.03, 95 %CI= 0.003-0.25, P<0.001. No patients died in Group 1 and all were discharged, without complications. Of Group 2 50% were not admitted to the ICU, and were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged. The authors concluded that administration of the high dose of 25-(OH)-D significantly reduced the need for ICU treatment for patients requiring hospitalization and reduced the severity of the disease.	[113]
Geriatric patients (over 65 years), Nursing-home in France, (N = 96).	Intervention group. Vitamin D3 dose (80,000 IU), either in the week following the suspicion or diagnosis of COVID-19 or during the previous month. Comparator group. All other COVID-19 residents without recent vitamin D supplementation.	Quasi-experimental study.	The full-adjusted hazard ratio for mortality according to vitamin D3 supplementation was HR=0.21, 95%CI= 0.07; 0.63, P=0.005 in the unadjusted model, and HR= 0.11, 95 %CI= 0.03;0.48, P= 0.003 after adjustment for all potential confounders. Kaplan-Meier distributions showed that Intervention group had longer survival time than Comparator group (log-rank P = 0.002). Vitamin D3 supplementation during or just before COVID-19 was inversely associated with the Ordinal Scale for Clinical Improvement (OSCI) score for COVID-19 in the acute phase. Similar results were found before (β=-2.96, 95%CI=-4.79; -1.12, P=0.002) and after adjusting the analyses for potential confounders (β=-3.84, 95 %CI=-6.07; -1.62, P= 0.001). The authors concluded that patients who received vitamin D3 supplements taken during or just before COVID-19 were associated with lower severity of COVID-19 and a better survival rate.	[133]
COVID-19 Patients hospitalized in the geriatric acute care unit. France (N=77; range 78-100, mean 88±5 years).	Group 1: COVID-19 patients that received during the previous year oral boluses of vitamin D supplements (50,000 IU per month, or the doses of 80,000 IU or 100,000 IU every 2-3 months). Group 2: COVID-19 patients, who received an oral supplement of 80,000 IU vitamin D3 minutes after diagnosis. Comparator group 3: Absence of vitamin D treatment.	Quasi-experimental study.	In was showed an inverse association between regular vitamin D supplementation and 14-day mortality. Considering Group 3 as the reference (HR=1), the HR for mortality in Group 1 was 0.19, 95%CI=0.04; 0.85, P=0.03 in the unadjusted model, HR = 0.18, (95% CI=0.04; 0.85, P=0.03 after partial adjustment for age, gender and GIR score, and HR = 0.07, 95%CI= 0.01; 0.61, P=0.017 after full adjustment for all potential confounders. In contrast, being supplemented with vitamin D after the diagnosis of COVID-19 (Group 2) was not associated with lower mortality risk (HR=0.37, 95%CI=0.06;2.21, P= 0.28). A history of hematological and solid cancers was associated with greater mortality risk (HR=5.56, P=0.01). Kaplan-Meier distributions showed that COVID-19 participants in Group 3 had a shorter survival time than those in Group 1 (log-rank P=0.015, although there was no difference between Groups 2 and 3 (log-rank p=0.32) and between Groups 1 and 2 (log-rank P=0.22). Regular vitamin D supplementation (Group 1) was associated with a lower proportion of participants with severe COVID-19 in the acute phase OR=0.08, 95%CI=0.01; 0.81, P=0.033) compared to Group 3 without vitamin D supplementation. In contrast, Group 2 was not associated with any beneficial effect compared to Group 3 (OR=0.46, 95% CI= 0.07; 2.85, P=0.40). Patients with COVID-19, and vitamin D regular bolus supplementation (50,000 IU per month, or 80,000 IU or 100,000 IU every 2-3 months) are associated with less severe disease and better survival rate.	[134]

(Table 1) contd…

Clinical Characteristics, (n=)/ Country, Age	Dose and Time	Study	Effects/Outcome	References
Patients hospitalized with SARS-CoV-2 infection, mildly symptomatic or asymptomatic with or without comorbidities. India (N=40); age range 36-51 years.	Patients with 25-(OH)-D deficiency levels (<20 ng/mL) were randomized: Intervention group, to receive daily 60,000 IU of cholecalciferol (oral solution in nano droplet) for 7 days to reach 25-(OH)-D level >50 ng/mL Placebo or control group (5 mL distilled water) for 7 days.	Randomized, placebo-controlled.	High dose oral vitamin D supplementation helps to reach 25-(OH)-D levels >50 ng/mL, which promotes the SARS-CoV-2 RNA negativity in a greater proportion of asymptomatic vitamin D-deficient individuals and with a significant decrease in inflammatory marker fibrinogen levels with an intergroup difference of 0.7 ng/mL, P=0.007. However, D-dimer, C-reactive protein (CRP) and procalcitonin have not-significant levels. The authors concluded that vitamin D-deficient individuals with SARS-CoV-2 achieve viral RNA reduction along with a significant decrease in fibrinogen with vitamin D supplementation.	[135]
COVID-19 patients (men and women) mean age of 45 ± 13 years and range 20-83, N=130; India	Patients with hypovitaminosis D (<30 ng/mL) with mild to moderate illness (SpO2 > 90%): Experimental group/vitamin D group (VD Group). Subjects with body mass index (BMI) of 18-25 received 60,000 IUs of vitamin D (aqueous nano solution) for 8 days, 10 days for subjects with BMI > 25). Active comparator/control group (NVD group). NVD group.	Randomized prospective open label parallel assignment interventional clinical trial.	Vitamin D levels increased from 16 ± 6 ng/mL to 89 ± 32 ng/mL after Vitamin D therapy (VD) and all the measured inflammatory markers decreased (CRP, LDH, IL-6, ferritin and ratio neutrophil/lymphocyte ratio; (P<0.01) but not difference was found in the inflammatory markers after treatment between the genders in VD *vs* NVD groups, except for higher CRP in women (P=0.02) and higher ferritin in men (P= 0.002) in NVD group. The authors concluded that therapeutic improvement in vitamin D reduced inflammatory markers associated to COVID-19.	[136]
Patients considered with moderate to severe COVID-19. Men and women (N=240) Brazil.	Group 1: vitamin D3 group received a single oral dose of 200 000 IU of vitamin D dissolved in a 10 mL peanut oil solution. Group 2: placebo group received 10 mL of a peanut oil solution.	Multicenter, double-blind, parallel-group, randomized, placebo-controlled trial.	The mean baseline 25-(OH)-D level was 20.9 ng/mL. Median interquartile range length of stay was not significantly different in both groups, also for mortality, admission to the ICU or need for mechanical ventilation. Therefore, a single high dose of vitamin D did not significantly reduce hospital length of stay. This study does not support the use of high dose of vitamin D for the treatment of moderate to severe COVID-19 in hospitalized patients.	[137]
COVID-19 patients with sub-optimal vitamin D status (N=69). Male and Female 20-75 years old. Saudi-Arabia.	Group 1: Patients that receive 5000 IU of vitamin D (Ultra-D® 5000 IU containing 125 µg cholecalciferol). Group 2: Patients that receive 1000 IU of vitamin D (Vita-D® 1000 IU containing 25 µg cholecalciferol) Both supplements were taken orally daily for 2 weeks.	Multi-center, randomized clinical trial.	Unadjusted Kaplan-Meier survival analysis was used to determine the differences in recovery times and revealed that the number of days to resolve cough was significantly shorter in the 5000 IU group than the 1000 IU group (6.2±0.8 *vs* 9.1 ± 0.8; unadjusted P=0.007). The same shorter period was observed for ageusia, again in favor of the 5000 IU group (11.4±1.0 *versus* 16.9±1.7; unadjusted P= 0.035). The authors concluded that 5000 IU daily oral vitamin D supplementation for 2 weeks reduces the time to recovery for cough and gustatory sensory loss among patients with sub-optimal vitamin D status and mild to moderate COVID-19 symptoms.	[138]
Patients infected with COVID-19 and with levels of 25-(OH)-D <25 nmol/L of three hospitals (N=951). The mean age of 73.3 years old. The United Kingdom.	In the patients were measured the 25-(OH)-D levels and those with levels <25 nmol/L were supplemented with cholecalciferol using high-dose booster therapy (approximately ≥ 280,000 IU in a time period of up to 7 weeks). In the study, were supplemented 151 patients for a maximum 7 weeks.	Patients are opportunistically recruited.	Vitamin D booster therapy was associated with a reduced risk of mortality (OR adj =0.25, 95%CI=0.12-0.49), P< 0.001).	[139]

have been the subject of this analysis by other authors, who have highlighted the therapeutic potential of vitamin D in the scientific literature, in addition to demonstrating that vitamin D is an accessible, inexpensive, adjuvant option with a wide margin of safety and other health benefits [85, 124, 125]. Thus, it may represent an effective, affordable, and well-tolerated adjuvant treatment for COVID-19 and its role in the endocrine system may favorably modulate host

responses to SARS-CoV-2, both in the early viremic phase and in the hyperinflammatory phase of the disease [113]. Other studies have provided evidence of the potential usefulness of the vitamin D metabolites 25-(OH)-D (calcidiol or calcifediol) and 1,25-$(OH)_2$D (calcitriol) as adjuvants to improve the prognosis of COVID-19. Treatment with cholecalciferol (>250 μg) was associated with slight protection against SARS-CoV2 infection (HR=0.95, 95%CI=0.91-0.98, P=0.004). In addition patients achieving 25-(OH)-D levels ≥30 ng/mL had lower risk of severe COVID-19 and lower mortality, both for cholecalciferol treatment (HR=0.72, 95%CI=0.52-1.00, P=0.050 and HR=0.66, 95%CI= 0.46-0.93, P=0.018) and for calcifediol (HR= 0.61, 95%CI=0.46-0.81, P=0.001 and HR=0.56, 95%CI=0.42-0.76, P< 0.001) [126]. Two independent studies reported that oral calcifediol (0.532 mg on admission, 0.266 mg on days 3 and 7, and then weekly until discharge or ICU admission) decreased the rate of admission to the ICU (OR=0.02, 95%CI=0.002-0.17, P<0.001) of patients hospitalized for COVID-19 over 40 years of age [113] and decreased the risk of mortality (OR=0.21, 95%CI=0.10-0.43, P=0.0001) [127], (OR=0.22, 95%CI=0.08-0.61, P<0.05) [128]. Another study reported that the use of 1,25-$(OH)_2$D in patients with advanced chronic kidney disease reduced risk of SARS-CoV-2 infection (HR=0.78, 95%CI=0.64-0.94, P=0.010), reduced risk of severe COVID-19 and mortality (HR=0.57, 95%CI=0.41-0.80, P=0.001) [129]. Furthermore, an association was identified between treatment with calcifediol and calcitriol 15 and 30 days before hospitalization and survival of patients with COVID-19. The association was stronger when prescribed 15 days prior to hospitalization for calcifediol (LHR =-1.27±0.32) than for cholecalciferol (LHR=-0.56±0.15), suggesting a greater prophylactic effect the closer the treatment is to hospitalization [130]. A recent study with an update summary of epidemiological and intervention studies conducted during the COVID-19 pandemic, also supports that vitamin D supplementation has a potential role for the prevention of COVID-19 infection, severe course of the disease, and death, as well as being a cost-effective therapy and a readily available tool to prevent millions of infections and deaths from this disease but employed as an adjunct to vaccination, social distancing, use of masks, and hygiene measures [131].

Finally, until August 2021, 108 clinical trials around the world are currently developing (48 in recruiting, 15 not yet recruiting, 6 in enrolling by invitation, 7 in active not recruiting, 3 terminated, 28 completed and 1 withdrawn), where specific aspects of vitamin D are being studied in relation to patients with COVID-19. These studies are analyzing: a) the serum levels of vitamin D and its effect in the progression, severity and mortality of the disease, b) the effect of vitamin D deficiency in the risk of severe COVID-19, c) the effect of supplementation of vitamin D in the prevention, in the duration of the symptoms, in the patients recovery, in the rate and time period of hospitalization and in the progression, morbidity, severity and mortality of the disease, d) the effect of vitamin D supplementation with or without other antioxidants or dietary supplements in pregnant women and COVID-19, e) the effect of vitamin D supplementation with or without other antioxidants or dietary supplements in obese people and COVID-19, f) the effect of vitamin D supplementation with other antioxidants or other dietary supplements in the duration of symptoms, progression and severity of COVID-19, g) the correlation between vitamin D levels with some biomarkers of severity or mortality of the disease and with sociodemographic, clinic and pathological variables and h) the differences in genetic variants in vitamin D related genes between COVID-19 patients with different degrees of disease severity [132].

4. ROLE OF VITAMIN D AS A POSSIBLE ADJUVANT IN THE NEUROLOGICAL CONDITIONS PRESENTED IN COVID-19

4.1. Role of Vitamin D in Neurological Diseases

Vitamin D has been used as a neuroprotector in different neurological conditions and its role as a neuroprotector has been shown in different clinical studies. In the last decade, the research regarding the role of vitamin D in the brain has increased. The 1,25-$(OH)_2$D active form of vitamin D act as a neuro-steroid through VDR, which is expressed in neurons and glial cells and shows neuroprotective effects by decreasing inflammation and OS, and through of inhibition of RAS activity in the CNS [140]. The extensive VDR distribution in the brain suggests a possible role of vitamin D in the modulation of neurotransmitters, in this sense, evidence exists where vitamin D is related to dopaminergic, glutaminergic, and serotoninergic transmission [141-146]. The supplementation with vitamin D has a protector role in Parkinson´s disease due to its effect on the dopamine pathway [42]. It has been shown the role of 1,25-$(OH)_2$D and VDR in the control of the expression of genes associated with cellular proliferation and differentiation [147, 148]. In some studies, it has been shown that 1,25-$(OH)_2$D modulates the calcium entry in neurons, influencing a wide range of neuronal functions [149, 150]. On the other hand, adequate levels of vitamin D are neuroprotective and, pretreatment with 1,25-$(OH)_2$D can decrease the consequences of brain injury [151, 152]. Vitamin D also exerts neuroprotective effects in the brain by induction of Klotho proteins, components of endocrine fibroblast growth factor receptor complex and related to life expectancy [153, 154]. Other studies show that the actions of vitamin D as an immunoregulator, anti-inflammatory, antioxidant in the regulation of calcium homeostasis and nerve growth factor (NGF) release and in the β-amyloid deposition. Thus, it can protect against a wide range of neurological and psychiatric diseases such as AD, PD, depression and anxiety [155-157]. In Fig. (**4**) we showed the hypothetical neuroprotective effects of vitamin D against COVID-19. In relation to this, it has been showed that in subjects with AD the levels of a total 25-(OH)-D, free 25-(OH)-D, bioavailable 25-(OH)-D and the bioavailable 25-(OH)-D/Total 25-(OH)-D ratio is significantly lower (P<0.05) in Alzheimer disease (AD) patients in comparison with healthy subjects [158]. In Table **2** the information of some clinical studies' information on the neuroprotective role of vitamin D in some clinical conditions.

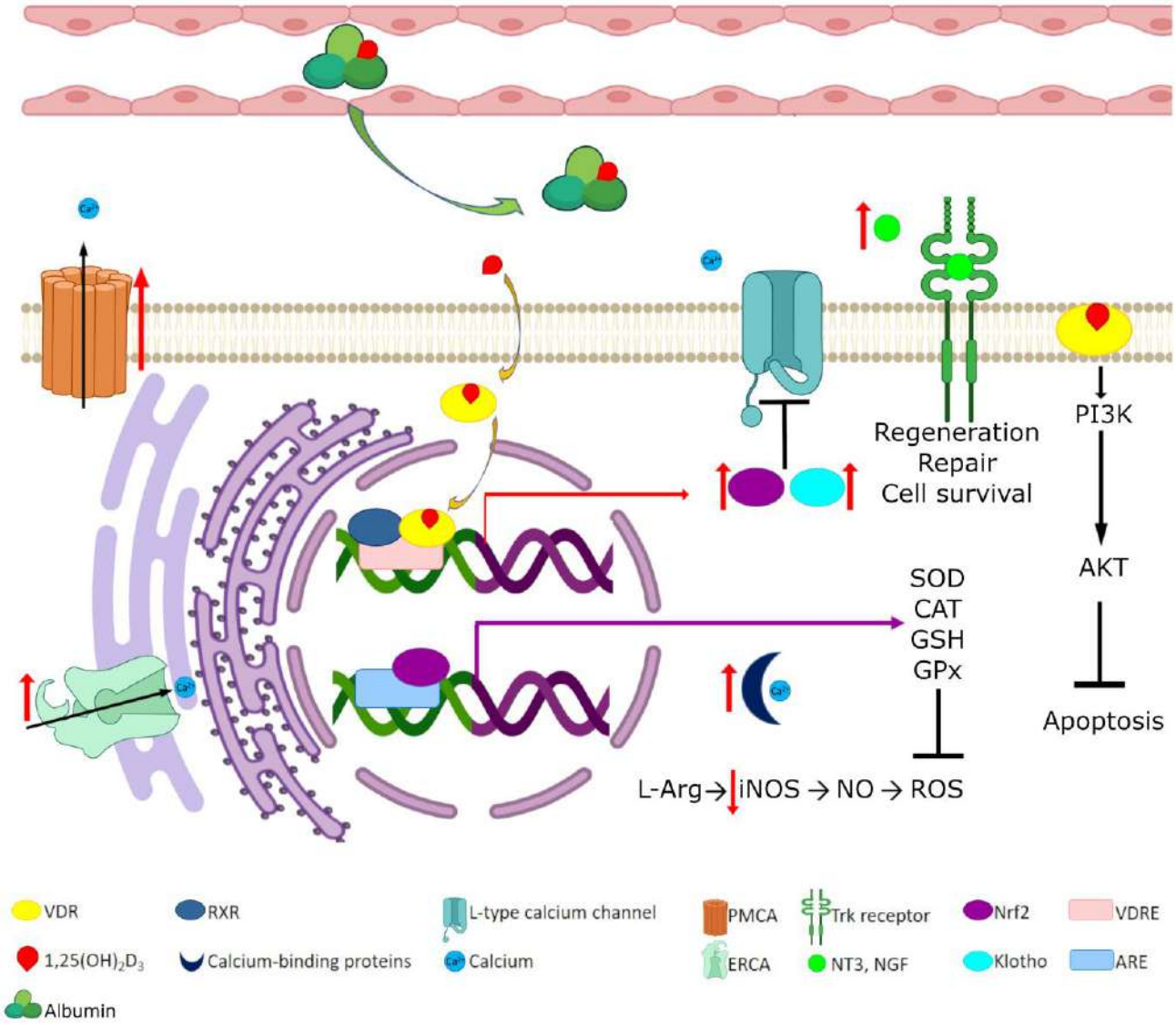

Fig. (4). Hypothetical neuroprotective effects of vitamin D against COVID-19 in the neuron. Evidence indicates that vitamin D can be synthesized locally in the nervous system through of mitochondrial CYP27B1 in the neurons and glia. Moreover, it has been seen that vitamin D and its metabolites, 25-(OH)-D and 1,25-(OH)-D, bound to albumin, cross the blood-brain barrier (pink cells) by its reduced permeability and plasma protein binding effects. Then, these compounds are metabolized by microglia exerting its activity through interaction with VDR/RXR complex distributed in multiple brain regions in the different cell types, including neurons, astrocytes, and oligodendrocytes**.** Once it interacts with its receptor, the vitamin exerts its neuroprotector capacity through various mechanisms. Vitamin D has both genomic and non-genomic actions; when it acts as a transcription factor, it increases the expression of neurotrophins (NT3), nerve growth factor (NGF), proteins related to calcium homeostasis, Klotho proteins and Nrf2 (all showed with red arrows), preventing neuronal death. The activation of both receptor protein tyrosine kinase and phosphatidylinositol 3-Kinase (PI3K)/Akt (non-genomic action), promotes regeneration, repair and cell survival and decreases the apoptotic signaling. During COVID-19 infection, there is the activation of apoptotic processes and an increase of reactive oxygen species (ROS) by means of the increase of intracellular calcium concentration. Vitamin D modulates the entry of calcium into the cells by increasing the expression of plasmatic membrane calcium ATPase (PMCA), endoplasmic reticulum calcium ATPase (ERCA), and calcium-binding proteins such as calbindin, it also decreases the expression and activity of L-type calcium channels (the last *via* Klotho-Nrf2 complex). All these mechanisms lead to a decrease in intracellular calcium concentration and promote neuronal survival. Finally, vitamin D decreases iNOS expression, which may mediate neuroprotective effects since large amounts of nitric oxide (NO) are toxic for both neurons and oligodendrocytes. The NO can rapidly react with oxygen species to form highly harmful products such as hydroxyl and nitrogen dioxide radicals. Additionally, Nrf2 (a gene overexpressed by Vitamin D action), in turn, binds to the antioxidant response element (ARE) in DNA to control the expression of antioxidant genes (purple arrow), that counteract the harmful effects of oxidant agents. Thus, vitamin D through the decrease in intracellular calcium concentration, the overexpression of neurotrophins and antioxidant species result in an important neuroprotective effect. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. The neuroprotective role of vitamin D in some clinical conditions showed in patients.

Clinical Condition	Methods	Principal Findings	References
Benign paroxysmal positional vertigo (BPPV)	The study was conducted as an investigator-initiated, blinded-outcome assessor, parallel, multicenter, randomized controlled trial in 8 hospitals between December 2013 and May 2017. Patients with confirmed BPPV were randomly assigned to the intervention (N=518) or the observation (N= 532) group. Patients in the intervention group had taken vitamin D 400 IU and 500 mg of calcium carbonate twice a day for 1 year when serum vitamin D <20 ng/mL.	The intervention group showed a reduction in the (Annual Recurrence Rate (ARR) [0.83 (95%CI= 0.74-0.92) *vs*. 1.10 (95%CI=1.00-1.19) recurrences per one-person year] with an incidence rate ratio of 0.76 (95%CI= 0.66-0.87, P<0.001) and an absolute rate ratio of -0.27 (-0.40 to -0.14) from intention to treat analysis. The proportion of patients with recurrence was also lower in the intervention than in the observation group (37.8 *vs*. 46.7%, P=0.005). Supplementation of vitamin D and calcium may be considered in patients with frequent attacks of BPPV.	[32]
Migraine	The study was randomized double-blind placebo-controlled trial, performed in a tertiary headache clinic in 16- week (12-week intervention following a 4-week baseline period) recruiting 80 patients diagnosed with episodic migraine for at least 6 months prior to the study. The patients were supplemented with 2000 UI/day of vitamin D.	Vitamin D supplementation resulted in a significant improvement in Migraine Disability Assessment Questionnaire (MIDAS) score after 12 weeks in the intervention group (21.49 (16.22-26.77) compared to placebo (31.16 (25.51-36.82), P=0.016). Moreover, the calcitonin gene-related peptide (CGRP) levels were significantly lower after vitamin D supplementation in patients in comparison with placebo (P=0.022). Vitamin D supplementation improved migraine headache characteristics by decreasing CGRP levels.	[35]
Incident dementia	In the study, 13,039 participants of the Atherosclerosis Risk in Communities (ARIC) was analyzed in patients with the determination of 25-(OH)-D levels in the midlife and that showed a diagnosis of incident dementia occurring over its 20-year follow-up.	After a median follow-up of 20 years, low 25-(OH)-D concentrations were associated with increased risk for incident dementia (P = 0.01 for trend across categories), with HR of 1.26 (95%CI= 1.06-1.49) for participants with deficient 25-(OH)-D, compared to sufficient concentrations. However, an association between mid-life 25-(OH)-D levels and late-life performance on functional ability or depression was not present.	[36]
Pain	The study was a randomized clinical trial from July 2017 to November 2018 in patients with brain tumor, 60 patients with vitamin D serum levels ≤20 ng/dL were randomly assigned to 2 groups equally. The study group received an intramuscular injection of 300,000 IU of vitamin D before tumor surgery.	Serum level of vitamin D on day 5 of surgery was 22.5 ± 4.3 and 13.7 ± 3.8 in the study and control groups, respectively (P<0.001). A total of 50% of patients had pain on the first postoperative day, but this decreased with the time compared to the control group but with no significant difference. The pain in the study group was less than that in the control group, indicating that a chronic high level of vitamin D may lead to promising results against pain.	[37]
Quality of sleep	The study was a double-blinded clinical trial realized from November 2015 to February 2016, 89 subjects (44 in intervention group) with sleep disorders based on Pittsburg Sleep Quality Index (PSQI). The intervention group patients received 50,000 IU vitamin D supplements once a fortnight for 8 weeks.	The patients who received vitamin D supplementation significantly improved their sleep quality by reducing sleep latency anincreasing sleep duration (P<0.05).	[38]
Language dysfunction	This study recruited 82 cases of children with cerebral palsy and language dysfunction from March 2011 to June 2014, 43 received vitamin D auxiliary rehabilitation (combination group) and 39 rehabilitation treatment. After three months of treatment, language development, Gesell Child Development Scale, Bayley Infant Development Scale score, and vitamin D and calcium levels were compared.	The language development, Gesell Child Development Scale, Bayley Infant Development Scale score, and vitamin D and calcium levels for two groups were improved after treatment compared with pretreatment (P<0.05). In the combination group, the efficiency in language development was higher than in the rehabilitation-only group ((95.3% *vs*. 74.4%, $\chi 2$=2.486, P=0.032). Moreover, the vitamin D and calcium levels were statistically increased compared to the only rehabilitation treatment group.	[40]
Autism	The study was the case-controlled cross-sectional analysis conducted on 122 patients with the diagnosis of autism spectrum disorder. The levels of serum vitamin D were determined and patients with low-serum 25-(OH)-D levels (<30 ng/mL) received vitamin D3 (300 IU/kg/day not to exceed 5000 IU/day) for 3 months (N=106 patients). The relation between vitamin D deficiency and the severity of autism was analyzed.	The mean 25-(OH)-D levels in patients with severe autism were significantly lower in comparison with patients with mild/moderate autism. Serum 25-(OH)-D levels had significant negative correlations with Childhood Autism Rating Scale (CARS) scores. Of the 106 subjects that received vitamin D supplementation, 83 completed its treatment and 67 of them (80.7%) had a significantly improved outcome, which was mainly in the sections of the CARS and aberrant behavior checklist subscales that measure behavior, stereotypy, eye contact, and attention span.	[39]

(Table 2) contd…

Clinical Condition	Methods	Principal Findings	References
Alzheimer´s disease (AD)	The study was a randomized, double-blind, placebo-controlled trial; 210 patients with AD were recruited and randomly divided in patients with vitamin D supplementation and control group. The effect of this supplementation in cognitive function and amyloid beta (Ab) biomarkers measured at baseline, 6 and 12 months were analyzed. The supplementation group received for 12 months 800 IU/day of vitamin D.	The results showed that in AD subjects with vitamin D supplementation improved in plasmatic Ab biomarkers and in information, arithmetic, digit span, vocabulary, block design and picture arrange scores in the study period in comparison with the control group (P<0.05). Moreover, the vitamin D supplementation group showed an increase in scale IQ during the follow-up period (P<0.001).	[41]
Parkinson disease (PD)	A randomized, double-blind, placebo-controlled, parallel-group trial was conducted. In this study, 104 patients with PD were randomly assigned to receive vitamin D supplements (n=56) and a placebo (n=58). The supplement group received 1200 IU/day of vitamin D3 for 12 months. Clinical evaluation was performed with the modified Hoehn and Yahr (HY) stage, Unified Parkinson's Disease Rating Stage (UPDRS) total score. Additionally, analyzed VDR polymorphisms were analyzed: rs10735810, rs1544410, rs11568820, rs7976091, rs731236 and vitamin D binding protein GC1 (rs7041)/GC2 (rs4588).	The results showed that vitamin D3 significantly prevented the deterioration of the HY stage in patients in comparison with the control group (P=0.005). Interaction analyses showed that VDR rs10735810 genotypes modified the effect of vitamin D3 on changes in the HY stage and UPDRS and significantly prevented deterioration of the HY stage in patients with rs10735810 TT (P=0.009) and CT (P=0.02) genotypes with similar results in UPDRS in comparison with placebo.	[42]

4.2. Role of Vitamin D in Neurological Manifestations of COVID-19

In relation to neurological or psychiatric conditions, it has been observed an association between SARS-CoV-2 infection and the presence of inflammatory, vascular, sensorial, behavioral, peripheral and anatomical complications in the CNS [159]. To this day, a cure for COVID-19 does not exist, however, its treatment has been directed to reduce symptomatic manifestations, maintain vital functions, and control and prevent secondary diseases. The World Health Organization (WHO) has recommendations for the use of therapeutics in the treatment of COVID-19 being, the most recent the use of IL-6 receptor blockers (tocilizumab or sarilumab monoclonal antibodies), and systemic corticosteroids in critical or severe conditions and the conditional use of remdesivir considering the latest evidence [160]. In relation to the management of neurological and mental manifestations associated to this disease, the use of antipsychotic medication or benzodiazepines is recommended, along with standard protocols for stroke and behavioral therapy for anxiety, insomnia and depressive symptoms [160]. Vitamins and mineral supplements do not cure COVID-19, although it is recognized that micronutrients such as vitamins D and C and Zinc, are critical for the immune system function and our overall health. Clinical trials are being developed in order to demonstrate the use of Vitamin C, D, E and Zinc and other antioxidants as adjuvants in the treatment of COVID-19 [132, 159, 160]. In relation to this, in a recent work, we proposed the possible mechanisms of antioxidants against SARS-CoV-2 and its possible potential role in protecting against neurological manifestations in this disease [159]. Considering the clinical and experimental evidence where the protective role of vitamin D in neurological diseases and in COVID-19 displayed in this review, we now summarize the evidence where it has been proposed that vitamin D could be a possible protector against the neurological manifestations in patients infected with COVID-19. Fasano and coworkers conducted a case-controlled survey in 105 patients with PD and 92 controls, in Lombardy, Italy, that were diagnosed as confirmed or probable COVID-19 cases. In PD patients, it was identified that the use of vitamin D as supplement was not present, and the researchers found a significant association between COVID-19 clinical status with vitamin D-no supplementation in comparison with non-PD patients (OR=0.56, 95%CI=0.32-0.99, P<0.05) [161]. In another clinical study, a significant association between the risk of COVID-19 infection with lower vitamin D levels in multiple sclerosis patients (P=0.048) has been identified [162]. In a systematic review, it was shown that vitamin D supplementation is associated with lower COVID-19 cases in people with PD (OR=0.5, 95%CI=0.30-0.83, I2=0%) [163]. It has been proposed that the supplementation with Vitamin D3 (2000-5000 IU/day) in patients with PD, schizophrenia and multiple sclerosis could slow the disease progression and protect against COVID-19 or even decrease the risk of developing severe manifestation [164-166].

Perdomo and coworkers proposed the supplementation with vitamin D for reducing the progression of neurological damage in patients with COVID-19 because of its role as an anti-inflammatory agent [167]. Xu and coworkers proposed that vitamin D could prevent the loss of neural sensation in COVID-19 by means of stimulating neurotrophins and NGF expression and by its immunomodulator properties [168]. Moreover, in a meta-analysis, it is shown that the presence of cardiovascular diseases is linked to an insufficient vitamin D supply and this is a risk factor for severe development of COVID-19 (OR=3.219, 95%CI=1.486-6.972) [169] the authors recommended vitamin D supplementation in psychiatric patients (50,000 IU monthly) because in can also prevent severe COVID-19 [170].

Additionally, the effect of vitamin D on mental health during COVID-19 lockdown in people with some neurolog-

ical condition has been studied. Di Nicola and coworkers realized a cohort of patients with major depressive disorder (N=59) or bipolar disorder (N=53), they evaluated through a survey the COVID-19 related distress and they determined the 25-(OH)-D levels in the three months preceding the outbreak and after a seven-week period of lockdown measures. Of all patients (N=112) 74.1% displayed psychological distress, moreover, low 25-(OH)-D levels were significantly related to the severity of distress in the subjects (P=0.005) during the COVID-19 outbreak [171]. In a study that recruited 40 females with multiple sclerosis during the COVID-19 outbreak, vitamin D supplementation (50,000 IU one day/week) in combination with aerobic training significantly improved physical and emotional problems, pain, social function, cognitive and sexual function (P=0.001) [172]. In a cross-sectional study to evaluate mental status, an online survey was conducted on Saudi adults during COVID-19 lockdown; the study recruited 958 subjects, they presented anxiety, depression, and insomnia 25.4%, 27.7%, and 19.6%, respectively and the authors showed an association between vitamin D intake with the risk of developing depression (OR=1.53, 95%CI=1.08-2.16, P <0.05) anxiety (OR=1.71, 95%CI=1.22-2.39, P<0.01) and insomnia (OR=1.48, 95%CI=1.02-2.15, P<0.05) [173].

Regarding clinical trials, >100 studies currently are being developed and the effect of vitamin D in patients infected with COVID-19 is being studied. Of them, only 9 studies have assessed the relation between the effect of vitamin D administration in neurological manifestations induced by COVID-19. The characteristics of this study are presented in Table **3**.

Table 3. Clinical trials where the effect of vitamin D in neurological manifestations of COVID-19 are being evaluated.

Aim	Status of the Study/Location(s)	Treatment	Neurological Manifestation Studied
Assess the safety and efficacy of Nigella Sativa *versus* Vitamin D3 *versus* Nigella Sativa / Vitamin D3 combination as supplement for management of COVID-19.	Recruiting/ Kobry Elobba Military Medical hospitals, Cairo, Egypt.	Intervention model: Controlled Parallel Open Label Randomized Clinical Trial Patients will be administered only the standard treatment regimen (n=25) Patients will be administered a single dose (900mg) of Nigella Sativa capsule twice daily plus standard therapy (n=25) Patients will be administered a single dose (2000 IU) of vitamin D3 tablet once daily plus standard therapy (n=25) Patients will be administered a single dose (900 mg) of Nigella Sativa capsule twice daily, and single dose of vitamin D3 tablet (2000 IU) once daily plus standard therapy (n=25). N=100	Headache, loss of taste and/or smell during 14 days.
Evaluate the effect of vitamin D on morbidity and mortality of the COVID-19.	Recruiting/ Hospital Universitario Central de Asturias Oviedo, Asturias, Spain.	Intervention Model: Interventional randomized study. Patients receiving 1 dose of 100.000 IU of Cholecalciferol when the COVID 19 Disease is diagnosed. Patients without intervention N=100	Headache, anosmia, ageusia during 12 days.
Evaluate how useful vitamin D supplementation is in reducing the severity of COVID-19 symptoms and the body's inflammatory and infection-fighting response to COVID-19.	Recruiting/ Medical University of South Carolina Charleston, South Carolina, United States.	Intervention model: Parallel assignment, interventional randomized. Participants will be randomized to vitamin D3 (6000 IU) per day for 12 months. All participants will receive a multivitamin containing 800 IU of vitamin D3/day. Participants in this arm would receive placebo for 12 months. Participants will be randomized to vitamin D3 as a bolus (20,000 IU) per day for 3 days followed by a high dose of vitamin D (6000 IU) per day for 12 months. All participants will receive a multivitamin containing 800 IU of vitamin D3/day. N=140	Dizziness, sense of smell during 3, 6, 9 and 12 months in negatives and daily for 2 weeks in positives. Perceived stress and pandemic stress monthly for 1 year.
Evaluate the cholecalciferol effect in outcomes of COVID-19 patients.	Completed/ Hospital de Alta Complejidad en Red El Cruce Florencio Varela, Buenos Aires, Argentina.	Intervention Model: Parallel assignment and randomized interventional. Patients that receive 5 capsules containing 100.000 UI of vitamin D each. The intervention will be 5 capsules given in a one-time oral intake. Patients that 5 capsules containing placebo. The intervention will be 5 capsules given in one-time oral intake. N=218	Stroke events (focal neurological loss lasting >24 h) during 30 days.

(Table 3) contd…

Aim	Status of the Study/Location(s)	Treatment	Neurological Manifestation Studied
Evaluate the effect of high dose vitamin D substitution in patients with COVID-19.	Recruiting/ Cantonal Hospital Aarau Aarau, AG, Switzerland Cantonal Hospital Baselland Liestal Liestal, BL, Switzerland Cantonal Hospital St. Gallen Saint Gallen, SG, Switzerland.	Intervention Model: Parallel assignment, randomized and interventional. Patient will receive a single high dose of vitamin D (140,000 IU) in addition to daily 800 IU of vitamin D. Patient will receive a single dose of placebo, orally administered and then treatment as usual. N=80	Impaired consciousness during 14 and 22 days.
Evaluate the effects of the dietary supplement vitamin C, vitamin D, vitamin K and zinc in COVID-19.	Recruiting/ The Centre for Health Innovation, Ottawa, Ontario, Canada.	Intervention Model: Parallel assignment, randomized and interventional. Patients that receive capsule. Each capsule will contain 500 mg (50,000 UI) cholecalciferol, Dose: One capsule on day 1 of the intervention period. Patients that receive liquid. Each 0.0285 mL drop will contain 30 µg menaquinone-7 (MK-7, vitamin K2) and 3.125 µg (125 UI) cholecalciferol (vitamin D3). Dose: 0.114 mL (four drops) twice daily for 21 days resulting in 240 µg MK-7 and 1,000 UI cholecalciferol per day. Patients that receive capsule. Capsule. Each capsule will contain 666 mg ascorbic acid (vitamin C) and 8.3 mg of zinc acetate Dose: Three capsules three times daily for 21 days resulting in 6 g ascorbic acid and 75 mg zinc acetate per day. Patients that receive placebo (microcrystalline cellulose). N=200	Headache, myalgia/arthralgia, loss of taste and loss of smell daily for 21 days.
Evaluate the effect of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc in the Prevention of COVID-19 Infection in medical workers.	Recruiting/ Progena Biome, California, United States.	Intervention Model: Single Group Assignment, randomized and interventional. Medical workers who are exposed to COVID-19 and as such are at higher risk for infection receiving Hydroxychloroquine, Vitamin C, Vitamin D and Zinc. Medical workers who are exposed to COVID-19 and as such are at a higher risk for infection receiving a placebo. N=600	Difficulty speaking and headache were recorded daily for 24 weeks.
Evaluate the effect of cold liver oil in COVID-19 prevention.	Recruiting/Oslo University Hospital, Oslo, Norway.	Intervention Model: Parallel assignment, randomized and interventional. Patients that receive 5 mL of cod liver oil as a source of 10 ug of vitamin D and 1.2 g of long-chained n-3 polyunsaturated fatty acids (DHA 0,6 g and EPA 0,4 g) per day for 6 months x 1 time/day together with the first meal of the day. 5 mL of cod liver oil also contains 250 µg vitamin A and 10 mg vitamin E. Patients that receive placebo (corn oil). N=80,000	Incident dementia for 30 months.
Analyze the effect of nutritional support system in patients with COVID-19 and comorbidities in stage III.	Not yet recruiting/Anáhuac University, México, México.	Intervention Model: sequential assignment, randomized and interventional. Patients who received the nutritional support system (NSS) and the standard diet. Standard diet: The distribution of macronutrients will be 50% for carbohydrates, 30% for lipids and 20% for proteins. Nutritional support: Neurobion 10 mg solution for injection (1 every each 24 h for 5 days, i.m.); 400 mL of water each, contain: Spirulina Maxima 2.5 g, folic acid 5 mg, Glutamine 5g, Cyanomax Ultra (10 g of powder), ascorbic acid 1 g, zinc 20 mg, selenium 100 µg, cholecalciferol 2000 IU, resveratrol 200 mg, concentrated omega 3 fatty acids (10 g of powder), L-Arginine 1.5 g, and magnesium 400 mg. During the entire intervention, 500 mg of Saccharomyces Bourllardii will be administered 1 250 mg capsule every 12 hours during the first 6 days. Patients who received the standard diet (control group). N=240	Cephalea (Daily, 2 shifts, 21 days), Sense of smell and Taste and skin sensitivity (Daily, morning, 21 days), pain (every 2 days, morning, 21 day), rebound sensitivity (daily, evening, 21 days) and sensitivity of the tibial tract (every 2 days, evening, 21 days).

U. S. National Library of Medicine. ClinicalTrials.gov https://www.clinicaltrials.gov/ (accessed Aug 27, 2021) [132].

CONCLUSION

Even though more data from clinical trials pointing to the benefit of vitamin D supplementation for the treatment of patients infected with COVID-19 are still necessary, it is plausible to observe that vitamin D decreases the severity of lung damage, the need for intensive care, the severity and mortality of this disease, as well as improving survival in these patients. According to the previous observations, it can be suggested that vitamin D could present protective properties against the neurological manifestations of COVID-19 given that in some studies it has been suggested that supplementation with this vitamin may reduce the progression of the disease towards neurological damage, probably due to its immunomodulatory, anti-inflammatory effect that secondarily may limit the damage of endothelial cells and decrease the prothrombotic state characteristic of this disease; in addition to the fact that in patients with neurological or psychiatric diseases supplementation with vitamin D may decrease the risk of developing a severe manifestation of SARS CoV-2 infection while during the COVID-19 pandemic lockdown it also improves the mental health of patients with neurological or psychiatric diseases. However, it is necessary to await the results of ongoing clinical trials to demonstrate that vitamin D supplementation can prevent or decrease the occurrence of SARS-CoV-2-induced neurological symptoms and to conduct further studies to demonstrate the biochemical or molecular mechanisms by which vitamin D exhibits benefits (including neuroprotective) properties in COVID-19. This becomes even more important because currently, there is no specific treatment and the available one does not preserve life in all cases. Taking into account the current situation, there is the possibility of periodic lapses of contagion and deaths due to severe COVID-19 in months when the population has less sun exposure. Therefore, to be able to define between cholecalciferol, calcidiol or calcitriol, which is the most useful form, in addition to other specific aspects such as dosage for pre-hospital or hospital use in patients with COVID-19 in order to decrease progression to critical illness, hospital care costs and improve the prognosis of patients' life is pressing.

Finally, other studies indicate that vitamin D can attenuate other virus infections, and further knowledge of this may provide useful indications for reducing mortality caused by other viruses that trigger systemic hyperinflammation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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