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COVID-19 and neurological sequelae: Vitamin D as a possible neuroprotective and/or neuroreparative agent

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ABSTRACT

SARS-CoV-2, the etiological agent of the current COVID-19 pandemic, belongs to a broad family of coronaviruses that also affect humans. SARS-CoV-2 infection usually leads to bilateral atypical pneumonia with significant impairment of respiratory function. However, the infectious capacity of SARS-CoV-2 is not limited to the respiratory system, but may also affect other vital organs such as the brain. The central nervous system is vulnerable to cell damage via direct invasion or indirect virus-related effects leading to a neuroinflammatory response, processes possibly associated with a decrease in the activity of angiotensin II converting enzyme (ACE2), the canonical cell-surface receptor for SARS-CoV-2. This enzyme regulates neuroprotective and neuroimmunomodulatory functions and can neutralize both inflammation and oxidative stress generated at the cellular level. Furthermore, there is evidence of an association between vitamin D deficiency and predisposition to the development of severe forms of COVID-19, with its possible neurological and neuropsychiatric sequelae: vitamin D has the ability to down-modulate the effects of neuroinflammatory cytokines, among other anti-inflammatory/immunomodulatory effects, thus attenuating harmful consequences of COVID-19. This review critically analyzes current evidence supporting the notion that vitamin D may act as a neuroprotective and neuroreparative agent against the neurological sequelae of COVID-19.

1. Introduction

In addition to the main pathophysiological consequences of SARS-CoV-2 infection, i.e. the atypical acute respiratory syndrome that gave rise to its name, the virus can affect the gastrointestinal tract, the kidneys, the heart, and the reproductive system. The disease has recently been characterized as a multi-organ syndrome and multi-systemic nosological entity [1]. Although the long-term effects of COVID-19 are not yet fully understood, coronaviruses have been shown to possess neurotropic and neuroinvasive properties in various hosts, including humans [2,3]. This is because SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 receptor (ACE2) to cross the blood-brain barrier and invade neuronal and glial cells [3,4]. Recent studies pose the hypothesis that neuroinflammation resulting from this viral invasion is due to an increase in the concentration and interaction of angiotensin 2 (Ang-II) with its receptor. This triggers the production of inflammatory mediators and the activation of immune cells, leading to a state of central nervous system (CNS) injury preceded by vascular damage and destruction of the blood-brain barrier, responsible for the installation of acute inflammation [4,5].

The neurological and neuropsychiatric consequences of COVID-19 are abundant. SARS-CoV-2 can induce immune-mediated demyelinating disease, stroke, anxiety and depression and even neurodegeneration, among other complications [6–8]. A meta-analysis performed on more than 100,000 patients showed that 1.4% of these developed strokes, mainly of ischemic origin [9]. This kind of

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neurovascular sequelae may appear more frequently in COVID-19 patients with severe forms of the disease and who have preexisting vascular risk factors such as hypertension, diabetes mellitus or coronary heart disease [10].

Regarding neuropsychiatric sequelae, a cohort study analyzed the health consequences of patients discharged 6 months after the development of COVID-19. In this work, it was reported that 26% of patients developed sleep disorders and 23% developed anxiety and depression [11]. Although it is still too early to provide information on the possible predisposition to developing neurodegenerative diseases secondary to SARS-CoV-2 infection, it is evident that the ability of the virus to remain latent within cells for long periods of time, as well as the high degree of neuroinflammation due to the so-called "cytokine storm", tend to lead to a worse neurological prognosis of these patients [8]. One could therefore hypothesize that viral invasion of the CNS may accelerate the process of these neurodegenerative pathologies [12].

A recent meta-analysis of the literature on COVID-19 and vitamin D (54 independent studies) concludes that patients with low 25-hydroxy-vitamin D levels exhibit a higher susceptibility to SARS-CoV-2 infection and related hospitalization, increased risk of acute respiratory disease, requiring admission to an intensive care unit, and enhanced SARS-CoV-2-related mortality [13–20]. This scenario highlights the need to search for possible palliative as well as preventive interventions in order to avoid potential neurological consequences. The purpose of this review is to summarize the scientific evidence supporting vitamin D as a possible neuroprotective and neuroreparative treatment in SARS-CoV-2 viral infection.

2. The gateway: angiotensin-converting enzyme 2 (ACE2)

ACE2 (the canonical binding target for the SARS-CoV-2 spike protein), is quite ubiquitous in the body and mediates multiple physiological functions, including control of blood pressure and inflammation. SARS-CoV-2 has a high affinity for the ACE2 protein abundantly expressed on the surface of bronchial epithelial cells and endothelial cells, among others [21,22]. Although the level of ACE2 expression in both neurons and glial cells is lower than in other organs, these cells are also potentially vulnerable to SARS-CoV-2 infection [23,24]. ACE2 plays a key role in the recognition of the SARS-CoV-2 spike protein (see [25] for a recent review on the structural aspects of the virus and its host-cell receptors). Various cell-surface proteins have been co-opted by the genus *Coronaviridae* as molecular targets, including serine proteases and metalloenzymes like transmembrane serine protease 2 (TMPRSS2) that constitute entry points for viral infection. Among these are proteins that play an adjuvant role in SARS-CoV-2 invasion of the brain parenchyma [26], such as the CD147 protein [27]. An additional receptor or co-receptor that may act as an entry factor and enhance SARS-CoV-2 in vitro infectivity is neurophilin-1 (NPR-1), a member of a signaling protein family. This cell-surface receptor is important in angiogenesis, tumor progression, viral entry, axonal guidance, and immune function. Furthermore, it appears to be involved in several aspects of SARS-CoV-2 infection, including possible spread through the olfactory bulb and into the CNS. Nevertheless, evidence of the involvement of this protein in SARS-CoV-2 invasion and its potential as a therapeutic target is still inconclusive [28].

3. Central nervous system infection: direct and indirect routes

Although it has been shown that coronaviruses and other respiratory viruses can invade the CNS [29], the exact manner in which this occurs in the case of SARS-CoV-2 is one of the great unknowns in the neuropathogenesis of this infection. However, three possible routes of entry are known: a direct or axonal route, involving intranasal inoculation [30,31], an indirect or hematogenous route, via systemic circulation crossing the blood-brain barrier [32–34], and a third pathway, where the virus can enter the CNS through vagus nerve fibers that connect with enterocytes in the intestine. This third pathway is a current hypothesis that arises from the similarity between SARS-CoV-2 and other respiratory viruses such as influenza [35]. Other centripetal pathways originating in the intestinal mucosae and reaching the CNS have also been considered [36].

3.1. Axonal pathway

The direct route of entry of SARS-CoV-2 via the olfactory mucosae involves transport through the axons of the olfactory nerve, causing the inflammatory obstruction of the olfactory clefts and finally reaching the olfactory cortex, with consequent anosmia [37]. Eventually the virus could reach other brain structures such as the temporal lobe and potentially the brainstem [38]. This phenomenon could be additionally complicated by the release of pro-inflammatory cytokines, causing the destruction of olfactory neurons and supporting cells [39]. Moreover, the direct action of the virus on the epithelial cells from the oral cavity is believed to be the reason for another characteristic symptomatology of COVID-19, dysgeusia [24,37]. The available evidence in favor of this route is still scanty, and transcriptomic studies in particular tend to disregard the direct action of the virus on olfactory neurons, favoring the view that the higher content of ACE2 and its co-receptor TMPRSS2 in the non-neural, goblet and unsheathing cells of the olfactory mucosae makes them a better target for the virus [24].

In view of the possibility that SARS-CoV-2 may also affect the brainstem, it has been hypothesized that respiratory failure in COVID-19 patients could be caused, at least in part, by infection of the respiratory centers of the medulla oblongata and pons [33]. This invites speculation that the respiratory dysfunctions could be of neurogenic origin [40].

3.2. Hematogenous route

Spread of SARS-CoV-2 virus through systemic circulation during an early or late phase of infection could compromise the brain. It has been proposed that the slow transit of blood within the microcirculation could be one of the key factors facilitating the interaction of the virus with ACE2 expressed in the capillary endothelium of the neurovasculature [23]. SARS-CoV-2 spike protein can induce the elimination of the catalytically active ACE2 ectodomain from these endothelial cells and consequently lead to reduced ACE2 function, resulting in dysfunction of the renin-angiotensin system. This triggers an exacerbated inflammatory reaction and increased vascular permeability [41]. Viral crossing through the blood-brain barrier has been proposed as a hypothesis to explain the development of ischemic strokes of large vessels, cerebral venous thrombosis and intracerebral and subarachnoid hemorrhages associated with COVID-19 [42].

Among the indirect effects of the virus on the brain are hypoxia due to respiratory failure which, together with an aberrant immune response results in various forms of encephalopathy, white matter damage, and abnormal blood clotting, all of which increase the chances of stroke [43]. Regardless of whether the brain is compromised through the primary or secondary pathway by SARS-CoV-2, it is not always clear whether the resulting neuropathologies are strictly associated with direct neurotropic invasion, indirect pathological consequences, or a combination of both.

4. COVID-19, neuroinflammation and neurodegenerative disorders

As the mechanisms involved in the neurological symptoms of COVID-19 are progressively elucidated, the concept of "Neuro-COVID-19" is becoming increasingly accepted in research and clinical circles [44]. The most relevant neurological manifestations following SARS-CoV-2 infection include headache, ischemic or hemorrhagic strokes, neuroinflammation, neurodegeneration and neuropsychiatric disorders [45–47]. Some additional neurological-derived manifestations are quite

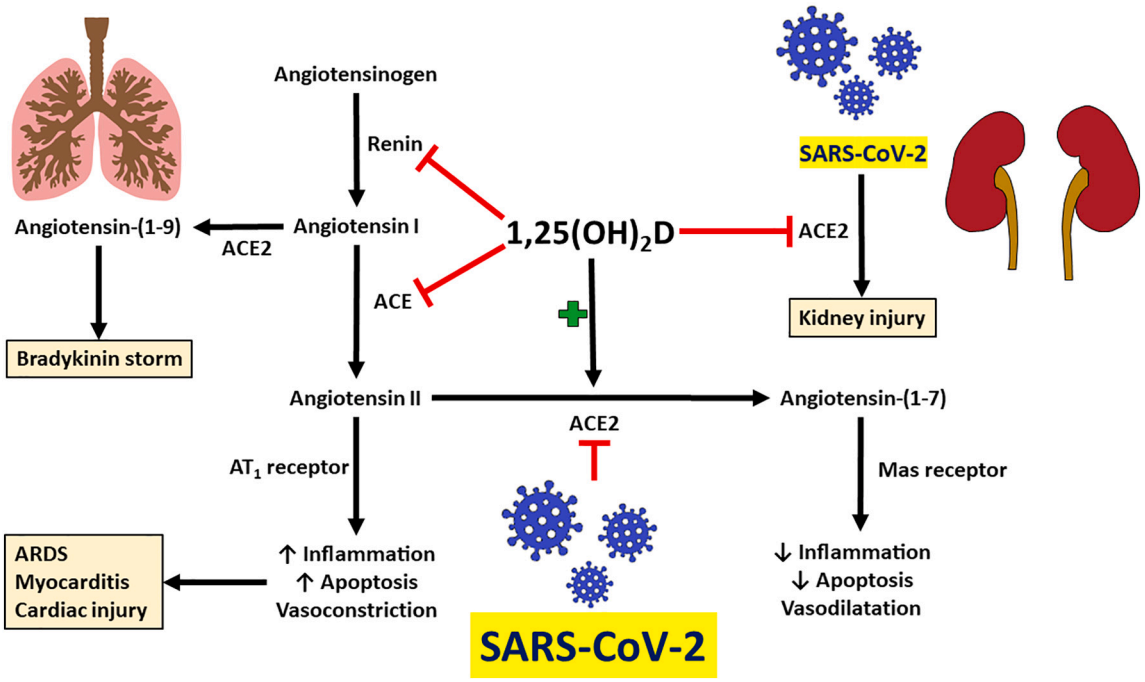

Fig. 1. Schematic representation of the effects of 1,25(OH)2D on the renin-angiotensin-aldosterone system. SARS-CoV-2 uses the ACE2 as the main receptor entry site and downregulates ACE2 in the lungs. This causes the accumulation of angiotensin II, which causes inflammation and apoptosis in the lungs and systemic vasoconstriction by interacting with the AT1 receptor, leading to COVID-related complications including ARDS, myocarditis, and cardiac injury. 1,25(OH)2D inhibits renin and ACE and induces the expression of ACE2 in the lungs, thereby reducing the accumulation of angiotensin II. Inhibition of renin expression may also result in decreased flux of angiotensin I to angiotensin-(1–9), thereby mitigating bradykinin storm. Additionally, 1,25(OH)2D may inhibit ACE2 expression in the renal tubular cells, which is thought to be protective against COVID-associated kidney injury by reducing the viral direct cytopathic effects on the cell. 1,25(OH)2D = 1,25-dihydroxyvitamin D; ACE = angiotensin converting enzyme; ACE2 = angiotensin converting enzyme 2; ARDS = acute respiratory distress syndrome; AT1receptor = angiotensin II type 1 receptor; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus 2.
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pathognomonic of COVID-19 disease caused by most variants of SARS-CoV-2 (though not others, such as Omicron [48]). These symptoms include anosmia (loss of smell) and ageusia (loss of taste), while others are less specific such as delirium and seizures [45,49,50]. One of the main factors responsible for these secondary manifestations is neuro-inflammation resulting from virus infection at both central and peripheral nervous system level.

4.1. Neuroinflammation

Since the SARS-CoV-2 virus is a newly emerging pathogen, our immune system has not yet developed an immunologic memory of it, so the first line of defense is innate immunity. To highlight, this type of defense produces -in some instances [51]- an exacerbated immune response known as “cytokine storm” [47]. One of the main consequences of this process at the brain level is acute necrotizing hemorrhagic encephalopathy, a cerebrovascular pathology observed in patients with COVID-19 [52]. Furthermore, when SARS-CoV-2 invades hematopoietic cells, such as dendritic cells, monocytes or macrophages, it induces not only a decrease in the expression levels of antiviral cytokines such as IFN-ϒ, but also an overexpression of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 and 6 (IL-1 and IL-6). In addition to these phenomena, there is also an overexpression of proinflammatory chemokines such as CCL3, CCL5, CCL2, and CXCL10 [53]. These circulating biomarkers are associated with increased disease severity (of both COVID-19 and its derived neurological pathologies) and could be useful in categorizing the most compromised patients and selecting appropriate therapeutic options [47].

According to extensive studies, many of the antibodies generated in this neuroinflammatory environment may react against elements of the immune system, leading to brain autoimmune pathologies [54]. However, it is not yet known whether this process can also occur in uninfected individuals. A study performed on more than 30,000 healthy individuals showed the occurrence of autoantibody titers directed against type-1 interferon, and that their prevalence increases with age. This could explain why older people have a worse prognosis against both COVID-19 and its neuropathological consequences [55].

4.2. Neurodegeneration

In many instances, SARS-CoV-2 infection is linked to a strong innate immune response and a long-term increase in systemic cytokine levels [47]. Given that this systemic inflammation is often linked to cognitive impairment and various neurodegenerative diseases, there is a possibility that COVID-19 survivors may develop some form of neurodegeneration in the time-course of years [56].

It has been proposed that brain cells may act as latent reservoirs of SARS-CoV-2 as is observed in other tissues [57] and with other viruses [58]. Such latency could be associated with delayed apoptosis and oxidative stress pathways in the nervous system cells, leading to neurodegenerative pathologies such as Alzheimer's disease (AD). Therefore, it is plausible that there is a population at risk of developing neurodegenerative disorders, a risk that has been masked by a silent viral infection in the brain. Moreover, it has been observed that the cytokine storm triggered by COVID-19 may combine with an amyloid protein-stimulated type I interferon (IFN) response in AD patients, resulting in a condition coined “perfect storm” [59]. This could explain why, in pre-symptomatic individuals with pre-symptomatic or undiagnosed AD, a bout of systemic inflammation caused by SARS-CoV-2 infection may trigger the appearance or worsening of symptoms [59]. Thus, from a pathogenic standpoint, the exacerbated immune response could be causing pre-existing neurocognitive disease acceleration/

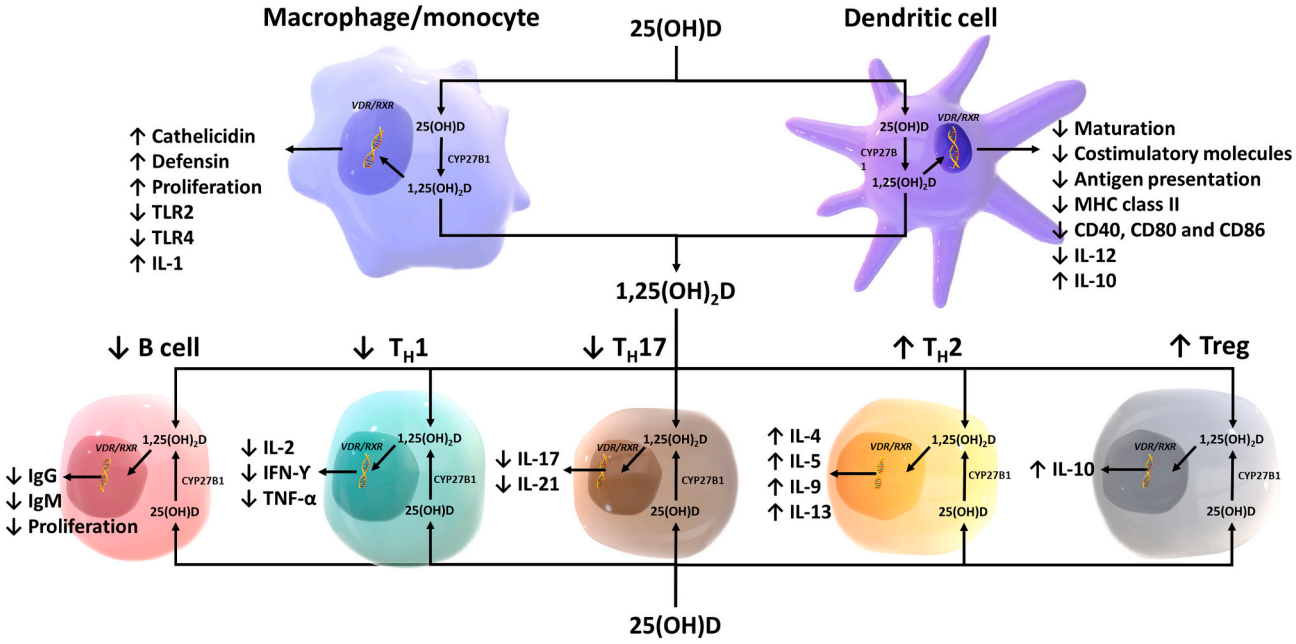

Fig. 2. Schematic representation of paracrine and intracrine function of vitamin D and its metabolites and actions of 1,25-dihydroxyvitamin D on the innate and adaptive immune systems. 1,25(OH)2D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; IFN-Y = interferon-Y; IL = interleukin; MHC = membrane histocompatibility complex; TH1 = T helper 1; TH2 = T helper 2; TH17 = T helper 17; Treg = regulatory T cell; TLR2 = toll-like receptor 2; TLR4 = toll-like receptor 4; TNF-α = tumor necrosis factor- α.
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worsening or the development of a new neurodegenerative disease.

Likewise, although the association between the pathophysiology of COVID-19 and Parkinson's disease (PD) is still unknown, SARS-CoV-2 has been reported to cause an increase in alpha-synuclein synthesis which in turn triggers the release of various cytokines and chemokines characteristic of PD [60,61]. Furthermore, the binding of SARS-CoV-2 to ACE2 may alter GABA (gamma-aminobutyric acid) neurotransmission in the amygdala and possibly in other parts of the brain, as well as produce alterations in dopaminergic neurotransmission, which may represent another possible target of the virus, possibly related to other neurodegenerative sequelae associated with COVID-19 [46,62]. It has also been proposed that antibodies directed against SARS-CoV-2 epitopes also react against the nicotinic acetylcholine receptor or other molecular elements of the neuromuscular junction, thus accelerating neurodegenerative pathologies such as myasthenia gravis, which has also been linked to COVID-19 [63].

5. Vitamin D and COVID-19

Vitamin D deficiency and insufficiency is more prevalent in African Americans, smokers, obese individuals, and people with chronic diseases such as diabetes, hypertension, and various gastroenterological disorders [64–67]. In COVID-19, the high-risk patients with the greatest complications and death rates are also those with a poor vitamin D status [13,16–19,68–70]. Hence, vitamin D deficiency/insufficiency could be one of the main risk factors for COVID-19 complications and increased mortality. Patients who have survived COVID-19 and who have post-acute recovery can be expected to suffer different degrees of physical, cognitive and psychosocial impairment. For many of them, long-term rehabilitation and new treatment options will be necessary. Therefore, different studies have proposed vitamin D and 25-hydroxyvitamin D3 [25(OH)D3, calcifediol] as novel therapeutic options [13,19,69,71–74]. Vitamin D supplementation has been shown to enhance innate immunity such as early macrophage reaction to mucosal-invading viruses and bacteria, reducing the incidence and severity of acute respiratory infections [13,75]. This effect requires a sufficient plasma level of 25-hydroxyvitamin D [D refers to D2 or D3 for both, 25(OH)D3] to be converted into the hormone 1,25-dihydroxyvitamin D [1,25(OH)2D], which activates genes for the production of antimicrobial substances against fungi, bacteria and viruses [13,76–78], including SARS-CoV-2 [79]. In this context, Durrant and colleagues showed that supplementation with vitamin D3 result more efficient than with vitamin D2 concerning gene expression associated with type I and type II interferon activity (critical to the innate response to bacterial and viral infections) [80]. Furthermore, it is known that the overexpression of the vasopressor arm of the renin-angiotensin system and the consequent inflammatory response can be down-regulated by vitamin D [81]. 1,25 (OH)2D also contributes to inhibiting the action of renin by increasing production of ACE2 and decreasing Ang II levels [82] (for more details see Fig. 1). Additionally, 1,25(OH)2D reduces the cellular immune response provoked by the cytokine storm during SARS-CoV-2-induced pneumonia [72,83,84]. Finally, the possible optimization of SARS-CoV-2 vaccine efficacy by vitamin D supplementation is also currently being evaluated in various clinical trials (see e.g. [74]). Vitamin D supplementation would be crucial in COVID-19 subpopulations with low vitamin D status [serum concentrations of 25(OH)D] to improve the prognosis of the disease and avoid lethal consequences [85].

6. Vitamin D, neuroinflammation and neurodegeneration

Vitamin D has a significant impact on the development and function of the CNS. VDR is expressed in neurons and microglia, and they may directly metabolize 25(OH)D3 due to the presence of 1-hydroxylase [86]. Glial cell line-derived neurotrophic factor and nerve growth factor expression can be regulated by 1,25(OH)2D3. The potential of 1,25 (OH)2D3 to control inflammation and regulate specific neurotrophic factors has led to the concept that 1,25(OH)2D3 is neuroprotective. In fact, in recent research, 1,25(OH)2D3 has been demonstrated to reduce reactive oxygen species-induced cell death while increasing anti-oxidant species in glial cells [86].

Studies on different animal models of neuroinflammation report that vitamin D plays an important neuroprotective role against this

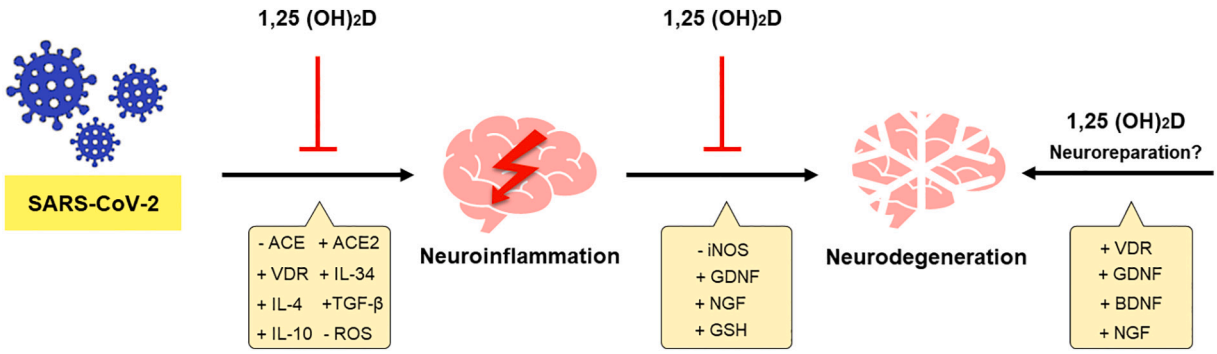

Fig. 3. SARS-CoV-2 invasion leads to a neuroinflammatory and neurodegenerative process due to a potentially connected reduction in the angiotensin II converting enzyme (ACE2) activity. Vitamin D controls this enzyme, which has neuroprotective and neuroimmunomodulatory activities. In addition, vitamin D, among other anti-inflammatory/immunomodulatory actions, can down-modulate the effects of neuroinflammatory cytokines, reducing COVID-19's detrimental effects. This research supported the hypothesis that vitamin D may function as a neuroprotective and neuroreparative agent against the neurological consequences of COVID-19. Signs (+) or (−) mean stimulation and inhibition, respectively. Signs (+) or (−) mean stimulation and inhibition respectively. 1,25(OH)2D = 1,25-dihydroxyvitamin D; ACE = angiotensin converting enzyme; ACE2 = angiotensin converting enzyme 2; VRD = vitamin D receptor; IL-34 = interleukin 34; IL-4 = interleukin 4; IL-10 = interleukin 10; TGF-β = transforming growth factor-beta; ROS = reactive oxygen species; iNOS = inducible nitric oxide synthase; GDNF = glial cell-derived neurotrophic factor; NGF = neurotrophin nerve growth factor; GSH = reduced glutathione; BDNF = brain-derived neurotrophic factor.

inflammatory process [87–90], some showing that adequate sun exposure may confer beneficial immunomodulatory effects against established multiple sclerosis [83,91]. Likewise, a combination of omega-3 fatty acids and vitamin D has also been shown to modulate neuroinflammatory processes in an animal model of traumatic brain injury [92], thus underscoring the potential of vitamin D-based treatments against encephalopathies caused by SARS-CoV-2.

IL-34 is a cytokine that is necessary for microglia survival and homeostasis. Neurons primarily produce it in the CNS, and its expression is maximum during post-natal development and decreases in adults [86]. If vitamin D signaling in neurons promotes the synthesis of IL-34, this could protect the CNS against autoimmunity by preventing excessive microglia activation during inflammation in early life.

Vitamin D deficiency has been linked to several neurological illnesses such as Parkinson's disease, schizophrenia, depression, and cognitive decline, suggesting that it plays a vital role in maintaining normal CNS function [93–95]. Another study in an animal model of oxidative stress and neurodegeneration reported that vitamin D plays an important role in memory and cognition, and that its deficiency could accelerate cognitive impairment [96]: both the immunomodulatory and antioxidant effects of vitamin D significantly reduced different pro-inflammatory interleukins and increased the synthesis of anti-inflammatory chemical mediators (Fig. 2). These effects were accompanied by a decrease in amyloid β-protein formation and an increase in memory performance [96]. Taken together, these findings reinforce the hypothesis that vitamin D supplementation could be an effective option to avoid the development and progression of neurodegenerative pathologies such as Parkinson's and AD in post-COVID-19 patients [97–100].

7. Vitamin D as a treatment for COVID-19-derived neuropsychiatric disorders

Vitamin D deficiency/insufficiency has been associated with the increased risk of mental health problems. Indeed, low vitamin D status has been linked to depressive symptoms in various studies, leading to the conclusion that maintaining an adequate vitamin D status could prevent several mental disorders, such as depression [101,102]. This is of considerable importance since depression is the most common neuropsychiatric disorder associated with COVID-19. By modulating serotonin and dopamine metabolism, vitamin D has been shown to improve serotoninergic and dopaminergic neurotransmission in cellular models [103] and in an animal model of depression [98]. Activation of the vitamin D receptor by the active form of vitamin D, 1,25(OH)2D3, induces both tryptophan hydroxylase 2 and serotonin reuptake transporter expression as well as monoamine oxidase-A levels [104]. In addition, vitamin D may also modulate some chronobiological processes, possibly preventing the development of depressive symptoms when light-dark cycles are misaligned [68,104]. In this context, we know that one of the most common outcomes of social isolation due to SARS-CoV-2 is the development of stress, anxiety and depression, which have a direct impact on metabolic and psychological equilibrium [105]. It has been asserted that mental alterations of this nature may be palliated using a therapy involving melatonin and vitamin D [68]. Melatonin and vitamin D supplementation could promote the restoration of cellular and mitochondrial metabolic imbalances resulting from chrono-disruptive processes, leading to the recovery of psychological and physical well-being [106].

8. Conclusion and prospects

COVID-19 is a complex and still poorly understood disease whose adequate characterization remains to be elucidated. This, as well as the ability to predict the increasingly frequent long-term neurological and neurocognitive-associated pathologies of the disease, call for further investigation [107]. Rigorous and systematic longitudinal follow-up studies of COVID-19 patients will provide the required data to evaluate the diagnosis, prognosis and treatment of these neurological sequelae. In the meantime, vitamin D monitoring and supplementation in both current COVID-19 patients and in those who have recovered should be considered as a possible strategy to add to our therapeutic arsenal from a neuroprotective and/or neuro-reparative perspective (Fig. 3).

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Declaration of competing interest

The author(s) declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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