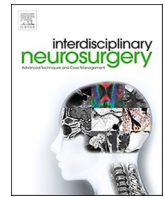Contents lists available at ScienceDirect

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Vitamin D and its' role in Parkinson's disease patients with SARS-CoV-2 infection. A review article

Ahmed Y Azzam [a,*], Sherief Ghozy [b], Mohammed A Azab [c]

[a] October 6 University Faculty of Medicine, Giza, Egypt
[b] Department of Radiology, Mayo Clinic, Rochester, MN, USA
[c] Department of Biomolecular Sciences, Boise State University, Boise, ID, USA

ABSTRACT

A novel coronavirus reportedly called 2019-nCoV started to spread around the world at the end of 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was later renamed after links with SARS were observed. Multiple studies have reported possible connections between the COVID-19 virus and neurodegenerative diseases, including Parkinson's disease. Theories support that vitamin D deficiency plays a part in the pathogenicity of Parkinson's disease or the credibility of the associated dopamine system. Administration of vitamin D3 was shown to significantly enhance the motor and non-motor manifestations of Parkinson's disease and enhance the quality of life. Also, multiple recent reviews have shown specific ways in which vitamin D reduces the risk of pathogenic infections. Recent studies supported the potential role of vitamin D in reducing the risk of COVID-19 infections and mortality. On the immunological level, immune response regulation remains one of the well-recognized actions of vitamin D. Vitamin D deficiency has been linked to complications in patients with SARS-CoV-2 infection and Parkinson's disease. Whereas more studies are required, Vitamin D supplementation with a moderate and well-calculated dosage of vitamin D3 in patients with Parkinson's disease can help minimize the risk and burden of COVID-19 complications.

1. Introduction

1.1. COVID-19: An overview

A novel coronavirus reportedly called 2019-nCoV started to spread around the world at the end of 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was later renamed after certain SARS links were observed [1]. The subsequent SARS-CoV-2 disease was referred to as coronavirus disease in 2019 (COVID-19). SARS-CoV-2, like SARS and Middle East Respiratory Syndrome (MERS), is a beta coronavirus primarily engaged in bats [1]. Like most of the other coronaviruses, SARS-CoV-2 is a non-segmented, positive, single-stranded RNA virus. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor on pneumocytes type I and type II [1]. Several manifestations of COVID-19 include fever, cough, and dyspnea, with pneumonia development in addition to sepsis in more severe cases [2]. The more severe cases will lead to conspicuous hypoxemia and a need for respiratory support therapies. This pro-inflammatory condition can contribute to acute respiratory distress syndrome and cytokine storm syndrome (CSS), possibly induced by a maladaptive immune reaction involving interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-ɪɪɪ), interferon-gamma (IFN-y), interleukin-1 beta (IL-1β), and other provocative signaling pathways [3]. Potential immune-impacting options have been introduced to provide preventive benefits or to reduce the incidence of COVID-19. Vitamin D is one of these options [3].

1.2. Vitamin D: An overview

Vitamin D level and its concerning regulation with the parathyroid hormone activity (PTH) and the maintenance of the calcium and phosphate levels to be balanced in according to needs [4]. Vitamin D is acquired into the body either by exposure to sunlight and by food or supplementation [5]. Vitamin D precursor (7-dehydrocholesterol) is synthesized in the human skin by ultraviolet (UVB) rays, where it becomes Vitamin D3. Vitamins D2 and D3 can be acquired directly from supplementation and fatty fish and milk products. Vitamin D supported cereals, beverages, and some non-dairy products [4,5]. Vitamin D deficiency any complications including neurological disorders [6]. On the

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immunological level, immune response regulation remains one of the well-recognized actions of vitamin D antigen-presenting cells that could effectively metabolize the precursor of 25-hydroxyvitamin D (25D) to active 1,25-dihydroxyvitamin D, And that supports the interplay of vit d with immunity [7]. Finding that immune activated cells expressed subcellular vitamin D receptors indicated a possible vitamin D role as an endogenous spatial modulation or immune responses [7]. At the current pandemic of COVID-19, some randomized clinical trials and *meta*-analyses claim that vitamin D supplementation has benefits protecting against the development of COVID-19 manifestations [8]. Some retrospective case-control studies have shown a link between vitamin D and COVID-19 incidents and complications, whereas other studies did not show any association when confounding factors were modified [8].

1.3. Vitamin D and Parkinson's disease: An overview

Studies on the relationship of vitamin D deficiency with Parkinson's disease (PD) have shown contradictory results. An observational prospective cohort study found that there was inadequate evidence to support the theory that vitamin D deficiency played a part in the pathogenicity of Parkinson's disease or the credibility of the associated dopamine system [9]. However, other studies, including a randomized control trial and comparative study, have indicated a higher prevalence of vitamin D deficiency in Parkinson's disease patients [10,11], clarifying the inverse association between serum levels 25-hydroxyvitamin D and the incidence of Parkinson's disease [12]. Vitamin D supplementation was shown to decrease the rate of loss of motor activity as defined by both the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS) in an RCT [13]. In another study, it was found that increased vitamin D levels could minimize the risk of Parkinson's disease [14]. It is still too early to know if COVID-19 will have long-term effects on PD and movement disorders patients. The global exposure of the frail and those with comorbid conditions, along with the increased incidence of PD with age, raises questions about the possible increased risk of COVID-19 in persons with PD and other movement disorders [15].

In contrast, the capacity to deliver routine neurological treatment is undermined by the burden on medical services exacerbated by this outbreak. In a current manner, presently there is inadequate evidence to suggest that PD alone raises the risk of COVID-19 [15]. Hypothetically, vitamin D may affect the outcome for COVID-19 patients with PD due to its' role in regulating the response Figure.1 [7].

2. Discussion

2.1. Vitamin D and Parkinson's disease: A more defined picture

The global burden of vitamin D deficiency in PD patients could be attributed to decreased general physical activity and reduced exposure to sunlight due to restricted mobility. A retrospective case-control study found that a higher serum level of 25(OH)D was correlated with improved spontaneous posture reactions in the targeted PD cases [16]. In addition to affecting motor activity, vitamin D can add neurological benefits in PD cases. All rodent studies have shown a prominent role of vitamin D on the extent of toxin-induced loss of dopaminergic fibers, excluding absurdly high vitamin D levels or extraordinarily high vitamin D amplification within serum in mice, which has increased neurotoxic effects [17,18]. Those observations are consistent with human studies' findings in which high doses of vitamin D have shown to improve overall fractures [19]. An essential consideration is that the loss of toxin-induced dopaminergic neurons in PD mouse models differs from the much-reduced loss of substantia nigra in PD. On the level of genetic studies, it was shown that a potential relationship between PD and VDR polymorphism FokI, the FokI 'CC' allele has been strongly correlated with relatively mild PD forms, presumably due to the increased and more convenient functionality of this VDR allel variant. This is

consistent with the findings of other analyses of FokI polymorphisms [20,21]. Patients with FokI 'T' allele and (presumably) less functionality were more responsive to vitamin D supplementation [13]. However, the findings remain inconsistent since two experiments found a slight but substantially higher incidence of the 'FokI C' allele VDR in PD and indicate the contrary, i.e., potential increased risk of PD in the setting of a FokI C allel [22,23]. Further studies are required to validate and discuss the relationship between FokI VDR polymorphisms and PD. The current literature review aspect offers a perspective of what is established about the relationship between vitamin D and PD in a current manner. Fig. 1

2.2. Vitamin D and COVID-19: Exploring the links

Multiple recent reviews have shown some ways through which vitamin D reduces the risk of infections [24–27]. Vitamin D helps by three mechanisms to minimize the risk of common infections: physical barrier, cellular immunity, and adaptive immunity [28]. A recent study also supported the potential role of vitamin D in reducing the risk of COVID-19 infections and mortality [29]. It helps by retaining cell junctions and gap junctions, increasing cell immunity by lowering the cytokine storm with effect on interferon-gamma and tumor necrosis factor-alpha [29], and controlling adaptive immunity suppressing T-assistant cell type-1 reactions and promoting T-cell induction [30]. Vitamin D supplementation improved CD4 + T cell count in HIV infection [31]. Cellular pathways involving Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding, M−protein−mediated type-1 IFN induction disruption, and MDA5 and RIG-I host-recognition evasion have been described in the highly associated COVID-MERS virus [32,33]. Human DPP-4/CD26 correlated with the S1 domain of COVID-19 spike glycoprotein, indicating that it may also be a prominent virulence factor in Covid-19 infection [34]. Disturbance in the regulation of the DPP-4/CD26 receptor is greatly diminished in vivo due to the insufficiency of vitamin D [35]. There is currently no clear indication that vitamin D supplementation reduces the incidence and mortality of COVID-19. Specific randomized controlled trials have been registered to determine the role of vitamin D in COVID-19 infections and severity but have not yet published their results. To date, a prospective cohort study [36] has shown the protective benefits of combination vitamin D, magnesium, and vitamin B12 against the clinical progression of COVID-19. Throughout the previous *meta*-analysis, vitamin D supplementation was reliable and effective in reducing acute respiratory infections [37]. Individuals with extreme vitamin D deficiencies had the highest benefit from supplementation. The authors also observed that the beneficial effect of vitamin D was high in respondents with baseline serum 25(OH)D levels < 25 nmol/L relatives to respondents with serum 25(OH)D levels > 25 nmol/L [38]. Vitamin D supplementation has also been shown to improve antioxidant-related gene expression on glutathione reductase modifier subunit [39]. Increased development of glutathione decreases the use of vitamin C, which has possible antimicrobial activity [40,41] and has been proposed to prevent and treat COVID-19 infection [29]. There is minimal evidence to date that ingestion of vitamin D at 20–50 μg/day has any adverse health effects. Ingestion of vitamin D at doses up to 100 μg/day is safe for adults [42], and several specialist groups now recommend supplementation in older people but at lower amounts than that. The study stated that the consumption of vitamin D supplements at 100–250 μg/day over six weeks increased the baseline serum concentration of 25(OH)D from 2 to 3 times, accordingly, without adverse health effects.

2.3. COVID-19 and Parkinson's disease: Possible impacts

Multiple studies have also reported possible connections between the COVID-19 virus and neurodegenerative diseases, including PD recommendations [43,44]. These are focused on coronaviruses' capacity to
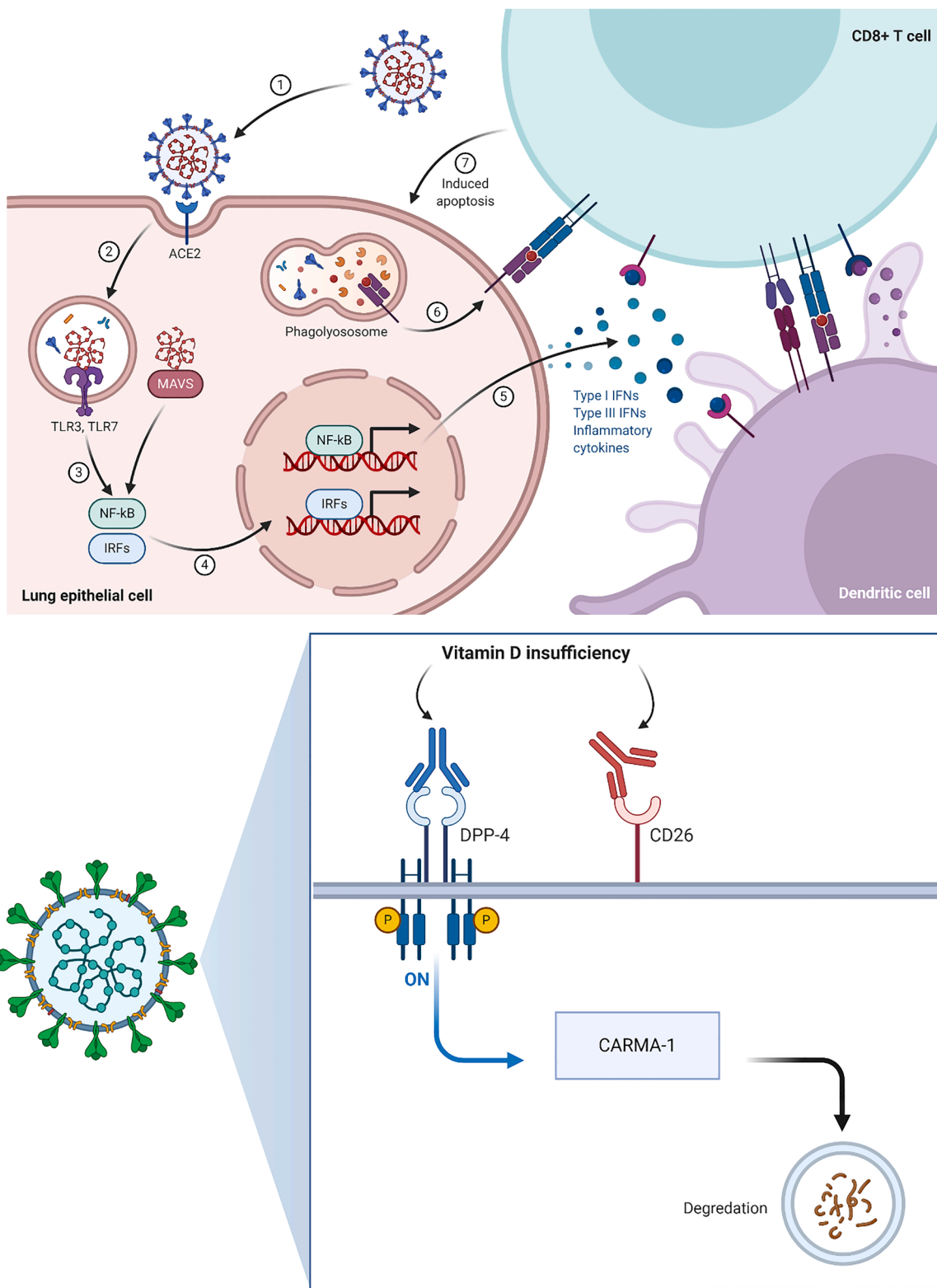
Fig. 1. Immunological responses to SARS-CoV-2. Created with BioRender.com.

penetrate the CNS via the nasal cavity with resulting neuronal death [45,46], as demonstrated in animal models. Hyposmia is well known in COVID-19 patients with no nasal congestion and rhinorrhea [47–49] and is also a typical paroxysmal characteristic of PD [50]. Basal ganglia lesions in COVID-19 [51,52] can emerge in the sense of thromboembolic encephalopathy. The existence of significant antibodies against the other coronaviruses that induce common infections in CSF patients with

PD relative to stable controls indicates a potential role of viral infection in PD [51] pathogenicity. There have been indications that ACE2 can be expressed in different nervous system areas [53,54]. Given this enzyme's interferon expression, it would be essential to investigate individuals with CNS inflammation or encephalitis. The latest syncope findings with no irregular cardiovascular rhythms indicate a possible role for neural-mediated syncope [55] against orthostasis, highlighting

the significance of these inquiries for PD patients frequently suffering from dysautonomia [56]. A case study of a woman who acquired myoclonus and acute but eventually reversible hypokinetic rigid syndrome, with DaTscan indicating a decrease in dopamine transporters' uptake in putamen and hyposmia [57]. The angiotensin pathway involved in the pathogenesis of COVID-19 could be essential in the neuroinflammatory and neurodegenerative pathways found in PD [58,59]. Resident immune cells in the CNS can be triggered by the release of cytokines and invaded from the periphery, resulting in brain cell damage. These cells can include activated T cells and microglia that may destroy neurons [60–62], astrocytes, and vascular cell types. This can result through the aggregation of cells that directly identify presented antigens from infection or prior infections, or by the general regulation of cytotoxic cells that recognise other antigens, including autoantigens, such as those originating from alpha-synuclein that are involved in PD, Lewy Body dementia, multiple organ atrophy, and multiple sclerosis [63,64]. Elevated concentrations of pro-inflammatory cytokines, such as TNF and IL-1beta, are implicated in PD development, whereas the use of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-TNF biologics decreases risk [65]. Anti-TNF biologics is reportedly under review for COVID-19.

2.4. Safety and side effects of vitamin D and clinical relevance

Having an overdose of vitamin D is very rare because it is considered a fat-soluble compound. In the same context, events related to extreme sun exposure are even rarer. On the other hand, increased supplementation of vitamin D beyond the pre-determined levels can develop hypervitaminosis D [66]. Boucher *et al.* [67] also expressed that the direct internal synthesis of vitamin D analogs does not contribute to such toxicity events because they poorly bind to the vitamin D binding globulins, while oral supplementations are deemed the best candidates for such binding. Grant *et al.* [29] showed that a limit of 7,500–10,000 IU/L could be considered, which is far higher than the previous limit suggested by the United States Institute of Medicine. Therefore, any approaches to increase the daily doses beyond this limit are not recommended and should always be done under the treating physician's supervision. To prevent potential respiratory tract infections, Grant *et al.* [29] also suggested that daily supplementation of 40–60 ng/L 25 (OH) D_3 should be adequate for such interventions. However, it is worth mentioning that previous studies showed that the daily limit should not exceed 30 ng/L when applying interventions to chronic disorders like hypertension and other skeletal and cognitive diseases [66,67]. Meehan *et al.* [66] reported that adverse events secondary to hypervitaminosis D are experienced when a daily dose of 60 ng/L of 25 (OH) D_3 has been reached. Such adverse events include nausea, vomiting, constipation, poor appetite, weight loss, and weakness. Other adverse events as confusion, disorientation, fatigue, arrhythmias, gastrointestinal and nephrological complications, and nephrocalcinosis and nephrolithiasis may also occur due to potential secondary hypercalcemia [66,67]. However, such complications and adverse events would always remain rare unless the pre-specified limits were exceeded.

Therefore, vitamin D supplementation should be recommended based on the previously discussed facts about the proven benefits of vitamin D on the immune system and the potential role in COVID-19 infected patients, in addition to the proven effect on PD patients and the rare adverse events that such supplementation may result. Supplementation can occur in many ways. However, the most non-expensive and affordable one is by supplying D3 or cholecalciferol. It has also been found that such compounds have high safety profiles which may reduce the possibility of overdosage even more. However, a daily limit of 2000–5000 IU/L of D3 has been previously recommended. It can be exceeded in some instances in specific management of some diseases. However, this should be done according to the attending physician's supervision. It has also been recommended that supplementation be done for a life-long period or as long as possible; in patients with PD to

prevent any remissions and enhance the prognosis. In addition to optimizing the maximum daily dose, the lowest value can also be determined by monitoring the clinical condition [68]. This is because patients present with PD are usually older and have vitamin D deficiency. Therefore, careful monitoring for dose optimization is essential in achieving optimal care. Evidence also indicates that vitamin D supplementation can also decrease the risk of having COVID-19 infections in these patients, in addition to reducing the non-motor and motor clinical pictures of PD and reducing the frequency of bone fractures [29]. If this can be achieved by vitamin D supplementation, enhanced quality of life for PD patients can be easily achieved [69].

3. Conclusions

Vitamin D may have antiviral effects and may play a significant role in defending against pathogens causing respiratory diseases. People are typically deficient in vitamin D, and people with PD seem to be more likely to be deficient. Administration of vitamin D3 can significantly enhance the motor and non-motor manifestations of PD and enhance the quality of life. Whereas more studies are required, Vitamin D supplementation with a moderate and well-calculated dosage of vitamin D3 in patients with PD can help minimize the risk and burden of COVID-19 complications.

Conflict of Interest:

The authors certify no conflict of interest with any financial organization about the material described in the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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