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Review Article

SARS-CoV-2 Infection and Multiple Sclerosis: Proactive Approach in a Vulnerable Patient Group through Daily Vitamin D Supplementation?

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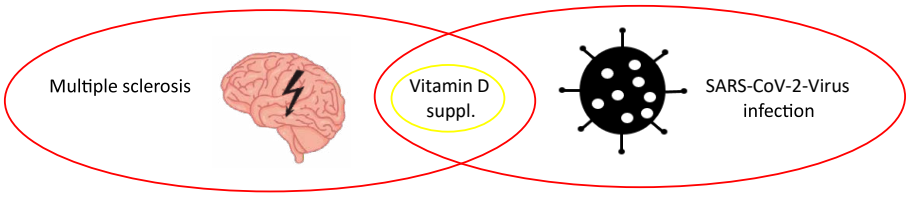
Graphical Abstract

Common immunological signaling pathways between multiple sclerosis and SARS-CoV-2 infection

- Dysregulation of the immune system in vitamin D deficiency
- Influence of early, preclinical vitamin D supplementation – a decisive factor for therapeutic effectiveness
- Modulation of the disease progression due to immunomodulatory properties
- VitD deficiency- risk factor for infection and severe pathology



Pro-inflammatory cytokines (e.g. TNF Alpha, IFN Gamma, GM-CSF, IL-17A, IL-6) ↑	Inhibition of pro-inflammatory Cytokines Reduction of cytokine storm	Inflammation (IL-1 Beta, IL-6, IL-12, IL-17, IL-18, TNF Alpha, IFN Gamma, Th1, Th17 a.o. (Cytokine storm) Inflammatory response by microglia ↑
Reduction Tregs cells (FOXP+regulatory T cells, Tr1) ↓	Promotion of Treg cells	
Microglia 1, Th1 cells, Th17 cells ↑ Astrocytes	VitD regulates the activation of microglia and astrocytes. In dentritic cells, it decreases IL-12, TNF alpha and IL-6 production and promotes IL-10 production.	
Disruption oft he CNS barriers (BBB) and cell migration ↑ Tight-Junctions (TJ) ↓	Calcitriol reduces disruption of the BBB 1,25(OH)2D3 prevents loss of TJs protein expression	Causes BBB dysfunction ↑
Epstein-Barr-Virus (EBV-Association)	Lowering anti-EBNA-1 antibody levels in MS Reduction risk of EBV infection	Reactivation of EBV by SARS Cov 2 ↑
Gut-Brain-Axis (GBA) affected (Dysbiosis of the intestinal microbiota, Reduction of short-chain fatty acids (SCFA) Activation of effector Th17 cells)	Positive effect on intestinal barrier function, microbiome, immune response	Microbiota-gut-brain axis damaged
Activation of inflammasomes ↑ (NLRP3 system)	Suspicion of activation of the NLRP3 signaling inflammasome pathway in vitamin D deficiency	Activation of inflammasomes (NLRP3) ↑ secretion of IL 1 Beta, IL-18
Fatigue ↑	Improves quality of life	Fatigue (Long COVID associated with low s25(OH)D levels) ↑
Neuroprotection	Reduction of inflammation and oxidative stress. 1,25(OH)2D3 suppresses activation of reactive astrocytes and M1 microglia. Promotion Neurotrophic factors	Neurological damage in the acute and post-acute stages (Post-COVID)

Introduction

An explicit goal of multiple sclerosis (MS) therapy is the "best possible disease control" taking into account the "best possible quality of life" of the patient, with the option of using highly effective therapeutic agents early or as early as possible in response to disease activity [1], but also a to seek proactive therapy by making use of all therapy options [2].

Multiple sclerosis (MS) is an inflammatory neurodegenerative disease with a suspected autoimmune origin. The disease begins earlier than current diagnostic criteria can detect. It affects the entire central nervous system and not just the white matter, as the original term-inflammatory demyelinating disorder-suggests [3]. It is characterized by a very heterogeneous course of the disease, which is represented by relapse-associated neurological deterioration, but also by an increase in disability that is independent of relapse [4]. It is generally accepted that infections in people with MS (PwMS) can have a negative impact on the course of the MS disease. This justifies that all potentially therapeutic and preventive options, especially for COVID-19, should be exploited.

MS is associated with reduced vitamin D status [5]. The molecular mechanisms in the pathogenic effect of vitamin D deficiency in MS are diverse and are orchestrated by encephalitogenic T cells with B cells, microglia, dendritic cells, interleukins (IL-1 beta, IL-6, IL-12, IL-17, TNF alpha, (tumor necrosis factor), MHCII, interferon gamma, among others) [6].

Not only is vit D deficiency associated with MS risk, but s25(OH) D levels are inversely correlated with risk of relapse, CNS lesions, and disability progression. Vitamin D suppl. reduces the number of new Gd+-enhancing or new/enlarged T2 lesions on MRI [7-10]. With MS, which is currently not curable, a high level of activity is required to prevent complications, especially infections of any kind. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an exceptionally transmissible and pathogenic coronavirus that emerged in late 2019, causing a pandemic of acute respiratory illness known as coronavirus infection 2019 (COVID-19). New omicron variants are constantly being discovered [11], for example BA.2.86 (Pirola), JN. New findings show that BA.2.86 efficiently enters lung cells and uses TMPRSS2 for entry into lung cells. The mutations S50L and K356T are for the efficient Lung cell entry of BA.2.86 is responsible. BA.2.86 has a high resistance to therapeutic antibodies and evades the antibodies induced by infection and vaccination [12,13]. COVID-19 can develop into a severe disease associated with immediate and delayed sequelae in various organs, including the central nervous system (CNS) [11].

Over the last 3 years, a complex connection between SARS-CoV-2 infection and MS has emerged [14].

Daily Vitamin D Supplementation is a Prerequisite for the Suppression of Inflammatory Processes

The risk of severe infection from COVID-19 should provide additional motivation for one daily high-dose vitamin D administration [15,16]. As part of prevention, it is worth mentioning that with circulating s25(OH)D values ≥ 55 ng/mL, the SARS-CoV-2 positivity rate was significantly lower than with values below or with deficiency [17]. Current data suggest a protective role for VitD, particularly with a lower risk of intensive care unit admission and a reduced risk of death [18,19]. In addition, the occurrence of Long-Covid is an aspect of implementing this simple, effective, safe and costeffective therapy with a broad therapeutic window for the prevention and treatment of COVID-19 disease [20-22]. Although there is still no indisputable evidence that Vit D supplementation (VitD suppl.) reduces the risk of SARSCov-2 infection in healthy individuals, there is collective evidence that it benefits vulnerable individuals [23]. PwMS with comorbidities, psychiatric illnesses, hypertension, obesity (an increased BMI may correlate with a severe course of Covid-19), age > 50 years, severe disability and methylprednisolone boost therapy as well as some DMTs (disease-modifying therapies) have a higher risk of infection and an increased risk of severe COVID-19 courses [24-26]. Infections (SARS-COV-2) can increase MS symptoms (pseudo-relapses) or cause real relapses [27]. In post-COVID syndrome (Long Covid), one in eight patients presents with symptoms such as fatigue, shortness of breath, cough, joint pain, chest pain, muscle pain, headache and paresthesia in the limbs after at least 3 months. The latter can also occur in PwMS per se [28,29]. If vitamin D administration results in a lower risk of infection, severity of illness with admission to the intensive care unit or a reduced risk of death in people at risk, Long-Covid occurs less frequently [18,19,21,22,30-33], it is not ethically justifiable to withhold high dose vitamin-D administration from people at risk.

Mechanisms of Action of Vitamin D in COVID-19

Barrea et al. list in detail 14 mechanisms as described by Vit D suppl. the risk of COVID-19 infection can be reduced and sufficient Covid 19 vaccination is supported [19,29,32,34-38]. Vit D and its metabolites inactivate viruses (increase in antimicrobial peptide cathelicidin, defensins), lead to reduction of the risk of cytokine storm, reduce matrix metalloproteinase-9 concentration and thereby increase the host's metabolic tolerance to damage, reduce the risk of pneumonia and myocarditis, lead to the reduction of the concentration of pro-inflammatory cytokines, especially interleukin 6 (IL-6), which promotes the permeability of the BBB, which leads to the potentiation of CNS damage in PwMS, is serious [29,39-42].

Vit D enables neuroprotection by reducing inflammation and oxidative stress. Low 25(OH)D levels were inversely correlated with high IL-6 levels and were independent predictors of COVID-19 severity and mortality [43]. 1,25(OH)2D3 inhibits immunoglobulin synthesis, regulates B cell activity and reduces auto-Ab production. It converts B cells into plasma cells [18]. Vit D reduces the risk of infection with EBV [29].

Current studies show evidence that chronic inflammation in Long Covid-19 Infection with reactivation of the latent Epstein-Barr virus (EBV) can lead to a worsening of the health status in PwMS [44-48]. In MS, there is a high level of molecular mimicry between the EBV transcription factor EBNA-1 and the CNS protein GlialCAM (glial cell adhesion molecule of the central nervous system [49]. Bernal et al. were able to detect EBV reactivation by detecting EBV DNA and antibodies against EBV-lytic genes [50].

In 66.7% of Long Covid patients, EBV reactivation could be demonstrated by a positive titer for EBV EA-D (early antigen-diffuse)-IgG or EBV-VCA (viral capsid-antigen)-IgM) can be provided [45]. Long COVID patients with fatigue and neurocognitive disorders were with serological evidence of recent EBV reactivation (early antigen-D [EA-D] IgG positivity) or high nuclear antigen IgG levels [51].

The triad of inflammatory markers IL-1ß, IL-6 and TNF can be found in both Long Covid and MS [52-54]. Low sun exposure acts synergistically with high EBNA-1 Ab levels and was associated with an increased risk of MS [55]. There is a connection between high EBNA-1 antibody levels and low s25(OH)D levels. On the other hand, a high dose of VitD suppl. the EBNA-1 antibody levels in PwMS [56-58]. Another parallel arises from the increase in GFAP (glial fibrillary acidic protein) as a dysfunction of the astrocytes about 4 months after the start of SARS-Cov2 infection [51]. The concentration of NfL (Neurofilament light chain), GFAP and total tau in CSF in patients with COVID-19 was often elevated with neurological symptoms [59]. Elevated sNfL has already been verified in mild to moderate COVID-19 disease [60]. On the other hand, the risk of mortality increased if sNfL and sGFAP levels were already elevated upon hospital admission [61].

Because there are no effective drugs that block EBV reactivation in Long Covid [62], there are multiple arguments for Vit D suppl. High-dose Vit D-Suppl (14,000 IU/day) for 48 weeks or 20,000 IU/week for 48 weeks selectively reduced anti-EBNA-1 antibody levels in PwMS (RRMS) [58,63].

Several mechanisms are under discussion:

1. VitD could induce better clearance of EBV infected B cells,
2. Vit D could directly target and impair viral replication in EBV-infected cells,
3. Produce better control of inflammation in general,
4. In an EBV-mediated inflammatory cascade, 1,25(OH)2D3 could suppress the activation of reactive astrocytes
5. It is likely that at high s25(OH)D levels, the VitD receptor EBNA 2 (Epstein-Barr virus nuclear antigen 2) is displaced upon DNA binding [58,63-68].

Early Start of Therapy is a Crucial Factor

The early start of therapy with VitD suppl. is crucial for influencing influenza and COVID-19 infections [69]. The Corona-19 mortality risk correlates inversely with the VitD status and a mortality rate close to zero could theoretically be achieved at over 50 ng/mL s25(OH)D [70]. The importance of Vit-D metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment of infections (COVID-19) is increasingly being considered in clinical practice as part of a multitherapeutic approach [34,71,72].

Dosage Suggestions for Vitamin D Supplementation

Currently, there are no consensus guidelines suggesting an appropriate concentration of serum 25(OH)D to prevent COVID-19 or reduce its morbidity and mortality. It is becoming increasingly clear to start with a "loading dose" with high VitD doses over a few days and then continue with a "maintenance dose", although various variants have been put up for discussion.

For example, one study used a weekly or fortnightly dose totaling 100,000-200,000 IU for 8 weeks (1800 or 3600 IU/day) [73].

To obtain 75 nmol/l s25(OH)D values, the following equation was described:

Dose (IU) = 40 x (75-serum 25(OH)D(3) [nmo/L] x body weight [73].

Over 30 ng/mL s25(OH)D values were also achieved with a single oral dose of 200,000-600,000 IU [38,74].

An s25(OH)D level of 40-60 ng/ml could be achieved by dosing up to 6,000 IU/day over several weeks [75,76]. A daily VitD intake of 10,000 IU/day for 4 weeks would lead to a faster optimal s25(OH)D level in the „status nascendi" of an infection [19].

Another dosage regimen was recommended: cholecalciferol 0.532 mg on day 1 and continued with 0.266 mg on days 3,7,14,21,28 (1 IU vitamin D3 = 0.025 µg vitamin D3 = 65.0 nmol Vitamin D3 [77]. The pharmacokinetic properties of calcifediol allow rapid absorption within hours, facilitating the immediate availability of 25(OH)D2 in target tissues.

This drastically reduced the need for intensive care unit admission and the mortality rate [77]. A key mechanism of 1,25(OH)D2 is its effect on Vit D receptors (VDR) on the adaptive immune system. The activity of TH1 and TH17 cells is reduced and the T regulator (Treg) cells are induced. This results in a reduced production of proinflammatory cytokines (IL-6, IL-8, IL-12, IL17, TNF alpha) and the cytokine storm is weakened [77,78].

The further daily VitD dose will depend on the s25(OH) values. The "maintenance dose" depends on the genetic polymorphism of the enzymes involved in VitD metabolism. Because interindividual differences in the organism's response to Vit D, particularly in PwMS, are established, one of many explanations for the controversy surrounding the clinical results of Vit D suppl. [6,78,79].

An example of this individual reaction to a Vit D suppl. with 3,200 IU daily for 5 months showed a strong response to peripheral blood mononuclear cells in 60% of healthy individuals, while only a mild to moderate response was recorded in 40% despite reaching 25(OH)D values of 60-90 ng/ML was [80].

Up to Date 2024

Clinical Manifestation of a SARS-Cov-2 Infection in PwMS as Ulcerative Colitis - A Novum

Another challenge in the diagnostic diagnosis of gastroenterological symptoms is exclusively COVID-19-induced colitis (enteropathic infection) without pulmonary manifestation or as the first manifestation of COVID-19 disease [81-87]. In the ileum and colon, there is extensive expression of the angiotensin converting enzyme 2 (ACE2) on the enterocytes, to which the SARS-CoV-2 corona virus binds, penetrates the cells of the intestinal epithelium and causes the inflammation or aggravates existing one chronic inflammatory bowel

disease (IBD) [84,87-90]. Molecular mimicry between SARS-CoV-2 and human proteins (enteric epitopes) promotes gut-associated autoimmune diseases [91].

SARS-CoV-2 as an autoimmunogenic virus is seen in association with another 10 autoimmune diseases and multidisciplinary management can be beneficial in long-COVID [92-94]. Vit D deficiency can promote autoimmune dysregulation [95].

PwMS are Predisposed to Comorbid Autoimmune Diseases

PwMS have a tendency to be polyautoimmune [96-98] and hundreds of common genetic susceptibility loci for autoimmune diseases have been identified [99,100]. Up to 18% of PwMS suffer from additional comorbid autoimmune disorders.

Inflammatory bowel diseases (IBD) [ulcerative colitis, Crohn's disease]) are among the most common autoimmune diseases accompanying MS [101]. About beneficial and adverse effects of DMTs and comorbid autoimmune diseases details in [102]. Knowledge of the tendency towards polyautoimmunity is the key to the precise interpretation of symptoms, even in contrast to treatment-related undesirable side effects of anti-CD20 therapy.

Disease-Modifying Therapies (DMT) Can Increase the Risk of Infection

Long-term observation has shown an increased incidence of respiratory tract infections, urinary tract infections and SARS-CoV-2 during therapy with monoclonal anti-CD20 antibodies in MS (ocrelizumab, ofatumumab, ublituximab, rituximab) [103-105]. The predominant depletion of CD20+ B cells, but also CD20+ T cells and the effect on CD8 T cells by ocrelizumab as well as the additional reduction in immunoglobulins (IgG, IgA, IgM) explains the increased risk of infection [103,106].

Discussion

The connection between Vit D and COVID-19 has been critically examined in over 120 clinical studies, including 41 RCTs, and a strong connection between Vit D and clinical outcomes in Covid-19 has been proven.

Several mechanisms have been discussed:

1. Affects 1,25(OH)2D3 antimicrobial peptides (cathelicidin), tigth junction proteins and adherenc junction proteins (ZO-1, occludin, claudin-10, ß-catenin, VE-cadherin) [107].
2. 1,25(OH)2 D3 suppresses the activity of TH 1 and TH 17 cells and induces Treg cells. As a result, there is a reduced production of proinflammatory cytokines (IL-6, IL-8, IL-12, IL-17, TNF alpha) and a weakening of a cytokine storm [79].
3. Vit D plays an important role in controlling the renin-angiotensin-aldosterone system. Details in [78].

Furthermore, genetic polymorphisms of the Vit D metabolism pathway and nongenetic reasons could explain the controversies surrounding the clinical results of Vit D supplementation [78,79,108]. If the physiological basis for the use of Vit D to improve the health of the general population has already been found with Vit D daily doses of 5000-7000 IU/day [109], it is biologically plausible to use a Vit D suppl. to be carried out preventively in the event of impaired immune homeostasis in PwMS to improve immune function. The daily dose of Vit D is crucial for the therapeutic success of broad gene expression. A daily dose of 10,000 IU leads to genomic changes that were several times higher than with 4000 IU/day [80].

Through the immunomodulatory effect of 25(OH)D and its anti-inflammatory mechanisms, immune-mediated colitis caused by anti-CD20 antibody therapy or ulcerative colitis caused by SARS-CoV-2 could be suppressed or alleviated. This form of manifestation of COVID-19 disease is particularly important in vulnerable people (PwMS) receive attention. [81-94].

Calcitriol may play a supportive role in neuroprotection particularly in PwMS by attenuating neuroinflammation and protecting the endothelial integrity of the blood-brain barrier (BBB) [110,111]. The steep learning curve in assessing clinical symptoms in LONG COVID-19 reveals new manifestations of autoimmune diseases, particularly after severe SARS-CoV-2 infections. In addition to the risk of rheumatic diseases, the occurrence of Crohn's disease and ulcerative colitis must be taken into account in long-term care [112-116] and is a challenge in the future. Comorbidities affect PwMS more frequently than people without MS and are associated with greater physical and cognitive impairment,lower health-related quality of life,and increased mortality [117].In long-term management,one goal is to potentially avoid comorbidities.Due to the predisposition to polyautoimmunity,thyroid diseases (Hahimoto's thyroiditis,Graves'disease) are not uncommon as comorbidities [118]. An infection of the endocrine system with SARS-CoV-2 (e.g. thyroid, adrenal gland, pituitary gland, etc.) is possible and the virus has been detected in post-mortem samples [119]. SARS -CoV-2 also mainly penetrates here the main receptor ACE2 and its co-receptor TMPRSS2 into the host cells. ACE2 protein expression was detected in about 87% of deceased COVID-19 patients. Pathological thyroid function tests correlated with the severity of the disease [119,120]. People with one already existing autoimmune disease and Covid-19 were 23% more likely to be diagnosed with another autoimmune disease [112]. In patients with comorbidities, advanced age and SARS-Cov-2, overactivation of T cells, overproduction of proinflammatory cytokines (IL-1 beta, IL-2R, IL-6, IL-8, IL-17, TNF alpha, IFN beta) and a reduction in Treg cells are confirmed [121]. Infections with SARS-CoV-2 and mRNA vaccines can trigger the clinical onset of an autoimmune disease [122]. So it must be during and after the SARS-CoV-2 infection, subacute thyroiditis, Graves disease and Hashimoto's thyroiditis are expected [122] and the PwMS should be monitored accordingly in the event of clinical symptoms. The immunomodulatory function of vitamin D could be used as part of an early treatment strategy , as vitamin D deficiency increases the risk of autoimmune thyroid diseases [123]. There is a negative relationship between anti-thyroid antibodies (TPO-Ab, TgAb, TSHR Ab) and a sufficient serum 25(OH)D level. A Vit D suppl. led to a decrease in thyroid antibodies and in hypothyroidism, TSH levels decreased. Vit D positively influenced Hashimoto's thyroiditis and graves disease [124-137].

A Covid-19 cohort showed a significantly higher risk of IBD and celiac disease [138]. Patients with ulcerative colitis were more likely to develop a severe form of Covid-19 than the general population [139]. Despite partly contradictory results of studies on the relationship between vitamin D, Covid-19 and IBD, it can be recognised that 25(OH)D levels above 30ng/mL can exert a protective function [140].

As Covid-19 is not a thing of the past and appears to be here to stay, an easy-to-use and inexpensive vitamin D supplement is needed and should be offered to at-risk groups. The active form of Vit D not only shows a dual effect on SARS-CoV-2 and MS, but also has a versatile spectrum of action on MS.

Summary

People with multiple sclerosis could proactively influence the course of their disease and reduce the risk of infections with possible complications through long-term prophylaxis with daily vitamin D supplementation. The immunomodulatory influence of vitamin D is undisputed and cytokine storms (COVID-19) as well as a severe course of the disease could be prevented. 25(OH)D serum values of over 50 ng/mL should be aimed for through individual daily vitamin D supplementation. The 25(OH)D serum values obtained in studies in the general population with daily doses of 5000-10,000 IU/day cannot be adequately transferred to people with multiple sclerosis and must be titrated individually. Due to the known immunopathological mechanisms of vitamin D and its benefits, it would be desirable to integrate this add-on therapy into standard clinical care.

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