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Multiple sclerosis with comorbidity depression and its association with vitamin D deficiency in a narrative review of the current literature

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Abstract

Over the past decade, knowledge of the pathophysiology and immunology of multiple sclerosis (MS) and depression, and the complex links to vitamin D (VitD) balance, has increased rapidly. Both diseases are characterized by an imbalance of proinflammatory and antiinflammatory cytokines, increased serum neurofilament light chains (sNfLs), disruption of the blood-brain barrier (BBB), abolition of the physiological function of the various types of microglia (MG), decreased calcidiol-serum levels, and disorders of the gut microbiome in combination with hyperactivity of the hypothalamic-pituitary-adrenal (HPA)-axis/microbiome-gut-brain-axis characterized. In depression, stress initiates cellular and molecular changes in the brain via increased cortisol release in the HPA-axis. Microglial activation and neuronal damage as well as dysregulation of neuroplastic and neurotrophic factors complete the spectrum of pathological damage. It is shown that gut dysbiosis leads to increased gut permeability, which favors endotoxemia and ultimately paves the way to systemic inflammation. A VitD supplementation could restore the balance of microorganisms in the intestine and reduce the inflammatory processes at various levels. VitD promotes regulatory T cell (Treg) proliferation, inhibits the expression of T helper 1 (Th1) cells and Th17 immune cells, and inhibits proinflammatory interleukin-17 (IL-17). 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] reduces also the secretion of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α). Increased calcitriol levels lead to a reduction in MG activation, oxidative stress, and lower BBB permeability. An early, permanent, daily sufficient VitD supplementation as an add-on therapy under control of the serum 25-hydroxyvitamin D [s25(OH)D] levels is an essential therapeutic tool to slow down the disability caused by MS and thereby primarily prevent or reduce the stress and subsequently the manifestation of depression. Through the future continuous measurement of the biomarkers serum neurofilament ligth chains and glial fibrillary acidic proteins as well as the s25(OH)D level in MS and comorbidity depression, future therapy successes or failures can be avoided.

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Keywords

Depression, multiple sclerosis, pathophysiology, immunology, vitamin D supplementation, 25-hydroxyvitamin D levels, serum neurofilament light chains

Introduction

Comorbid psychiatric disorders, especially depression, are serious complications in the course of multiple sclerosis (MS). Immune dysregulation is associated with depressive disorders but is also a central element of the pathology of MS [1]. Intrathecal inflammation in people with MS (PwMS) and depression leads to increased neurodegeneration and thus progression of disability [2]. However, depression can also indicate inflammatory reactivation in MS [3].

Depression as a comorbidity occurs in PwMS in up to 50% of cases [4–8]. Fatigue is present in 35–97% of people living with PwMS, severely affecting the quality of life [9–12].

MS is a complex, autoimmune-mediated central nervous system (CNS) disease characterized by inflammatory demyelination and axonal/neural damage [13]. In general, up to 50% of patients with autoimmune diseases show a reduced health-related quality of life. The activated immune system not only leads to inflammation in affected organs but also to depression-like symptoms [14]. The increased prevalence of depression in MS correlates with elevated serum levels of proinflammatory cytokines and the general deregulation of monoaminergic neurotransmitters in MS [15].

Vitamin D (VitD) deficiency is recognized as a risk factor for the presence and severity of depressive symptoms in both depressed patients and PwMS [4, 16–19].

Previous theories on the etiology of depression include the monoamine neurotransmitter deficiency hypothesis, disorders in the system of neurotrophins (NTs) and neurogenesis, involvement of the hypothalamic-pituitary-adrenal (HPA)-axis as a result of stress, excitatory and inhibitory neurotransmission, mitochondrial dysfunction, (epi)genetics, inflammation, the opioid system, and disorders of myelination and the gut-brain-axis. The gut-brain-axis is of great importance in the activation of the microglia (MG) and may also be a potential therapeutic target [20–23].

Table 1. Common features/similarities to pathophysiological mechanisms in MS and comorbidity depression

Criteria	Depression/mood disorders	MS
HPA-axis dysfunction/stress/elevated cortisol release	[24, 28, 37, 38]	[26, 27, 30, 34–36]
Imbalance of proinflammatory and antiinflammatory cytokines	[39–42, 44]	[12, 98, 154, 261]
sNfL, an early biomarker for neuronal damage (“troponin of the neurologist”)	[45–47, 50–53]	[56–60, 62]
sGFAP for diagnostics to detect “smoldering MS” and monitor the severity of the depression	[65, 68, 70]	[66, 69, 70]
BBB disorders	[113–119]	[109, 110, 113]
Microglial pathology	[20, 123, 128, 129]	[124–126]
Gut microbiome disorders	[150, 151, 154, 156–158]	[145, 146]

VitD insufficiency is associated with MS and depression

Similarities in the pathophysiological and immunological mechanisms between MS and depressive disorder:

(1) Dysfunction of HPA-axis activity.

(2) Imbalance of proinflammatory and antiinflammatory cytokines.

(3) Increased serum neurofilament light chains (sNfLs), serum glial fibrillary acidic protein (sGFAP).

(4) Disruption of the blood-brain barrier (BBB).

(5) Elimination of the physiological function of the different types of MG.

(6) Decreased serum 25-hydroxyvitamin D [s25(OH)D] levels.

(7) Disorders of the intestinal microbiome in combination with hyperactivity of the HPA-axis/microbiome-gut-brain-axis [21–23] (Table 1).

HPA-axis activation is a hallmark of the stress response

Increased stress leads to increased inflammatory reactions in the brain and periphery with increased plasma concentrations of proinflammatory cytokines, but also highly sensitive C-reactive protein (hsCRP) and cortisol (also in older people) [24]. VitD deficiency is correlated with an increase in C-reactive protein (CRP) and a sufficient s25(OH)D level can reduce chronic inflammation [25].

It is generally accepted that psychologically stressful situations can trigger MS flare and fuel neuroinflammation through the dysregulation of the HPA-axis [26, 27]. Patients with major depressive disorders also show both hyper and hypoactivity of the HPA-axis, especially with stress in early life [28]. On the other hand, an association of stress-related disorders with a significantly increased risk of subsequent autoimmune diseases could be established [29].

There is evidence that MS is associated with hyperactivity of the HPA-axis and elevated endogenous cortisol levels can be measured [30]. However, HPA-axis activity also correlates with MS disease severity, comorbid mood disorders [31, 32], lesion type, and gene expression in normal-appearing white matter (NAWM) [33]. Proinflammatory cytokines are considered to play a major role in the (hyper)activation of the HPA-axis ("impairment of corticoid receptor signaling accounts") and chronically progressive PwMS also showed increasing HPA-axis activity [34–36].

However, high cortisol levels from hyperactivity of the HPA-axis from chronic stress increasingly impair the ability of these endogenous glucocorticoids to regulate inflammation in MS as immune cells become desensitized their cortisol [27]. However, high cortisol levels have also been linked with slower MS progression, particularly in women with secondary progressive MS (SPMS). In contrast, PwMS with low cortisol levels had a larger number of active lesions and showed a tendency to have fewer remyelinated plaques than PwMS with high cortisol levels [33].

In depression, there is also dysregulation of the HPA-axis with a disturbance in the feedback mechanisms [37]. An early stressful situation could trigger this dysregulation of the HPA-axis and may be related to early MS manifestation [28]. The stress system is hyperactive, and a 5% enlargement of the left hypothalamus could be measured with 7 Tesla magnetic resonance imaging (MRI). The larger the hypothalamus, the more severe the depression. It confirms that stress response may be related to structural and functional asymmetry in the brain [38].

Impact of inflammation on MS and depression

Up to 50% of PwMS experience depressive states during their lifetime. The prevalence of fatigue is even higher than that of depression, with a prevalence as high as 75%. In later phases of MS, the prevalence of fatigue can increase up to 95% [39].

It has been established that depression goes along with a dysregulation of the immune system and activation of the inflammatory cascade and that acute depression is a proinflammatory state [40]. As early as 13 years ago, a meta-analysis showed that significantly increased levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and CRP are found in depression [41, 42]. Thus, while an increase in proinflammatory cytokines such as TNF-α, interferon-γ (IFN-γ), IL-1a, IL-1b, IL-2, and IL-6, increase of IL-12, IL-13, IL-18, IL-1 receptor antagonist (IL-1Ra), and soluble TNF receptor 2 (sTNFR2) was observed, the activity of natural killer (NK) cells and regulatory T cells (Tregs) was suppressed [12, 39, 43].

There are also conflicting data on immune activation and immunosuppression in depression. A decrease in the proinflammatory cytokine IFN-γ was also observed. On the other hand, increased IL-6

values and increased CRP levels have been confirmed to be causal in depression [40] and are relevant prognostic parameters [39].

A reduced IL-10 and transforming growth factor β (TGF-β) as well as an increased IL-6/IL-10 ratio and reduced Treg expression and/or function were found in depressed patients. Furthermore, examination of $CD4^+CD25^+$ Treg expression in depression showed a reduced Treg percentage associated with reduced IL-10 and TGF-β levels [44].

Relationship of sNfL to neurological and psychiatric diagnoses

sNfL in depression

SNfLs are recognized as biomarkers of CNS neuroaxonal damage and are referred to as the "neurologist's troponin". In the future, they will also make it easier for psychiatrists to classify neuropsychiatric symptoms. Increased sNfL as a neuron-specific marker can be observed in a variety of diseases of the CNS (and also in the peripheral nervous system) [45]. Patients with depression had significantly increased neurofilament light chain (NfL) values and these could serve as a biomarker in depression as in PwMS [46, 47].

However, significantly lower cerebrospinal fluid (CSF) NfL values were seen in psychiatric disorders than in neurological diseases [48]. At the same time, the TNF-α levels were also increased in depression. There was a positive relationship between sNfL and TNF-α levels. This points to the important role of neuroaxonal injury by proinflammatory cytokines in depression [49]. SNfLs as an indication of axonal damage are also increased in cognitive dysfunction [50].

In a study, significantly elevated sNfL values were observed in 41 patients with depression, which were above the age-specific cut-off values and corresponded to reduced cognitive performance [tested using Digit Symbol Substitution Test (DSST) scores (cognitive processing speed)] [51]. The increase in sNfL levels also correlated with neuroimaging studies showing subtle, widespread white matter changes and reduced brain volumes in patients with depression [51, 52].

Treatment resistance in major depression was associated with elevated sNfL levels [53].

Studies in patients with bipolar diseases showed a complex interaction of increased sNfL and VitD deficiency [49, 54].

A considerable problem, therefore, is the evaluation of sNfL in patients suffering from both MS and depression as a comorbidity. This marker can be used to assess the severity of depression but can indicate an acute MS flare.

For the early detection of suicidal behavior, the determination of inflammatory markers (IL-2, IL-4, IL-6, TGF-β) and the increase in sNfL as a result of complex neuroinflammatory processes could be used in the future. The sNfL values were significantly higher in patients with suicide attempts than in the controls (40.52 ng/mL ± 33.54 ng/mL *vs.* 13.73 ng/mL ± 5.11 ng/mL) [55].

In addition to activation of the HPA-axis and MG during suicidal behavior, there is another chain of biochemical and neuropathological changes resulting in neuroaxonal damage [55].

SNfL in MS

SNfLs were documented in over 200 studies as an indication of activity in MS [56].

Longitudinal studies of PwMS have shown that sNfL levels rise 5 months before the acute MS flare, peak at the clinical onset of the flare, and recover within 4–5 months [57]. In the preclinical phase of MS, sNfL increases could be verified 6 years before the onset of clinical symptoms [58]. Premorbid cognitive deficits and frequent physician visits and hospitalizations, including psychiatric consultations, demonstrate the early onset of neurodegenerative disease prior to the definitive diagnosis of MS [59, 60]. As early as 2016, an inverse association between s25(OH)D and CSF NfL levels could be demonstrated. 25-hydroxyvitamin D [25(OH)D] levels above 40 ng/mL were associated with lower CSF NfL levels regardless

of ongoing MS treatment [61]. High sNfL levels within the first year of illness were associated with a long-term deterioration of the disability in PwMS [62].

With a 96-week VitD supplementation in relapsing-remitting MS (RRMS) with weekly administration of 20,000 IU, a decrease in the sNfL level by 32.6% was shown even without disease-modifying therapy (DMT) [63]. However, in a small number (n = 24) of PwMS with RRMS, 48 weeks of VitD supplementation (14,000 IU/day) failed to lower the sNfL levels [64].

Glial fibrillary acidic protein in MS and depression

In the future, the determination of sGFAP, an intermediate filament of astrocytes in serum and a marker of astrocyte activation, will play an important role in the assessment of the clinical picture and monitoring of both depression and MS [65–67]. The level of sGFAP was linked with depression severity and age [65, 68], while, in MS, sGFAP will be a biomarker to assess a chronic progression independent of relapse activity (PIRA) [66, 69]. With the simultaneous determination of sNfL as a biomarker for neuronal damage, the activity of both diseases can be better assessed, which is of great importance for therapy management [70].

It is known from experimental studies that increased vitD intake in neuronal, axonal, and glial damage causes a reduction in sGFAP [71] (Table 2).

Table 2. Relationships of biomarkers to disease activity and effects of VitD/VitD supplementation on disease progression in depression and MS

Criteria	Depression	MS
sNfL (follow-up monitoring of the activity by the drop in serum levels)	[45–50, 54]	[61–64]
sGFAP (lowering in serum values as an indication of improvement in neuronal, axonal, and glial damage)	[65, 68]	[66, 69–71]
HPA-axis/serum cortisol levels	[28, 74]	[31, 32, 73]
VitD deficiency	[18, 71, 82–84, 91–96, 164, 165]	[97–101, 138, 140–143]
Antiinflammatory/proinflammatory cytokines	[4, 84, 86, 88, 89]	[110, 149]
Sealing the BBB	[113–118]	[109–112]
MG	[20, 123, 128, 129]	[98, 121, 127]
Disorders of the gut microbiome, HPA-axis, and microbiome gut-brain-axis	[21–23, 150, 151, 153]	[103, 144, 149]
Pregnancy/postpartum phase	[166–174]	[169]

Relationships between the HPA-axis and VitD supplementation

Despite clinical data on dysregulation of the HPA-axis in depression, no drug has been approved that affects specific components of the HPA-axis [72].

Several studies show that VitD can influence the stress axis [73]. Higher cortisol levels have been associated with severe disease progression in MS [31, 32]. In a small group of PwMS, VitD supplementation with 4,000 IU/day which confirms a trend toward suppression of the HPA-axis by determining the levels of cortisol in saliva [73]. A high cortisol awakening response (CAR) is an important predictor of depressive episodes and there are complex interactions between depressive symptoms and daily cortisol release patterns in PwMS [32]. An elevated CAR indicates a hyperactive HPA-axis with increased daily cortisol release [32].

Depression and VitD supplementation

In the literature service alone (PubMed, 2023), over 160 works were published in the last 50 years on the problem of "depression and VitD" and over 163 publications on the subject of "MS and VitD". Controversial opinions on this topic have accumulated over the last decades [74]. The causes are extremely diverse and complex. Different study designs, in particular a lack of international agreement on the "normal calcifediol [25(OH)D] levels in serum in autoimmune diseases" complicate the assessment. Because of the multiple immunomodulatory effects of VitD on the innate and adaptive immune system as well as the nervous

system, the normal value for s25(OH)D defined for immunologically competent individuals cannot be considered a recommended benchmark for autoimmune diseases.

An autoimmune attack on the CNS requires high circulating s25(OH)D up to 130 ng/mL [75]. Serum VitD concentrations are determined by dose and absorption. There are several genetic polymorphisms that control VitD metabolism and contribute to the serum VitD concentration and thus to the physiological required level [76]. There is therefore no one-size-fits-all dose, and everyone likely needs their own (personalized) level of supplementation. This speaks against blanket guidelines for PwMS. The spectrum of the different responder rates to the VitD supplementation in the healthy population is approximately as follows: 24% are "low responders", 51% are "mid responders", and 25% are "high responders" [77–79].

Daily doses of 5,000 IU to 10,000 IU of VitD are not associated with any risk, especially since checking the s25(OH)D levels, calcium (Ca), and phosphorus, initially, every 3 months and later every 6 months, reveals an overdose [76]. When used with a high degree of caution, the determination of serum parathyroid hormone can provide additional security.

There is also no uniform definition of the terms "VitD deficiency", "VitD insufficiency", or "VitD sufficiency" in the studies, whereby the "clinical practice guideline of the Endocrine Society" defines serum concentrations of ≤ 20 ng/mL as VitD deficiency, 21–29 ng/mL as VitD insufficiency, and 30–100 ng/mL as VitD sufficiency [80, 81]. Misinterpretations of studies are therefore inevitable.

The exact mechanisms involved in the relationship between VitD deficiency and depression are not known. It is theorized that VitD can affect the synthesis of serotonin, dopamine, and norepinephrine in the hippocampus, substantia nigra, and prefrontal cortex [82]. It has also been shown that VitD is involved in controlling the expression of genes responsible for maintaining homeostasis of both Ca^{2+} and reactive oxygen species (ROS) [83]. VitD deficiency has been associated with high intracellular Ca^{2+} levels [18]. An increase in the formation of ROS, which can have a negative effect on neuronal function, has been observed in depression [4]. The phenotypic stability hypothesis argues that VitD acts by reducing the elevated neuronal Ca^{2+} levels that drive depression [18].

There is more and more evidence that the imbalance between antiinflammatory and proinflammatory cytokines plays a major role in depression and MS [4, 84, 85], with the proinflammatory cytokines being able to exacerbate disease activity in MS [86]. VitD increases the brain-derived neurotrophic factor (BDNF) and modulates multiple brain areas including the prefrontal cortex, which is an important brain area in the pathogenesis of depression [4, 87–89]. In addition, VitD is involved in the regulation of brain morphology and neurogenesis [90]. Preclinical results indicate a brain plasticity modulating activity of VitD, especially in the pathogenesis of comorbidity depression in MS [4, 84].

In PwMS, there was a negative correlation between VitD status and depressive symptoms [91].

VitD deficiency has been observed in depression in women more than in men [92] and the incidence of depression in people with VitD deficiency is greater than in people with normal s25(OH)D [93]. Twice as many women suffer from depression (sexual dimorphism) [94]. Early diagnosis and intervention are of paramount importance as the coexistence of VitD deficiency and depression has serious negative health consequences. In particular, higher VitD levels [s25(OH)D > 30 ng/mL] in older age went along with an improvement in depressive symptoms [17].

A randomized clinical study with 18,353 adults aged 50 years and older shows how crucial an adequate VitD dosage is [95]. There, supplementation with a low dose of VitD3 (2,000 IU/day) over 5 years compared to placebo did not lead to statistically significant differences in the frequency and recurrence of depression or mood swings [95].

These findings do not support the use of VitD in adults to prevent depression but are not an argument against sufficient VitD supplementation in manifest depression or depressive states and depression as a comorbidity of an autoimmune disease. Eight weeks of supplementation with 50,000 IU/2 weeks of VitD increased 25(OH)D levels in people with mild to moderate depression and significantly reduced the severity of their depression [96].

Primary prevention of depressive states by influencing activity (autoimmunity) in MS

Immunologic mechanisms of Vit D supplementation on MS progression

The neuroprotective properties of VitD work through several mechanisms [97]. The direct neuroprotective effect of VitD is linked to the regulation of neurotrophic factors and the reduction of oxidative stress. Only adequate s25(OH)D levels (> 30 ng/mL) down-regulate oxidative stress, suboptimal VitD levels lead to the opposite effect [98]. Neurotrophic factors are crucial for the differentiation, survival, and maintenance of nerve and glial cells. VitD stimulates the expression of the glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), BDNF, NT3 [98, 99], and the p75 NT receptor ($p75^{NTR}$) in neurons, glial cells, and Schwann cells [97]. Reduction in vitD promoted neurotrophic factor expression due to vitD deficiency may result in neurons becoming more susceptible to damage [97, 98, 100, 101].

It is evident that in PwMS, the psychological burden and its consequences can be alleviated by slowing down the progression of MS. But also the fear and risk of side effects from various pharmaceuticals (DMTs) become a burden in the course of their lives.

VitD supplementation dampens the pathogenicity of the T helper 17 (Th17) cell IL-17 synthesis, increases sensitivity of effector $CD4^+$ T cells to extrinsic cell death signals, and promotes $CD4^+CD25^+$ forkhead/winged helix transcriptional factor P3 $(FoxP3)^+$ Treg cell and $CD4^+IL\text{-}10^+FoxP3^-$ type 1 regulatory T (Tr1) cell development [102]. High dose VitD supplementation reduces IL-17 producing $CD4^+$ T cells and effector memory $CD4^+$ T cells in PwMS when these s25(OH)D levels are significantly increased [103]. If 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] lowers the proinflammatory cytokines IL-1β, IL-6, IL-8, IL-12, IL-17, and IL-21 as well as TNF-α, promotes the ability of Tregs to migrate to the CNS, and antiinflammatory IL-10 production increases [103–105], the therapeutic efficiency is increased by additional therapy with VitD.

A recent finding is that a subset of Th17 cells, the Th17.1 cells, infiltrate the MS brain and are an important player in MS activity as they also produce a multidrug resistance protein 1 (*MDR1*) and can therefore be refractory to methylprednisolone (MP) in relapse therapy [106].

Simultaneous treatment with $1,25(OH)_2D_3$ reduces both the MDR1 expression and the secretion of IFN-γ and TNF-α by Th17.1 cells.

Through the VitD supplementation the glucocorticoid reaction is improved in MP pulse therapy [106]. There is probably a therapeutic time window for a VitD supplementation in the earliest relapsing phases of MS [106]. S25(OH)D concentrations are inversely correlated with a risk of relapse, CNS lesions, and disability progression in MS. The number of new gadolinium-enhancing or new increasing T2 lesions is significantly reduced by VitD supplementation [107, 108].

Therapy goal: sealing of the BBB in MS and depression

MS

The sealing of the BBB by MP in MS can be potentiated by VitD. The protective effect of $1,25(OH)_2D_3$ (calcitriol) on the fragile BBB in MS can be explained by the up-regulation of tight junction proteins and the down-regulation of adhesion molecules [109, 110]. The migration of autoreactive $CD4^+$ T cells into the CNS is blocked by calcitriol. The activation of macrophages (MK), MG, and astrocytes is regulated and reduces the passage of immune cells through the BBB. The differentiation of effector T and B cells is reduced while regulating subsets are supported [110]. The preventive administration of VitD is more successful the earlier it is used so that irreversible damage is reduced [111]. The aim of the therapy is to restore the integrity of the brain barrier and, thus, CNS homeostasis [111].

$1,25(OH)_2D_3$ also makes it possible to prevent the migration of Th cells into the CNS parenchyma on a second pathway. The autoimmune cells are kept in the periphery by slowing the migration from the lymph nodes into the CNS parenchyma [112].

Depression

There is ample evidence of a disruption of the BBB integrity in depression, with evidence of the presence of elevated inflammatory markers and immune cell dysfunction. Whether the disruption of the BBB primarily causes depression or is a secondary consequence of the disease cannot be answered at present. The comorbidity of depression in MS may indicate a common mechanism of BBB disruption. Stress and inflammation in parallel with MS disrupt the integrity of the BBB [113].

TNF, IFN-γ, Th17 cells, IL-17A, IL-23, IL-6, and lipopolysaccharides (LPS), for example, influence the permeability of the BBB [114–116]. T and B lymphocytes and monocytes have been found in the brain parenchyma of depressed patients (post-mortem studies) and in animals [114–116]. IL-17A expressing CD4 cells or Th cells accumulate in the hippocampus and promote susceptibility to depression-like behaviors [114–116].

The structure of the BBB differs significantly between healthy and depressed subjects at different cellular levels. Due to stress and inflammation, changes in the brain in depression include a reduction in the number of pericytes, loss and modification of the foot processes of astrocytes [117, 118], activated MG, and loss of tight junctions [113]. The tight junction claudin-5 expression is reduced in the hippocampus of patients with depression, the expression of claudin-5, claudin-12, and zona occludens-1 (ZO-1) correlates with the age of onset and the duration of the depressive episodes [119].

If the reduction in inflammation can lead to BBB integrity by reducing TNF and IL-6 and thereby achieve an antidepressant effect [113], VitD supplementation is a complementary therapeutic strategy.

Behavior of MG in MS and depression

MG are the primary resident immune cells responsible for protecting against attacks on the CNS.

They play an integral role in CNS development, immune surveillance, and also have a repair function [120]. Various phenotypes have been identified in the past. The MG0 or “resting MG” in the homeostatic state actively monitors the CNS and also responds to stress [120]. They produce neurotrophic factors such as the insulin-like growth factor-1 (IGF-1), BDNF, TGF-β, and NGF [121]. The MG1 phenotype (MK glia) releases proinflammatory cytokines such as IL-6, IFN-γ, IL-23, and TNF-α. The MG2 (MK) phenotype expresses antiinflammatory cytokines IL-4, IL-10, IL-13, and TGF-β [20, 121]. In addition, subgroups of M2a, M2b, M2c cells, and up to 9 classify further subtypes [122]. At the same time, a new phenotype called “dark” MG type was discovered and the M1/M2 dichotomy is no longer considered up to date as the MG phenotypes are transitory and show a temporal and spatial development [120, 123]. Pathophysiological key mechanisms are detailed in [123].

MS

In chronically active lesions that are responsible for insidious PIRA in MS, MG/MK mediated inflammation occurs [124]. During lesion development and MS progression, the MG activity may contribute to neurotoxicity through the release of proinflammatory cytokines, ROS, proteases, and glutamate [125].

MG activation is the earliest biomarker of inflammatory processes in the CNS in MS [126]. Because the proinflammatory MG1 type is particularly active in the early stages of MS, it is biologically plausible to use a VitD supplementation to start reducing inflammatory mediators to reduce myelin damage. Elevated levels of calcitriol lead to a reduction in MG activation, oxidative stress, and lower BBB permeability [98]. $1,25(OH)_2D_3$ effectively shifts MG from a proinflammatory M1 phenotype to a reparative M2 phenotype, particularly in early MS, resulting in the limitation of inflammation and demyelination [98, 121].

Neuron-specific VitD receptor (VDR) signaling induces antiinflammatory molecules that protect the CNS from autoimmunity. $1,25(OH)_2D_3$ causes a reduction of proinflammatory molecules and a reciprocal induction of antiinflammatory molecules in MG [127]. MG/MK mediated inflammation is a major obstacle to remyelination [124].

Depression

MG have also been identified as actors in depression, and the condition is interpreted as a "MG-associated disorder" (microgliopathy) [128]. Increased calcitriol levels lead to a reduction in MG activation, oxidative stress, and lower BBB permeability [20]. The neuroinflammation in depression results from intrinsic communication between peripheral immune cells, gut microbiota, and immune cells (MG) present in the brain, resulting in glutamatergic dysregulation, reduced synaptic plasticity and monoamine synthesis [123]. The interaction of neuroinflammation and the HPA-axis and their dysregulation could initiate the onset of depression [128, 129].

Relevance of the prodromal stage of MS for the management and early prevention of depression

The existence of a prodromal stage in MS is generally accepted [55, 59, 130]. $CD8^+$ T lymphocytes, $CD4^+$ T lymphocytes and B lymphocytes are involved in the very early stage of MS development [131] and early VitD supplementation could influence the pathology [132, 133]. A detailed (family) medical history (MS in first-degree relatives), questions about other autoimmune diseases and symptoms such as depression, anxiety, pain, and dermatological problems could currently serve as an aid in recognizing a prodromal phase at an early stage. Early determination of the *HLA-DRB1*1501* allele could point the way to intensive care and early therapy for MS.

Numerous findings support that *HLA-DRB1*1501* positive patients experience a rapid deterioration of their disability, greater annualized change in T2 (T2-weighted sequence in MRI) lesion volume, increased number of gadolinium-enhancing lesions, and faster rates of brain and spinal cord atrophy compared to PwMS who were *HLA-DRB1*1501* negative [134].

Clinical features of the MS prodrome can appear 5–10 years before, and in progressive MS even 20 years before. Five years before the clinical manifestation of MS, the rate of visits to the psychiatrist was 50%, hospitalization 78%, and family doctor visits 88% higher than in controls [59, 135]. In childhood MS, there was a higher rate of doctors' visits for mood and anxiety disorders compared to controls 5 years before the first demyelinating event [135]. The prescription of medication was increased by 49% compared to controls [135].

Anxiety, depression, migraines, and reduced cognitive performance have been recognized as part of the MS prodrome [136]. Depression can occur up to 10 years before the first demyelination event [137]. In young men (18–19 years old), lower cognitive scores were registered in the 2 years before the onset of the "classic MS outbreak" than in people without MS. Five years before the onset of MS, mental health had altered and this was documented by the fact that around 50% sought psychiatric care and around 50% more mood disorders were observed [138].

The fact that these symptoms correlate with the first demyelinating events is evident from the evidence of increased sNfL levels 6 years before clinical onset [58]. The increasing degree of neuroaxonal damage, documented by increasing sNfL levels, peaked after verification of the MS [58]. A low VitD level is associated with a higher risk of MS and at this stage it is opportune to achieve optimal VitD levels as part of prevention. A vitD supplementation over 5 years resulted in a 22% reduction in autoimmune disease [139]. An inverse association between higher 25(OH)D levels and the risk of developing MS could be observed by measuring the 25(OH)D levels 5, 8, and 9 years before the onset of MS symptoms [138].

A genetically low calcidiol level is associated with an increased risk of MS in adults and children [140–142]. Monitoring of the VitD levels is an essential part of the management in the prodromal phase and can potentially improve the prognosis in primary MS as well as in secondary prevention [138].

It will be crucial to introduce VitD supplementation at this early stage (window of opportunity), as vitD clearly plays a role in reducing disease severity and is to be favored in the management of care for PwMS [101, 143].

The scientific community continues to debate whether VitD deficiency causes MS or whether VitD deficiency is caused by the disease itself. This is irrelevant with regard to the question of supplementation since a sufficient calcidiol level is required to regulate and maintain "immunological homeostasis". A study supports the causal effects of genetically predicted s25(OH)D levels on MS risk. Low s25(OH)D values are associated with an increased risk of recurrence [108].

Disorders of the gut microbiome

Gut-microbiota-brain-axis involved in the pathogenesis of MS

A disrupted bacterial and viral gut microbiota is thought to be part of the pathogenesis of MS, mediated by an altered gut-microbiota-brain (GMB)-axis. The composition of gut microbiota affects the production of serotonin in the gut, which in turn affects the serotonin-mediated regulation of the systemic immune function [144].

In a systematic review of the gut microbiota composition of 286 PwMS until 2019, most studies found no difference in gut microbiota diversity [145]. However, taxonomic differences from controls were verified and immunomodulatory drugs showed separate taxonomic differences [145].

A recent study demonstrated that inflammatory markers (blood leukocytes, CRP, blood cell gene expression of IL-17A and IL-6) were positively associated with a group of bacteria that are more common in MS [146]. Bacterial species that were more common in disease-active, treatment-naive MS were also positively associated with the plasma cytokines IL-22, IL-17A, IFN-β, IL-33, and TNF-α, some of which are targeted by VitD [146].

Because high dose VitD supplementation with 10,400 IU/day reduced IL-17 producing $CD4^+$ T cells and effector memory $CD4^+$ T cells and was associated with a concomitant increase in the proportion of central memory $CD4^+$ T cells and naive $CD4^+$ T cells, a VitD supplementation should be used as a potential therapeutic agent [103]. After 6 months, the 25(OH)D level increased by 34.9 ng/mL [147], which demonstrates that a high dose VitD supplementation is necessary. The active form of VitD3, $1,25(OH)_2D_3$, inhibits IL-22 production and can be viewed as an adjuvant therapeutic to regulate IL-22 production [148]. The two proinflammatory cytokines (IL-22, IL-17) correlate with active brain lesions in MS [149]. The bacterial species richness of treatment-naive MS cases was associated with the number of relapses, which is a surprising finding [146].

GMB-axis in depression

The gut microbiome regulates the interaction with the brain, and this relationship is understood as the "GMB-axis (GMB-A)", the connection between the gut microbiome and the CNS [150, 151].

It presents itself as a complex and interactive system that includes a neuronal signaling network, an immune signaling network, and a chemical signaling network [150, 152]. In addition to the involvement of the vagus nerve and the HPA-axis, the pathophysiology involves the MG, Th17/Treg activity, and the gut microbiome [152]. A significant factor, such as psychological stress, can lead to depression via dysfunction of the HPA-axis and dysfunction of the GMB-A [153].

Numerous publications have shown that microbiota promotes both humoral immunity (B cell development and proinflammatory T cell responses) and immune regulation (regulatory B cells and Tregs) [154].

Changes in the gut microbiome (microbial dysbiosis) can affect the severity of autoimmune diseases [154] and patients with depression have a different microbiome than healthy individuals [153]. An altered composition of the fecal microbiota in depression has been pointed out [155, 156] and homeostasis of the gut microbiome should therefore be aimed at. VitD deficiency or VitD supplementation alters the microbiome, and manipulation of bacterial abundance or composition affects disease manifestation [154]. VitD, VDR, or cytochrome P450 family 27 subfamily B member 1 (*CYP27B1*) deficiency led to an increase in Bacteroidetes and Proteobacteria strains, resulting in dysfunction of the epithelial barrier of the gut and triggering intestinal inflammation [157, 158].

The HPA-axis is the main non-neuronal connection between the gut and brain and primarily regulates stress responses associated with the immune system and vagus nerve [153].

Target for VitD supplementation: containment of low-grade inflammation in MS

There has been growing evidence in recent years that the gut microbiota (microorganisms that inhabit the gut) has implications for immune function in MS [159, 160]. VitD acts through the VDR to regulate gene transcription. VitD regulates (protects) the integrity of the gut barrier by strengthening the tight junction and controls innate and acquired immunity in the gut [159, 160]. Besides the known inhibition of Th17 and Th1 responses, it boosts Tregs, affects B cells, and stimulates antimicrobial peptides from immune cells. VitD modulates the function of the gut microbiome [159].

VitD deficiency compromises physical and functional barrier integrity, and the natural innate immunological defenses are weakened. The permeability of the intestinal barrier and the immune activity is increased, and the microbial composition is changed (dysbiosis) [154, 160].

With an intake of 4,000 IU/day of VitD or 10,000 IU/day over 8 weeks, an increase in beneficial bacteria and a decrease in pathogenic bacteria could be achieved when medium levels [39 ng/mL or 67 ng/mL of 25(OH)D] were reached [161]. It was demonstrated that a vitD supplementation of 50,000 IU/week over a period of 12 weeks changed the composition and diversity of the intestinal microbiota [162].

In another study, over 8 weeks with a VitD supplementation over the first four weeks of 980 IU/kg body weight (BW) corresponding to a daily dose of 140 IU/kg BW (maximum 68,600 IU/week) and in the second 4-week period with 490 IU/kg BW [daily dose 70 IU/kg BW (maximum 34,300 IU/week)], mean s25(OH)D values of 55 ng/mL were reached. There was a reduction in opportunistic pathogens and increased bacterial abundance [163].

Sometimes, the contradictory results of VitD studies are the result of low calcidiol levels. A VitD supplementation should be done daily until s25(OH)D levels of 30–60 ng/mL are reached, which is required for adequate VDR binding. Due to the individually different, genetically determined resorption of VitD, doses of more than 3,500–5,000 IU/day are required [160] to influence the smoldering chronic inflammatory activity in MS.

An umbrella meta-analysis confirmed the potential benefits of VitD supplementation for reducing symptoms of depression and showed an inverse relationship between higher serum VitD levels and overall depression. VitD supplementation studies with a dosage of > 5,000 IU/day with an intervention duration of ≤ 20 weeks showed a better effect in reducing the symptoms of depression [164].

In addition, participants aged ≤ 50 years old with lower serum VitD levels were shown to be at greater risk of depression and VitD supplementation can offer protection to persons affected by depression [165].

Pregnancy, MS, and depression

Depression during pregnancy and postnatal depression should not be neglected, whereby antenatal depression also increases the risk of postnatal depressive phases [166]. Depression during pregnancy affects up to 10% of women and only 20% receive appropriate treatment [166, 167]. In women who wish to have children and are at risk of depression, low vitD levels are associated with more depressive symptoms in early and late pregnancy [168, 169].

A study with 2,000 IU/day VitD for at least 8 weeks and after giving birth showed a lower perinatal depression rate [170].

Today, VitD represents an important biomarker for pregnant women and those with postpartum depression [171, 172]. It is therefore a valid request that a VitD supplementation be started at the beginning of a pregnancy and especially for women with known depressive mood swings, since these mothers had a negative perinatal outcome under VitD deficiency [172, 173]. Early VitD supplementation

reduced the risk of a shortened gestation period when s25(OH)D was above 40 ng/mL, increased birth weight, and increased infant length in the first year of life [169].

An Australian study, however, cast doubt on the role of VitD in the pathophysiology, prevention, or treatment of depression in individuals without MS in the perinatal period [174].

Influence of VitD supplementation in the elderly and as adjuvant therapy in connection with antidepressants

In an Australian preventive study of people aged 60–84 with a monthly VitD supplementation of 60,000 IU over 5 years, only one subgroup showed an improvement in the Patient Health Questionnaire-9 (PHQ-9) score when 25(OH)D levels were < 20 ng/mL and antidepressants were taken at baseline [175]. Due to the fluctuating s25(OH)D values (see above), a bolus dose of VitD not only has unfavorable effects on immunomodulatory effects of VitD but also increased the risk of an increased risk of falls in people with a body mass index (BMI) of < 25 kg/m^2 [176].

Supraphysiological bolus doses of VitD have the potential to saturate the VitD-binding protein, leading to the displacement of 1,25(OH)D and s25(OH)D into the circulation in the days following supplementation and beyond and resulting in large differences in the serum metabolites profiles [177].

Discussion

Depression and MS can be classified as "multifactorial diseases" and therefore require "polytherapy treatment".

Due to the extreme complexity of genetic, epigenetic, hormonal, nutritional, geographic, and cultural influences, it is a challenge to positively influence the course of the previously incurable disease with depression as an additional comorbidity in PwMS [178]. The probability of developing depression is significantly higher for PwMS with a VitD deficiency than for those with an s25(OH)D > 30 ng/mL [93].

Immunological mechanisms

Despite the multifactorial causes of MS and depression, the increased inflammatory activation and dysregulation of the immune system in both diseases is undisputed as a major contributor to the pathophysiology.

The observed association of s25(OH)D deficiency and increased proinflammatory cytokines as well as increased CRP makes correcting the calcidiol levels by VitD supplementation in order to curb chronic inflammation a logic consequence [179].

In addition, activated MG, active T lymphocytes, loss of oligodendrocytes, demyelination, axon damage, and axon loss are potentiating factors [178, 180]. From this perspective, the aim of a VitD supplementation is to slow down the activation of the immune system in PwMS and in the comorbidity of depression.

Calcitriol inhibits the synthesis of IL-6, TNF-α, and nitric oxide (NO) through activated MG [181]. It is undisputed that calcitriol reduces the expression of IL-12 and increases the expression of the antiinflammatory cytokine IL-10, IL-14, and TGF-β and has a dampening effect on various inflammasomes [NOD-like receptor family pyrin domain containing 3 (NLRP3)] [182]. There is evidence that VitD supplementation can increase serum serotonin in people with depression [183]. VitD increases the biosynthesis of monoamines by expressing the enzyme's tyrosine and tryptophan hydroxylase [123].

VitD as a "pharmacological" treatment to influence the inflammatory activity in the CNS, at least as an add-on therapy, constitutes a biological plausibility.

SNfL as an important diagnostic biomarker

The biomarker sNfL as a marker of neuroaxonal integrity allows for a better clinical characterization of the depression and is useful for monitoring the therapy. Increased sNfL levels indicate active pathological processes [51]. There is evidence that sNfL levels are a biological marker of inflammatory processes in the

CNS and that successful therapeutic agents must be measured by their ability to reduce the sNfL levels [45–51, 54–58]. The outcome of supplementation studies in MS and depression will depend on whether s25(OH)D of more than 50–100 ng/mL can be achieved under daily vitD supplementation [184].

Recognizing that ketamine exposure leads to increased sNfL with persistent neurocognitive impairment and depression, these interactions must be taken into account when interpreting sNfL values [185, 186]. A study with simultaneous high dose vitD supplementation aiming at neuroprotection through $1,25(OH)_2D_3$ while controlling sNfL levels would be of great value.

Lack of international consensus on the definition of target values for s25(OH)D in autoimmune processes

The controversial opinions and results from various studies (study designs) could not be more contradictory. Different initial s25(OH)D values and measuring methods, dose level, daily or bolus doses, type of VitD supplementation (VitD2/VitD3), duration of intervention, age groups (young/older), and missing international levels [definition of deficiency, insufficiency, sufficiency, optimal values in autoimmune diseases of s25(OH)D] stand in the way of PwMS benefiting from VitD supplementation. A frequently cited study by Rolf et al. [187] with a small number of patients with depressive symptoms (n = 20) with a high dose VitD supplementation (14,000 IU/day) over 48 weeks showed a significant decrease in depressive symptoms, but no significant reduction compared to the placebo group.

In order to influence the dysregulation of autoimmunological processes, the duration of VitD supplementation and the s25(OH)D levels reached are crucial [188]. It has been shown that, with a daily intake of 10,000 IU of VitD, a steady state of s25(OH)D of about 80 ng/mL could only be reached after 18 weeks [188]. In the study of Rolf et al. [187], an optimal calcidiol level could therefore only be expected to be achieved at 30 weeks.

The workload of clinicians and general practitioners often only allows the abstract to be read in the secondary literature and less in the original literature. In the case of "supplementation studies with a negative outcome", the content of the discussion in a publication is often more detailed, in particular, the chapter on "limitations of the study", in detail: the number of subjects, rare recording of expanded disability status scale (EDSS), selected dosage level/dosage schemes of VitD possibly with a masking effect instead of higher 25(OH)D levels to achieve effectiveness, study duration too short, etc.

A prime example of confusion is a study of the natural variations of VitD and sNfL in RRMS over a one-year period [189].

In conclusion, no significant association between naturally increasing s25(OH)D and neurodegeneration, as measured by sNfL, is supported for RRMS patients. S25(OH)D with more than 20 ng/mL was interpreted as "rather high" [189]. Specifically, s25(OH)D values were measured over a one-year period as an approximative mean value of s25(OH)D of between 18 ng/mL and 44 ng/mL, with 44 ng/mL only being registered over 4 weeks. From these results, it is concluded that "a large effect of VitD supplementation is lacking" [190]. In order to generate a therapeutic potential to influence pathological immunological processes, however, values in the middle or upper range of normal (up to maximum 100 ng/mL or 130 ng/mL) should be aimed at and maintained over a longer period of time in order to achieve long-term effects [75, 147, 191–200].

VitD could support the immune defense at s25(OH)D levels above 50 ng/mL in the fight against infection [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection] and thus prevent potentially stressful situations [201–203] and should be incorporated into the medical treatment plan. In "lifelong" autoimmune processes in progressive MS, the immunomodulatory activity of vitD can only reduce excessive inflammatory damage if optimal levels of s25(OH)D are sustainably achieved. Taking into account the dose-response relationship, this ongoing adjuvant therapy is therefore a rational approach.

VitD supplementation

VitD is a secosteroid hormone and acts through transcription in the cell nucleus and therefore takes a while to act [204]. Both for prevention and for the treatment of depression with VitD supplementation, women had the highest benefit when the VitD dose was over 2,800 IU/day and the duration of the intervention was longer than 8 weeks. The results also showed that high dose VitD supplementation was associated with a reduction in the incidence of depression, while low dose VitD supplementation (below 2,800 IU/day) was futile [204]. This is also confirmed by a study with 1,600 IU/day over 6 months, which showed no effect on the symptoms of depression but did show an effect on the symptoms of anxiety [205].

In a systematic review of a VitD supplementation at 1,500 IU/day to 2,800 IU/day or 50,000 IU weekly/biweekly over 8–12 weeks without checking the s25(OH)D values, the wide range of results did not provide any conclusions for real-life application [206]. Negative correlation between VitD supplementation and depressive symptoms have been recorded when s25(OH)D levels are above 32 ng/mL [91, 207].

If only 50% of patients respond to first-line antidepressant therapy and patients also are afraid of the side effects of antidepressants, a "permanent" VitD supplementation can be offered as an add-on therapy or as an alternative for milder forms [204].

To achieve a therapeutic effect of VitD on the (pathological) immunological mechanisms, a constant, continuous s25(OH)D measurement is required. Long-term supplementation is also necessary because depressive symptoms in PwMS can extend over 10 years [208]. A vitD supplementation with 10,000 IU/day over 12 months showed a significant improvement in symptoms [209].

A significant problem in assessing the results of such supplementation studies consists in avoiding "non-daily VitD doses" but bolus doses. After an oral dose of VitD, blood levels peak after 12 h and the half-life is around 12–24 h. Because of this short half-life, large bolus doses of VitD of 50,000 IU to 100,000 IU are cleared from the circulation within a week and are no longer detectable.

Continued daily supplementation of VitD results in a slow, sustained increase in s25(OH)D, reaching a steady state after 3–4 months. Bolus doses of VitD led to fluctuating levels in the blood, affecting the immune effects and, thus, the outcome of VitD supplementation [210]. These strong fluctuations have an adverse effect on the activity of the enzymes responsible for the synthesis and depletion of the active VitD metabolite, $1,25(OH)_2D_3$. This dysregulation results in decreased levels of this metabolite in the extrarenal tissue [211–213]. Randomized controlled trials (RCTs) of VitD supplementation in respiratory disease have shown that intermittent high dose bolus doses are ineffective, although sufficient 25(OH)D levels have been achieved [214, 215]. One possible explanation is that the bolus doses induce 24-hydroxylase activity and result in the inactivation of VitD3 through the formation of 24,25-dihydroxyvitamin D [$24,25(OH)_2D$]. This effect persisted for at least 28 days after the bolus [216].

In 18 studies on the effect of VitD supplementation on the occurrence and prognosis of depression, patients in 10 studies received bolus doses of 50,000 IU to 300,000 IU weekly, every 14 days or 4 weeks, and only in 8 studies daily [208]. In adults with a VitD supplementation the greatest benefit on depressive symptoms was registered with a daily dose of more than 4,000 IU [217].

With intermittent bolus doses of VitD and short-term administration, a study over 8 weeks with 50,000 IU VitD every 2 weeks showed significant improvement in the severity of depression without any effect on the measured neurotransmitters, IL-1β, IL-6, and hsCRP [96, 218].

However, after a period of 12 weeks, a decrease in the hsCRP values was registered [219]. VitD supplementation for the treatment of depressive symptoms in women led to a significant improvement in depressive symptoms, both at a dose level of VitD of 5,000 IU/week and at 50,000 IU/week, with no difference for either group [220].

An 11-year study showed that higher levels of VitD predicted better cognitive performance in patients with clinically isolated syndrome (CIS) [221]. A 20 ng/mL higher mean 25(OH)D level in the first 2 years was associated with a 20% lower sNfL level. VitD can be a prognostic marker for long-term cognition and neuroaxonal integrity [221].

Depression may be associated with reduced cognitive performance in PwMS [222, 223]. For about 10 years there has been evidence that the molecular biomarkers sNfL, VitD, and VitB12 play an important diagnostic role in cognitive impairment in PwMS, namely to predict long-term cognitive performance [221, 224]. A slower information processing speed (IPS) was confirmed in PwMS [225].

However, IPS was able to use a VitD supplementation and VitB12 as long-term neuroprotection [221, 224, 226, 227]. A recent study showed that sNfL and s25(OH)D correlate with measurements of the IPS [225]. This knowledge opens up the opportunity of an extended indication for a permanent sufficient vitD supplementation of PwMS and depression.

A high-quality diet in PwMS was already positively associated with lower severity of depressive symptoms and disability [198]. A systematic literature review on the influence of a VitD supplementation confirmed the positive effect on mental health in PwMS [228].

Not only because of the fear of side effects in the treatment of depression with antidepressants (e.g., restrictions on the ability to drive, etc.), PwMS with comorbidity depression want a "non-pharmacological treatment". Over 80% of PwMS used dietary supplements and 65% used vitD [229].

PwMS require medical advice on this concomitant therapy. If you leave this to your own initiative, it could confuse or overwhelm the patient [230].

In the future, probiotic treatment affecting the gut microbiota of PwMS will be increasingly in demand. The improvement in mental health parameters through probiotic supplementation can be demonstrated by reductions in the hsCRP and the proinflammatory IL-6 and increased levels of IL-10 [231–233]. Hypotheses on the mechanism of the multifactorial interaction between the intestinal flora, the nervous, immune, and endocrine systems (GMB-A), and therapy in PwMS are presented [234]. In the context of personalized medicine, supporting PwMS through a multitherapeutic approach could help in managing the disease.

Criticism of RCTs—an unsolved problem

Confusion concerning the value of a vitD supplementation has existed for decades due to the claim that only RCTs can be used as a benchmark for assessment, especially since there are considerable discussions concerning the evaluation of such studies [235–237]. However, there are potential limitations so that RCTs alone are not able to provide a definitive answer [238–241]. There is a demand for the improvement of statistical significance in randomized VitD control studies using Tregs as a benchmark [242].

It is undisputed that the Tregs respond to VitD supplementation. The proportion of Tregs (Treg percentage) should be considered as a biomarker in the results of vitD studies. After a 12-week vitD supplementation with 4,700 IU/day, s25(OH)D levels of 55 ng/mL were achieved and the Treg percentage had increased significantly compared to placebo [242].

The entire process, from the beginning of the study to its evaluation, could span an entire generation of PwMS, which is unacceptable for ethical reasons. RCTs are designed for therapeutic (pharmacological) drugs and not for a nutrient, such as VitD [177, 188, 243, 244].

The evaluation of individual studies with specific, high-aiming, and hardly achievable primary and secondary objectives [245] does not do justice to the complexity and range of effectiveness of a VitD supplementation at PwMS.

Prevention of depression by reducing acute episodes in MS—a primary goal

Epstein-Barr virus and MS

It is becoming increasingly clear that infection with the Epstein-Barr virus (EBV) is the main cause of MS [246–248]. The risk of MS after infection with EBV increased by a factor of 24/32 [249, 250]. EBV seroconversion preceded the increase in NfL levels in individuals who later developed MS [58].

Almost 100% of PwMS have had an EBV infection [58, 250, 251]. Low VitD levels could increase the susceptibility to EBV infection [252]. Low s25(OH)D levels were observed during the 24-month pre-CIS. Immunoglobulin G (IgG) against EBV nuclear antigen-1 (EBNA-1) during the 36-month pre-CIS interval was

increased. Low vitD may be associated with clinical MS breakthrough within 2–3 years [253, 254]. B cell depleting therapies, such as ocrelizumab, has an effect on the breakdown of memory B cells and can be supplemented by vitD supplementation [255–257].

Hence, the effect of high dose VitD supplementation to influence the humoral immune reaction against the latent EBV antigen EBNA-1 in RRMS [258, 259] can be regarded as an indication for the continuous administration of VitD.

Higher anti-EBNA-1 IgG levels are associated with an increased risk of MS [260] and predict a higher risk of active lesions in the MRI [259]. On the other hand, VitD as an add-on therapy to IFN was able to reduce MRI-confirmed activity [261]. Elevated anti-EBNA-1 IgG and decreased 25(OH)D levels were observed before the onset of MS [262]. The persistence of EBV in B cells in a latent state is chronic and lifelong [262].

The findings on the association between anti-EBNA-1 antibodies, neurological disability, disease activity, and cortical atrophy in the MRI [263–268] and the influence of VitD should pave the way to a permanent VitD supplementation.

Low VitD levels increase the risk of developing MS, the number of relapses, as well as neurological disability and MRI activity [192, 269–272].

High dose VitD supplementation (14,000 IU/day) over 48 weeks selectively reduced anti-EBNA-1 antibody levels in RRMS [259]. A 96-week high dose VitD supplementation (20,000 IU/week) and 12-week study with high dose VitD supplementation also showed reduced anti-EBNA-1 IgG levels in RRMS [258, 273].

At present, co-factors increasing the risk of infection and the development of autoimmune diseases are also being focused on. Psychological stress and depression increase the susceptibility to disease and can lead to a reactivation of the latent EBV [249, 274–279].

Economic benefits of increasing s25(OH)D levels

Study data suggest that an optimal s25(OH)D level could reduce the risk of depression and MS [4]. Therefore, the cost of a daily VitD supplementation is negligible in the treatment of autoimmune diseases. For the management of VitD supplementation is highly promising that in Canada, for example, calculations have shown that a reduced annual economic burden of disease in the general population of $12.5 billion ± $6 billion could be achieved. This would require that the s25(OH)D values be increased to 40 ng/mL. In the case of PwMS, the overall economic burden of the VitD supplementation estimated to be reduced by $1.5 billion [280, 281]. The estimated cost-saving effect of an improved VitD status in the population in Germany could add up to €37.5 billion per year [282]. The established biomarkers make it possible to record at least a subgroup of PwMS where a VitD supplementation promises optimal success and is economically justifiable.

"The practices of medicine remain more in art than a science" [283].

Conclusions

Relevant pathophysiological and immunological studies exist as a basis for high dose daily VitD supplementation in MS and depression. VitD, as a neurosteroid hormone influences multiple metabolic processes, is involved in immune modulation and the associated immune responses, regulates neurotrophic-neuroprotective processes, is involved in neurotransmission, and is relevant to synaptic plasticity. Immunomodulation can influence the course of MS and depression with the aim of improving the quality of life of PwMS.

Increased inflammatory responses as well as low VitD status are associated with MS and depression. Because the international community does not rely on normal values of 25(OH)D in the serum in autoimmune diseases, the frequency of determination of s25(OH)D, consideration of the individual absorption rate of VitD, the daily dose of VitD, the duration of intake in studies, and the minimum number

of subjects in studies that could agree on the consideration of forms of MS (smoldering MS), diverging results emerged in the VitD supplementation studies. These controversial opinions of "VitD does not help" or "it is a serious mistake not to recommend PwMS supplementation" is the cause of the lack of VitD supplementation in practice. The protective effect of VitD on the brain through neuroprotection alone implements this adjuvant therapy for PwMS.

Abbreviations

$1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3

25(OH)D: 25-hydroxyvitamin D

BBB: blood-brain barrier

BDNF: brain-derived neurotrophic factor

BW: body weight

Ca: calcium

CIS: clinically isolated syndrome

CNS: central nervous system

CRP: C-reactive protein

CSF: cerebrospinal fluid

EBNA-1: Epstein-Barr virus nuclear antigen-1

EBV: Epstein-Barr virus

GMB: gut-microbiota-brain

GMB-A: gut-microbiota-brain-axis

HPA: hypothalamic-pituitary-adrenal

hsCRP: highly sensitive C-reactive protein

IFN-γ: interferon-γ

IgG: immunoglobulin G

IL-17: interleukin-17

IPS: information processing speed

MG: microglia

MK: macrophages

MP: methylprednisolone

MRI: magnetic resonance imaging

MS: multiple sclerosis

NfL: neurofilament light chain

NTs: neurotrophins

PwMS: people with multiple sclerosis

RCTs: randomized controlled trials

ROS: reactive oxygen species

RRMS: relapsing-remitting multiple sclerosis

s25(OH)D: serum 25-hydroxyvitamin D

sGFAP: serum glial fibrillary acidic protein

sNfLs: serum neurofilament light chains

TGF-β: transforming growth factor β

Th1: T helper 1

TNF-α: tumor necrosis factor-α

Treg: regulatory T cell

VDR: vitamin D receptor

VitD: vitamin D

Declarations

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HKG: Conceptualization, Investigation, Writing—original draft, Writing—review & editing.

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The author declares that there are no conflicts of interest.

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