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Review Article

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Will there be Enough Evidence to offer Vitamin D Supplementation to Patients with Multiple Sclerosis in 2024?

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ABSTRACT

This narrative overview discusses the scientific findings of the biochemical and metabolic effect of vitamin D on multiple sclerosis up to 2024 with selected targets.

Since the clinical outcome of multiple sclerosis cannot be predicted in individual patients and there may still be a phase of "success and failure", vitamin D as an add-on therapy could make an early and lasting contribution to the control of dysregulatory inflammatory responses. . As an additional therapy to disease modifying therapies (currently 20 drugs are available, for example ocrelizumab, ofatumumab,ublituximab, rituximab, natalizumab), the B cell kinetics and radiological activity could also be influenced.Some negative vitamin D supplementation studies with zero results could be viewed retrospectively in a more differentiated way through the findings of the three immunologically different phenotypes of multiple sclerosis and with an accentuation of (severe) obesity. This new classification will open up an individualized therapeutic strategy through the targeted immunological effect of 1,25-dihydroxy-vitamin D 3. The relationship between high body mass index and response to vitamin D supplementation and metabolism and the weighting in supplementation studies will become more important in studies.

In an international consensus, daily oral cholecalciferol is preferred due to its safety and minimal need for monitoring in autoimmune diseases. 25-Hydroxyvitamin D3 (25(OH)D in serum is the recognized biomarker for vitamin D status. A connection between vitamin D status and the immune system is recognized. Genetically predicted low levels of 25(OH)D increase the risk of developing multiple sclerosis in adolescence or adulthood.

The findings of the complex pathobiological mechanisms of vitamin D through the immunomodulatory effects on autoimmune diseases in general and on multiple sclerosis in particular in 2024 justify integrating vitamin D supplementation into the multimodal approach to personalized medicine without the risk of significant side effects.

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating complex autoimmune disease of the central nervous system (CNS) that causes significant neurodegeneration in most people and is a common cause of chronic neurological disabilities in young adults, currently affecting 2.8 million people worldwide and with an increasing prevalence [1-3].

Neuroinflammation in MS results from a complex interplay of adaptive and innate immune cells. Inflammatory damage to the semi-permeable blood-brain barrier (BBB) allows infiltration of peripheral immune cells (active lymphocytes, monocytes) and factors that interact with resident immune cells in the central nervous system (CNS) into the CNS [4,5]. Autoreactive CD4+ (Th1/Th17), CD8+ T cells, and B cells attack the CNS, are present in active demyelinating lesions, and the inflammatory process culminates in demyelination and axon loss [6,7].

Selected literature evidence up to 2024 provides cumulative evidence that vitamin D supplementation must occur as early as possible. A clinical effect on demyelinating events requires a high daily supplementation dose because the modulation of the immune cell transcriptome is dose-dependent.

Proactive Action to Influence the Disease Mechanisms at an Early Stage

The clinician is required to create a treatment approach based on the underlying pathophysiological mechanisms that also drive disease progression [5]. In MS therapy, the focus is on controlling dysregulatory inflammatory reactions. Proactive action is required to influence the mechanisms of the underlying disease at an early stage. This approach is supported by the MS prodromes, which were described about 5 years before the onset of MS [8].

50 years ago, it was recognized that a reduced intake of vitamin D predisposes to the development of MS later in adulthood [9].

For over three decades, vitamin D (vit D) deficiency has been recognized as a risk factor for MS, especially in patients with multiple sclerosis (PwMS) from higher latitudes [10]. High serum

concentrations of Vit D may protect against MS [11]. Ultraviolet radiation (UV) and UVB is the main source of vitamin D [9,12-14].

The global and regional prevalence of hypovitaminosis is widespread, varying between 35 and 85%, depending on the country and culture. The global prevalence is < 30nmol/L s25(OH) D in 15.7%; <50nmol/L in 47.9% and <75nmol/L in 76.6%. Vit D deficiency is more common in women than in men [15]. If there is a global call to consider the prevention of hypovitaminosis D as a public health priority, it is likely to be imperative for PwMS to initiate preventive vitamin D supplementation (vit D suppl) on a mandatory basis based on the established knowledge of the pathophysiology and immunology of MS and its relationship to vitamin D [16].

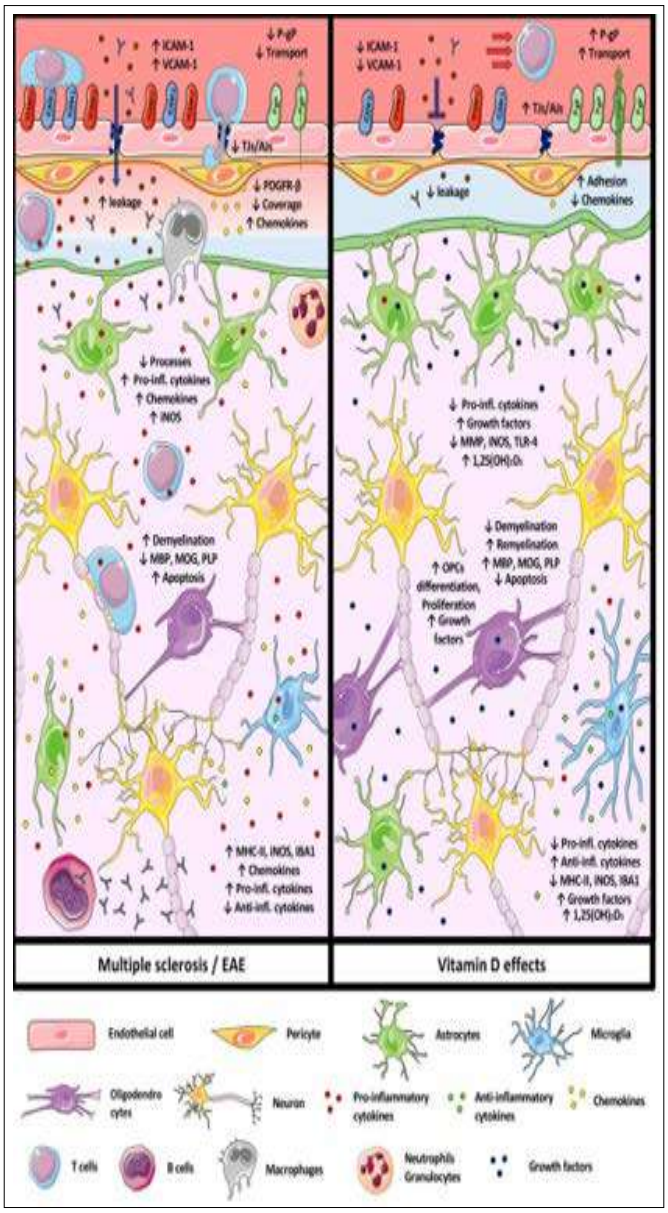

Figure 1: Original illustration from Galoppin M, Kari S, Soldati S, et al, [16]. Oxford University Press

VitD modulates different cellular and molecular mechanisms of CNS[central nervous system] -resident cells and of the blood–brain barrier (BBB) involved in multiple sclerosis pathology. (Left) Schematic representation of the cellular and molecular mechanisms involved in multiple sclerosis/EAE [experimental autoimmune encephalomyelitis] pathology at the level of CNS-resident cells and the BBB. (Right) Schematic representation VitD impact on cellular and molecular mechanisms involved in multiple sclerosis/EAE pathology at the level of CNS-resident cells and the BBB. Changes in the cellular and molecular mechanisms are given as (↑) increased and (↓) decreased. Drawings of the individual cell types were adapted from Servier Medical Art (http://smart.servier.com/), licenced under a Creative Common Attribution 3.0 Generic License.

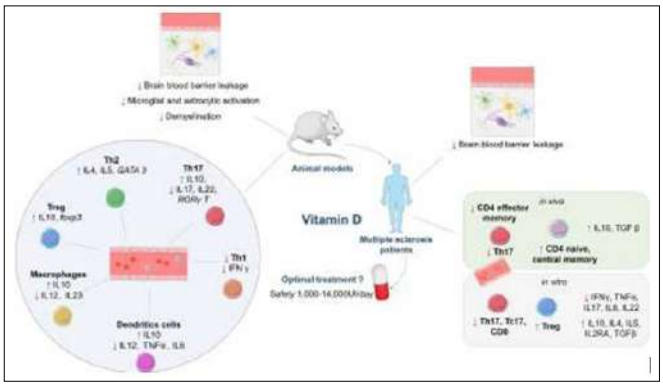

Figure 2: The Original Illustration from the Publication: Galoppin M, Kari S, Soldati S, et al, [16]. Oxford University Press

In PwMS, very low sun exposure is also associated with a poorer course of the disease and a poorer health-related quality of life [17]. Other autoimmune diseases are also associated with hypovitaminosis D, which can also manifest itself as polyautoimmunity in MS and could be treated therapeutically [18]. In a Greek study, the prevalence was 8.3% (e.g., thyroid disorders, vitiligo, inflammatory bowel disease) and there are overlaps in immunological mechanisms [19-21]. Again, women are more affected and 8 women are affected by 10 autoimmune diseases [22].

In vitro and in vivo studies have demonstrated that calcitriol (1,25-dihydroxy-vitamin D3=1,25(OH)2D3), the active form of vitamin D, exerts an anti-inflammatory effect by suppressing both the innate and adaptive immune systems [18,23]. Details in [18].

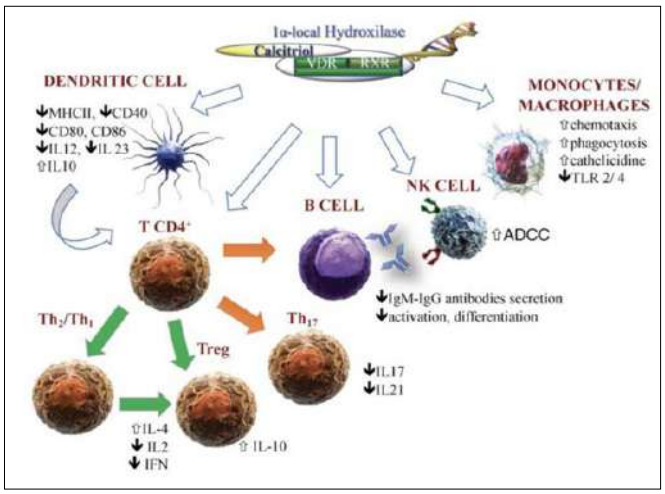

Figure 3: Vitamin D and immune cells Crosstalk

Vitamin D (calcitriol) directly and indirectly influences and regulates both innate and adaptive immune cells, which widely express the vitamin D receptor (VDR). RXR—retinoic acid receptor; NK—natural killer cells; ADCC—antibody-dependent cell-mediated cytotoxicity; IL—interleukin; MHCII—major

histocompatibility complex class II; Th-T helper; TLR-toll-like receptor; green arrow-stimulation; orange arrow-inhibition.

The original illustration from the publication: Gallo D, Baci D, Kustrimovic N, et al, [18]. MDPI

Calcitriol inhibits neuroinflammation, the local activation of macrophages/microglia and has an influence on BBB through sealing [4,7,16]. A higher risk of MS in individuals with low vitamin D intake or low circulating 25-dihydroxyvitamin D [25(OH)2D3] – as well as an inverse correlation between vitamin D status and MS activity – have been reported [24]. It is currently accepted that there is multifactorial immune dysregulation in MS [25].

MS as a multidimensional disease also includes a non-pharmacological intervention [26,27]. Since the prevalence of vitamin D deficiency (25(OH)D<50 nmol/L [20 ng/ml]) is high, supplementation could potentially benefit a large proportion of MS patients [28,29]. Genome-wide Association Studies (GWAS) identified 200 variants of susceptibility to MS in addition from smoking and CNS resilience and influence disease severity [2,30].

Calling for early, highly effective disease modifiying therapies (DMTs) is currently considered to be the best strategy to delay/mitigate disease progression in the earliest stages and to prevent long-term neurodegeneration [31-34]. In particular, delayed onset of DMT´s in pediatric MS was associated with increased relapse and motor disability [35]. However, this strategy could also be transferred to a vitamin D supplement, especially since parents and children/adolescents can be partially relieved of their fear of undesirable side effects with this add-on therapy with vitamin D. Long-term safety concerns, including those of healthcare providers with regard to DMTs 31, are not up for discussion in the case of continuous vit D suppl. Gaps in knowledge about the immunological effect of vit D on various mechanisms as well as therapeutic inertia are an obstacle [36]. The latter could be determined that this phenomenon affects 60 to 90% of neurologists worldwide and affects up to 25% of the daily treatment decisions in the treatment of PwMS [36].

The “dilemma of the undervaluation of vit D suppl by neurologists” is also evident in a recent study, where polypharmacy was examined in PwMS, but Vit D was not present [37].

Proactive management is required in clinical practice to maximise disease pathology through anti-inflammatory drugs (DMDs) through long-term administration [38]. The early, high-dose constant oral administration of vit D with the aim of physiological levels of s(serum)25(OH)D in the upper normal range (maximum 130ng/mL) is a prerequisite for influencing the decisive pathological events in the CNS involved in the immunopathogenesis of this disease, such as disruption of the permeability of BBB (Blood-Brain-Barier), accumulation and activation of inflammatory cells, oxidative stress and inflammasome activation [7,16,39].

The vit D suppl is not restricted by EMA (European Medicines Agency) or FDA (Food and Drug Administration) and requires fewer financial resources in public health. This does not seem insignificant, as access to DMTs is not freely and consistently accessible to all PwMS in all countries [40].

Update 2024

New aspects of vitamin D supplementation through verification of three immunologically different endophenotypes of multiple sclerosis.

Due to the heterogeneity of the clinical manifestation and the progression courses, the choice of therapy in the individual patients with multiple sclerosis (PwMS) is difficult to predict and is still associated with “trial and error”. Currently, three different immunological endophenotypes from peripheral blood have been identified in early-stage PwMS [25].

Determining a patient’s immune signature in the blood before initiating immunomodulatory therapy in the early stages of MS could facilitate the prediction of clinical disease progression and enable personalized treatment decisions based on pathobiological principles [25].

Immune Signature E1

Changes in the CD4 T cell compartment with increased proportions of CD4 memory subgroups that produce T-helper-17 (Th17) associated cytokines (interleukin - 17 A (IL-17A), IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF). There were increased signs of early structural damage, higher clinical disability, early cognitive deficits, increased sNfL (Serum neurofilament ligth chains) concentrations and intrathecal IgM concentrations [25]. Serum concentrations of NfL have been shown to be biomarkers of acute axonal injury and neurological disease activity (More details below).

Immune Signature E2

Changes in the natural killer cells (NK) cell compartment with fewer pro-inflammatory features [25].

Immune Signature E3

Disorders in the CD8 T cell compartment.
Although changes in the NK cell compartment were also found in E1 and E3, they were less pronounced than in E2 [25].

Two types emerged. One was the “degenerative” endophenotype associated with increased signs of early structural damage and disability progression. The second “inflammatory” endophenoty showed increased features of high inflammatory disease activity [25]. More details in [25].

Immunological Influence of 1,25(OH)2D3 on E1 Endophenoty

The biologically active form of vitD can significantly influence the risk and severity of autoimmune diseases by attenuating IL-17 synthesis of pathogenic Th17 cells, increasing the sensitivity of effector CD4+ T cells to extrinsic cell death signals, and promoting development and suppressive function of CD25 + FoxP3 + Treg cells and CD4 + IL-10 + FoxP3 − Tr1 cell development [41]. (Figure 4).

A high-dose vitD-Suppl. reduces IL-17-producing CD4+ T cells and effector memory CD4+ T cells in PwMS when they show a significant increase in 25(OH)D levels [42]. If 1,25-dihydroxyvitamin D3 lowers the pro-inflammatory cytokines IL-17 and IL-21, promotes the ability of regulatory T cells to migrate to the CNS and increases anti-inflammatory IL-10 production, [41,43] therapeutic efficiency is increased by additive therapy support with vitD. [Figure 4]

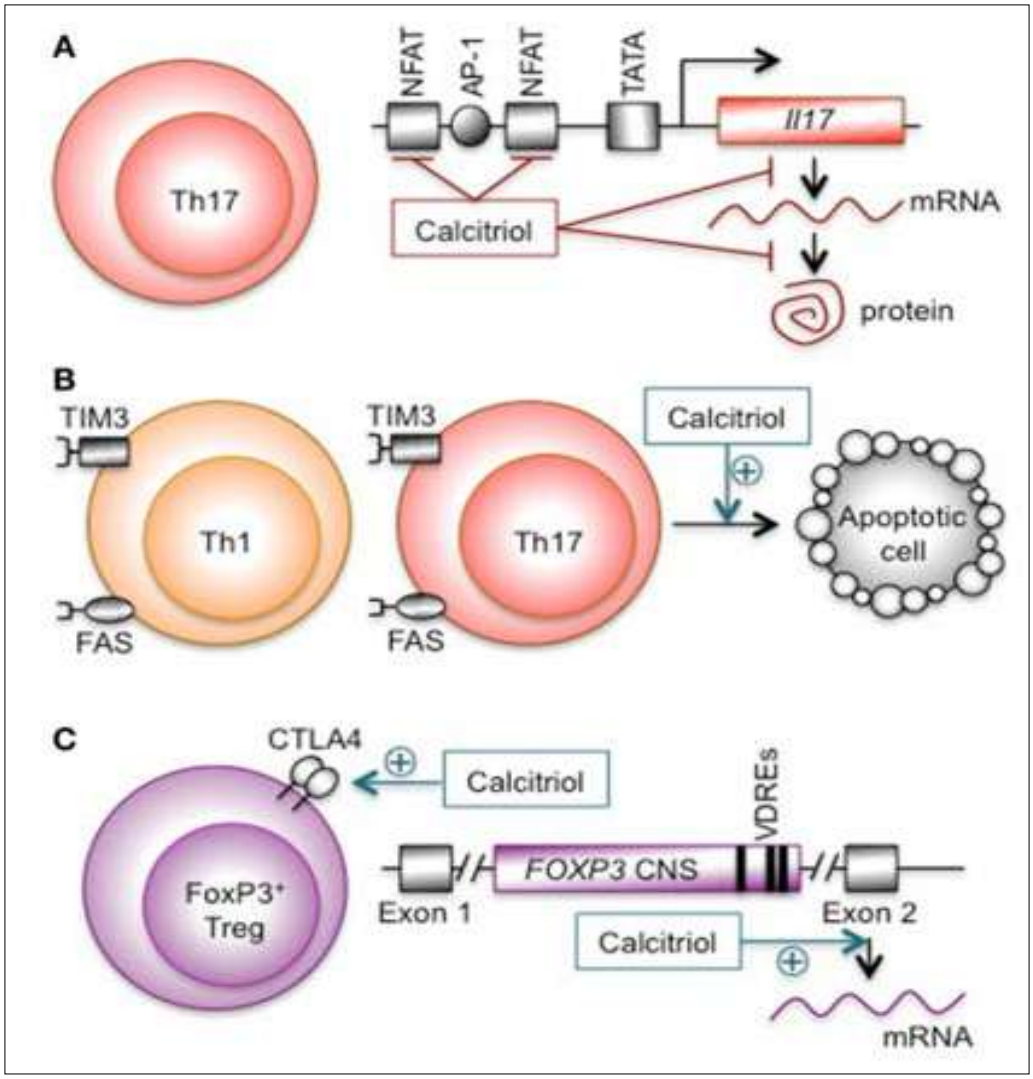

Figure 4: The Original Illustration from the Publication: Hayes CE, Hubler SL, Moore JR, Barta LE, Praska CE, Nashold F[41]. Frontiers in Immunology

Proposed calcitriol mechanisms in effector Th1, Th17, and FoxP3+ Treg cells.

(A) Calcitriol and IL-17 synthesis in Th17 cells. Calcitriol inhibited IL-17 synthesis in a VDR-dependent manner by a post-transcriptional mechanism. It also blocked NFAT, recruited histone deacetylase, and sequestered Runx1 to suppress murine Il17 gene transcription.

(B) Calcitriol and effector CD4+ T-cell apoptosis. Calcitriol increased CD4+ T-cell sensitivity to extrinsic cell death signals that may have been transduced through the FAS ligand–FAS–caspase-8 and/or the galectin-9–TIM3–calpain pathways.

(C) Calcitriol and FOXP3 gene transcription. Calcitriol increased the transcription of the murine FoxP3 and human FOXP3 genes. Three VDREs that functioned as calcitriol-dependent enhancers were identified in a conserved non-coding sequence (abbreviated CNS in this diagram) between exons 1 and 2. Calcitriol also increased CTLA4 protein expression.

1,25(OH)2D3 directly inhibits IL-22 production via a repressive vitamin D response element (VDRE). Vitamin D as a potential therapeutic agent for the regulation of IL-22 [44].

The function of regulatory T cells (Treg) is reduced in the pathophysiology of MS, resulting in the abundance of type 1 Th cells (Th1) and Th17 cells or GM-CSF-secreting effector T cells [45-49]. On the other hand, vitamin D may promote the ability of regulatory T cells to migrate to the CNS, promote Th2 and Tregs [16,50].

Early damage to BBB causes an influx of peripheral immune cells and factors that interact with resident immune cells in the CNS. It was shown that autoreactive CD4+ and CD8+ T cells migrate over the destroyed BBB and are also present in active demyelinating lesions. 6 The active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1α,25-[OH]2D3), is reported to have protective effects for multiple sclerosis [51].

Vit D suppl may be particularly beneficial in women with MS because vitD signaling plays a greater role in maintaining T cell tolerance in women than in men. In one study, a cooperative loop between vitD and estrogen was described, as calcitriol

promotes estradiol, which reduces the transcription of Cyp24A1, the catabolic enzyme for active vitamin, and increases VDR in T cells, which in turn promotes Treg development [16,52].

1,25(OH)2D3 and Association to the Immune Signature E2 (NK)

NK cells are a subgroup of innate lymphoid cells and are divided into two functional and phenotypically different groups based on their expression of CD16 and CD 56. They are found in peripheral blood in two main subgroups: CD3−CD56bright CD16− cells and CD3−CD56dim CD16+ cells [53,54].

There is evidence that NK cells make both a positive and a negative contribution to the pathophysiological processes in MS [25, 54-56] and CD56 bright and CD56 dim cells merely represent different stages of NK maturation and CD56 dim cells are less mature [57,58].

Due to their immunomodulatory properties, CD56+ bright NK cells can positively influence the course of MS by killing activated autologous T cells Granzyme-K dependently [54,59,60].
This subgroup could explain the control of inflammation in pregnancy because the number of CD56-bright NK cells increases during gravidity [61].

The higher the number of CD56 brigth NK cells, the lower the number of new or enlarging T2 hyperintense lesions in the brain under daclizumab therapy [62]. On the other hand, CD56+ bright NK cells are known for the strong secretion of various cytokines such as IFN-gamma and TNF-alpha, but this is increased during MS activity and their blocking would be beneficial [63-65]. In remission RRMS patients, although they were in an inactive stage of MS, circulating NK cells with an activation phenotype were detected [54].

Vit D has a direct or indirect effect on NK cells [16,44,55].

1,25(OH)D2D3 inhibits NK cell development by having a negative regulatory effect on NK cell development from CD34+ progenitor cells [66]. NK cells that differentiate in the presence of calcitriol showed attenuated inflammatory ability with reduced IFN-gamma secretion and reduced cytotoxicity [66].

After vit D suppl, the "NK cell-associated cytotoxicity pathway" increased, IFN-alpha subtypes and IFN-k were strongly expressed. The „interferon-gamma response" signaling pathway and other cytokine production and chemotaxis approaches showed a reduction [67]. With regard to VitD and NK cells, treatment of EAE-induced SJL mice (EAE=experimental autoimmune encephalomyelitis) with vitD3 has been reported to prevent EAE [68].

Anti-CD20 infusions (rituximab, ocrelizumab) resulted in an increase in absolute and percentage levels of NK cells three and five months after therapy. On the other hand, lower percentages of NK cells three months after anti-CD20 infusion correlate with the presence of disease activity six months after therapy, suggesting a possible protective function of NK cells in MS [69]. In other studies, ocrelizumab has not observed any changes in CD56 cells or even decrease [70,71].
However, natural killer cells can produce IL-22, on the other hand, 1,25(OH)2D3 inhibits IL-22 production in human Th22 cell calcitriol activates NK cells. Hypovitaminosis and/or deficiency of VDR (vitamin D receptor) can also lead to disruptions in the development of invariant NKT cells and their number, which is crucial for the control of autoimmune diseases, such as MS [72-74].

Endophenotype E3 (Disturbances in the CD8 T cell Compartment) and Calcitriol

Effector CD8+ T cells are found on MS lesions. 70% of T cells in acute and chronic lesions express the pro-inflammatory IL-17 [75,76].

1,25(OH)2D3 exerts an anti-inflammatory profile on CD8+ T cells and would target the endophenotype E3 [77]. High daily doses of vitamin D (e.g., 10,400IU/day) are required in correlation with s25(OH)D levels (30-60ng/mL), which are dependent on individuals with high, medium, and low responders to supplementation [16,78].

1,25(OH)2D3 modulates the glycolysis and function of CD8+ T cells, thereby inhibiting the proliferation, cytotoxicity and abnormal activation of CD8+ T cells as well as the undesirable IFN-gamma secretion and IL-17 [75,79-81].

Vitamin D could increase NK cell activity and possibly eradicate cells infected with SARS-CoV-2 and a prophylactic benefit could be achieved here [82].

In addition, serum NK levels correlate with disease activity in PwMS with ocrelizumab and rituximab [69].

Vit D has effects on both the innate and adaptive arms of the immune system. There is strong evidence for the role of vitamin D in the pathogenesis and in the course of MS by influencing immune cells [83]. (Figure 5)

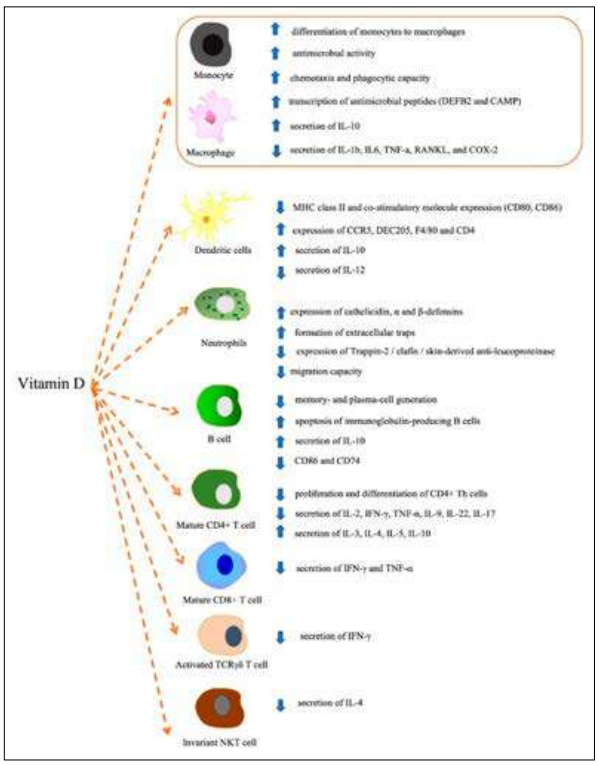

Figure 5: The Effects of Vitamin D on Immune Cells

Original figure from Platone et al. Int. J. Mol. Sci [MDPI] [83].

Update 2024
Affirmation of increased risk of infection due to B-cell depletion and intervention by vitamin D
Numerous studies, some with different results, confirm and affirm an increased risk of infection with B-cell depletion, also due to hypogammaglobulinemia (IgG) serum values [84-89].

The rate of severe infections caused by ocrelizumab and ofatumab was 16.8% in hypogammaglobulinemia [90,91].

It has been shown that B-cell-depleting anti-cluster of differentiation 20 (CD20) monoclonal antibodies (mAbs), such as ocrelizumab, not only reduce the B cell count, but also the CD8+ T cells and NK cells [92,93]. The loss of some antimicrobial functions of cytotoxic T cells and NK cells against various pathogens could possibly explain the observed increases in the infection rate with anti-CD20 agents [85].

A proactive approach is indicated to ensure that effective DMTs are not started or rejected by the PwMS because of the risk of infection (e.g. rituximab is twice as high as non-depleting therapy [85].

1,25(OH)2D3 induces the expression of the gene for the human cathelicidin antimicrobial peptide (CAMP) [94].

The transcription of the human antimicrobial peptide genes β-defensin 2/defensin-β4 (HBD2/DEFB4) and CAMP is stimulated by the VDR, which is bound to vitamin D response elements close to the promoter [95]. At the innate level, intracrine synthesis of 1,25(OH)2D3D by macrophages and dendritic cells stimulates the expression of antimicrobial proteins such as cathelicidin and lowers intracellular iron concentrations by suppressing hepcidin [96,97]. Hypovitaminosis D is associated with an increased susceptibility to viral infections (e.g. respiratory tract). In addition to its antibacterial and antifungal properties, the 1,25(OH)2D3 induced expression of the antimicrobial peptide CAMP/LL37 also has a key component in antiviral responses [97], and a vit D suppl could therefore support the immune function.

Hypovitaminosis D affects the quantity, quality, breadth (antigen-specific CD8-T cell effector and memory repertoires) and location (localization of effector and memory CD8+ T cells in the lymph nodes) of CD8+ T cell immunity against acute viral and bacterial infections [98].

How Could the Current Research Results be Incorporated into Practice?
Knowledge of the complex pathophysiological mechanisms, such as: the protective effect of 1,25(OH)2D3 on the mucosal homeostasis of the respiratory and urogenital tract as a basis for preventive measures could reduce the infection rate. The induction of antimicrobial peptides by Vit D promotes the killing of pathogens. The tight junction proteins and adherens junction proteins (ZO-1, occludin, claudin-10, ß-catenin, VE-cadherin) play an important role in maintaining the integrity of the lung barrier [99,100].

Daily vit D suppl can prevent and therapeutically influence the risk of acute respiratory and urinary tract infections [101-109].

Adequate vitamin D levels reduced the risk of very low NK in men and in vitro 65 ng/ml 25(OH)D was shown to be more effective in inducing antibody-dependent cellular cytotoxicity mediated by human NK cells [110,111]. In adults, s25(OH)D ≥ 38 ng/mL was associated with a lower incidence of acute viral respiratory infections compared to lower concentrations [112].

Influence of vitamin D supplementation on comorbidities, employment status, quality of life, Epstein-Barr virus infection

Update 2024
Fatigue
Fatigue is also one of the most common symptoms and is reported by at least 75% of MS patients at some point in the course of the disease. For many, fatigue is considered the single most debilitating symptom, surpassing pain and even physical disability [113]. Fatigue also has significant socioeconomic consequences, including loss of work and, in some cases, loss of employment [113-116].

A deteriorating employment status is additionally associated with more depression. Therefore, vocational rehabilitation should also be integrated into the therapeutic procedure [117]. Self-reported fatigue and depression are strongly correlated with quality of life (QoL) [14,118-120]. The cause of fatigue in MS is unknown, but appears to be a combination of disease-related mechanisms rather than disease-specific factors [121]. Understanding these mechanisms, predictors and relationships is important for the development of management strategies and the improvement of QoL. There is evidence that inflammation in the central nervous system, diffuse demyelination, axonal lesions and brain atrophy can lead to fatigue in addition to non-disease-specific factors such as sleep disturbances, heat and depression [122,123]. People who show moderate fatigue at the onset of DMT may represent a high-risk group that is susceptible to further worsening fatigue [121].

A vit D suppl could have a significant effect on reducing fatigue in people with MS [12,23,115,124,125]. Lower serum levels of 25-OH vitamin D continue to be associated with cognitive impairment and disability in MS. Attention, working and verbal memory correlate most strongly with vitamin D levels [126,127].

Employment Status and Quality of Life
In the case of PwMS and RRMS (Relapsing-Remitting-Multiple Sclerosis, there is a natural association between quality of life and professional activity [127]. Labor participation is recognized as the primary therapeutic outcome [128]. A stable, non-progressive MS disease has considerable socio-medical effects, because there is a risk of a reduced salary and the risk of disability if the disability increases and must be taken into account in the context of rehabilitation pathological studies have shown extensive demyelination, neuronal damage and synaptic abnormalities in the hippocampus of patients with multiple sclerosis, manifested as depression and memory impairment [129-131]. Depression, severe fatigue and subjective cognitive complaints have an influence on employment status. This could be well documented in a longitudinal observation over three years [117].

Several studies have shown that hypovitaminosis D decreases the immunomodulation of inflammation and serotonin synthesis, two processes associated with depression and suicide attempts. Therefore, they support the potential benefit of vit D suppl in reducing depression symptoms and a possible indirect effect in preventing suicide and suicide attempts [132].

Suicides are far too common in PwMS and have a significant connection. Multiple factors may contribute to the risk of suicide. In MS, depression is one of the strongest risk factors for suicidal

ideation and depression ist wo- to threfold more common than in the general population but remains undertreated [113-137].

Suicides can and must be prevented and special attention must be paid to prophylaxis [133, 136,138].

Depressed Individuals had Lower Calcidiol Levels [139].
The determination of the s25(OH)D level and the vit D suppl are affordable and safe. Therefore, both measures could be incorporated into current treatment programs, at least for depression, patients with suicidal symptoms and suicide attempts. In suicide attempts, s25(OH) levels were reduced and an increase in hsCRP (highly sensitive C-reactive protein) was registered. [139] Vit D modulates the pro-inflammatory cytokines (e.g. IL1ß, IL6, TNF-alpha [132]. Vit D suppl with values of at least 55ng/ml s25(OH) D showed an increased efficiency in depression [140]. Choleclaciferol-suppl with 10,400 IU/day are certainly well tolerated for PwMS and show in vivo pleiotropic immunomodulatory effect [141,142].

14,007 IU/day over 48 Weeks were well Tolerated [143].
In an imminent suicide situation, a fast, high-dose daily dose of Vit D saturation could be considered as an additive therapy and the fear of vit D intoxication could be taken away. When a condition of deficiency has been identified, a cumulative dose of 300,000 to 1,000,000 IU, over 1-4 weeks is recommended. As a result, values above 30ng/mL can be reached quickly (cumulative dose 1,000,000 IU at <10ng/mL; 10-20ng/mL 600,000 IU; 20-30ng/ml 300,000 IU [144].

A 70 kg (non-obese) adult with sufficient or insufficient vitamin D levels could consistently increase their s25(OH)D levels in the bloodstream to over 50 ng/ml by taking about 5000 IU/day (4000 to 7000 IU/day). However, in the case of vitamin D deficiency, it would take a few months to reach this recommended therapeutic value [145].

For example, one study used a weekly or fortnightly dose of a total of 100,000–200,000 IU over 8 weeks (1800 or 3600 IU/day) [146].

To Obtain 75nmol/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 [146].

Above 30ng/mL s25(OH)D values were also achieved with a single oral dose of 200,000–600,000 IU [147,148]. However, in the case of deficiencies and the need for rapid onset of action, the administration of vitamin D doses between 100,000 and 400,000 IU as a bolus (saturation dose) is necessary to raise the 25(OH)D concentrations in the bloodstream within three to five days [149]. The wide optimal range of 25(OH)D (up to 80ng/mL [130ng/mL]) will depend on the current state of health [39,150].

The safety range at s25(OH)D values is between 30-100ng/mL. 16 The fact that a vitamin D was associated with higher physical quality is not insignificant in professional life [151].

Vitamin D Supplementation and Epstein-Barr- Virus (EBV)
It is becoming increasingly clear that EBV could be the main cause of MS [152-155]. Almost 100% of people with MS had a history of EBV infection and that there was an association between high EBV antibody titers and an increased risk of developing MS [156]. The risk of MS after infection with EBV increases 30-32 times [155,157].

The control of autoimmunity is severely impaired in PwMS [158]. Increased immune responses to EBV remain elevated during disease progression and correlate with disease activity [159]. These increased EBV-specific immune responses could transform EBV-specific CD8+ T cells into the CNS. The goal must be to improve this impaired immune control [157,160]. EBV is latent in B cells and anti-CD20 treatments have shown that they can successfully break down these cells in MS [161].

An effective effect on the increased immune response could be achieved by 1,25(OH)2D3 by altering the immune response to EBV core antigen 1 (EBNA-1) [162-168].

A high-dose vit D suppl (14,000 IU/day over 48 weeks) lowers anti-EBNA-1 antibody levels in MS patients [162]. The measured EBV viral load was significantly higher when VitD levels were low, showing an inverse correlation between vitamin D and EBV viral load [169,170]. People with higher 25(OH)D levels excreted EBV less frequently in saliva [171].

A high-dose vit D suppl (20,000IU/week) was able to prove the humoral immune response by reducing anti-EBNA1 levels [172].

If the genetic risk of elevated anti-EBNA1 titers is positively correlated with the development of MS, a vit D effect can be expected [173-175]. If EBNA-1 antibody levels increase 5–20 years before the onset of MS and remain constant throughout life, it is necessary to perform Vit D supplementation as early as possible and throughout life [176-178].

In addition, higher expression of CD86 on B cells serving as APCs has been reported in MS patients highlighting the important role of CD86 expressed on B cells in the pathoetiology of MS [179-181].

Ziaei et al. reported on gene-environment interactions in pediatric MS patients and underlined the potential crucial role of B cells in EBV-associated MS risk [182]. In a study on the interaction of human herpesvirus 6A (HHV-6A) and EBV the hypothesis that HHV-6A and EBV infection interact in MS development could be confirmed [183]. There was a statistical correlation between s25(OH)D and HHV-6A/B IgG titers with multiple sclerosis severity score (MSSS) so that a biological plausibility can be assumed that a Vit D suppl has a synergistic effect [169,170].

2024 Dual Therapy Principle (DMTs/Vitamin D) to Improve the Quality of Life of PwMS
The wearing-off phenomenon is reported by PwMS with ocrelizumab (anti-CD-20 monoclonal antibody) treatment in up to 50%, especially in obesity (BMI cut-off ≥25) [184,185]. The wearning-off phenomenon was observed between < a week or > 4 weeks before the next infusion [185].

This phenomenon is defined as an increase in MS-related symptoms, such as fatigue, cognitive impairment, balance problems, motor dysfunction, and sensory symptoms before the next ocrelizumab infusion. This phenomenon is doubted and attributed to natural fluctuations in MS symptoms and attribution bias as well as to suboptimal control of MS disease activity, reduced immunomodulation could be demonstrated by the detection of increased lymphocyte counts (CD8, CD3 and CD3CD27 lymphocytes) and increased plasma NfL(neurofilament light chains) levels [184].

The severity of the wearning-off phenomenon was associated with higher plasma NfL and CD8 lymphocytes [185] serum

concentrations of NfL have been shown to be biomarkers of acute axonal injury and neurological disease activity [185].

As a potential measure of disease activity, sNfL can provide insights into the current course of the disease during therapy and a correlate to the clinical presentation with the information provided by the PwMS on their condition [186]. However, since the maximum of sNfL levels was measured on average 9 weeks after the gadolinium (Gd+) lesions, a permanent vitamin D suppl would be biologically beneficial. Emergence of new Gd+ lesions did not always show elevated sNfL levels that exceeded the 95th percentile threshold [186]. In a longitudinal study of sNfL values (2,4,8,16,24 and 48 weeks), 20% with recurrence and/or Gd+ enriching lesions showed no significant altered sNfL values [187].

If PwMS are not prepared for long-term supplementation with daily vitamin administration, it would be debatable whether the administration of high oral doses of Vit D, e.g. three months before the next ocrelizumab administration, could attenuate or prevent this wearing-off phenomenon. Obesity in PwMS in particular could be the cause of a reduced response to treatment due to the higher volume of distribution and thus lower therapeutic concentrations [185]. Before discussing higher doses and shorter intervals of orelizumab intervals with the possibility of hypogammaglobulinemia and/or infection, the direct additive effect of 1,25(OH)2D3 on the immunomodulatory effect directly on CD8+ T cells should be exploited while maintaining regulatory intervals [77].

The basis for this hypothesis is the evidence that a vitamin D suppl with effective s25(OH)D target values exerts an influence on B cell kinetics. Serum 25(OH)D levels below 30 ng/mL were associated with a higher likelihood of early recurrence of B cells after six months of follow-up [188]. Another justification for vitamin D supplementation would be the experience of patients with chronic inflammatory bowel disease (IBD), whereby patients with active disease daily doses of vitamin D doses of 5,000 and 10,000 IU/day reduced symptoms [189].

However, because there is also an increased risk of developing an additional IBD with orcrelizumab or rituximab, [190]. Vit D could enable a therapeutic double effect. An add-on therapy with vit D to orelizumab showed an influence on both B-cell kinetics and radiological activity [188].

Wearning-off- Phenomen- often Associated with Depression

PwMS also reported a so-called „Wearning-off- phenomen“ in more than 50% of patients treated with the monoclonal antibodies ofatumumub and rituximab as well as natalizumab [191]. Shortly after the DMT was administered, a symptomatic improvement was noticed, but the benefit diminished before the next dose. PwMS and depression as a comorbidity had a higher risk and fatigue manifested itself in 62% of individuals with this phenomenon and this problem also affects treatment satisfaction [191]. However, with ocrelizumab, the wear effect was observed in 61% of PwMS without affecting treatment satisfaction [184]. Ocrelizumab, ofatumumab, rituximab and natalizumab are injectable modifying drugs.

If there is a correlation between depression and lower adherence to DMTs (38.2%) compared to PwMS without depression it is biologically plausible to incorporate a vitamin D supplementation into the pharmacological management of DMT´s treatment [192]. Veterans who adhered to their DMTs showed a 12x higher chance of survival than those who did not [193]. Adherence in RRMS is between 41-88%, on the other hand, it is associated with worsening of MS, increased mortality and increased health care costs [193].

Although the causes of adherence are varied, depression occurred in 64.8% of men as side effects of DMT´s [193]. In a long-term observation over 20 years, 53.0% were not adherent. Mortality shows a decrease of 28% in those PwMS who maintained therapy with DMTs [193].

Discontinuation of therapy also showed a considerable economic burden [194].

Brain Atrophy and Vitamin D

Gray matter (GM) atrophy is common in PwMS, especially RRMS. Vit D deficiency is associated with increased brain aging and s25(OH)D levels are positively associated with total brain volume and GM [195,196]. A positive effect of 1,25(OH)2D3 on various structures such as the prefrontal cortex, hippocampus, gyrus cinguli , thalamus, hypothalamus and substantia nigra can be expected, as this substance suppresses oxidative stress in neurons, inhibits inflammation by downregulating inflammatory mediators and also upregulates a large number of neurotrophins [197].

Discussion

In 2024, after the diagnosis of PwMS, it is not possible to predict how the course of the disease will develop into old age in an individual case, because the individual pathobiology of the individual MS patient cannot be predicted. The etiology of MS is still unknown [5]. Prior to diagnosis, an MS prodromal stage of 5-10 years may be seen in individual PwMS, but where neurodegenerative changes have already begun [198,199]. Neuropsychiatric and cognitive impairments in this phase and after diagnosis of MS require all therapeutic registers, especially since it has been proven that sNfL (serum neurofilament light chain) (a biomarker for axon injury) was elevated 6 years before a definitive diagnosis of MS [199,200]. At present, there are no available treatments to effectively repair CNS injuries, which is why even a potentially small benefit of one form of therapy in the development of the disease must also be exploited in the early stages of MS [201]. Findings from prospective studies are consistent with the hypothesis that high circulating vitD levels are associated with a lower risk of MS and it gave a clear picture indicating that the earlier the disease was treated, the better the outcome [7,10,202-204]. Despite extensive pathophysiological knowledge about the effect of vitamin D on the adaptive and inert immune system, “hypovitaminosis as an etiological factor of MS” divides the neurological community into a “yes” camp and a “no” camp. There is a wealth of evidence that vit D is a causal factor in MS [16]. The Bredford-Hill criteria are met for vit D deficiency as an etiological factor in MS, in particular dose-dependency and biological plausibility, but also causation, consisteny, specificity [151].

Since PIRA (progression independent of relapsing activity) is the main driver of the accumulation of disability in MS and two-thirds of all disability-aggravating events are attributable to PIRA, which occurs in the earliest phases of the disease and is associated with irreversible disability, prevention becomes a conditio sine qua non [205]. Since early DMT therapy (there are currently 20 disease-modifying drugs available) can reduce the risk of deterioration of EDSS, preventive adjuvant therapy with vitamin D could increase the success of the therapy, since a protective effect of vitamin D in vivo cannot be ruled out [16,32,206].

Worldwide, almost 50% of the general population is affected by vitamin D deficiency, in some countries up to 90%, depending on the definition of vitamin D deficiency [207,208].

2024: Calcitriol ($1,25(OH)_2D_3$) - Equal Partner with Disease-Modifying Therapy (DMT's)?

The extent of vit D suppl on disease risk or clinical response to MS is largely determined by exceeding the threshold value of s25(OH) D (dose-response ratio), although there is still no agreement on this relevant laboratory finding. But it can be assumed that the s25(OH)D value is above 40ng/mL [202].

If participants in a cross-sectional study with both low s25(OH)D and very high s25(OH)D values are included, no significant data on the dose-response relationship can be obtained. Furthermore, there is essentially no determination in studies where free D3 and vitamin D-binding protein (VDBP), although it could play a major role [209-212].

Grut et al. determined the free 25(OH)D 3 and VDBP from presymptomatic samples. A high index of free vitamin D3 before age 20 was associated with a lower risk of developing multiple sclerosis later in life. High levels of VDBP after age 30 were associated with a lower risk of developing multiple sclerosis. Already 8 years before the onset of symptoms, relevant changes in the free D3 values became apparent [210].

If the s25(OH)D level had been raised to or above 40ng/mL as a preventive measure during this period (MS prodrome), e.g. in Canada in the general population, 40% of MS cases could have been prevented [29,105].

The presence of a so-called latency period between the onset of disease pathobiology and the appearance of typical clinical symptoms in MS has been generally accepted for some time. However, a newer concept is that of an MS prodrome an early set of signs and symptoms that occur before the onset of typical clinical symptoms-presumably during the latency period [213]. The fact that neuroaxonal damage occurs years before the onset of the typical clinical symptoms of MS could be objectified by the detection of elevated sNfL levels on average over 6 years [200]. Average s25(OH) levels in the first 12 months after diagnosis of CIS strongly predicted MS activity and progression over the following 4 years. In a follow-up of 5 years, PwMS with s25(OH) D values >20ng/mL showed four times less change in T2 lesion volume on MRI, two times lower rates of brain atrophy, and less disability (EDSS[Expanded disability Status Scale]) than those below 20ng/mL [24].

GM Atrophy is Widely used in RRMS [195].

The PREVANZ study of vitamin D suppl in high-risk clinically isolated syndrome (CIS) examined whether vitD suppl delays the time to new clinical or radiological activity. It was shown that vitD monotherapy alone is not an effective treatment for preventing the development of relapsing-remitting MS. However, the study only lasted 48 weeks and only 49 patients received a dose of 10,000 IU/day. Only a few patients had vitD deficiency (less than 50 nmol/l). It took 12 weeks to reach a steady state of 25(OH)D levels, so only 36 weeks allowed vitD to show its optimal effect [214,215]. One reason for a negative result of vit D suppl to reduce the development of CIS to manifest MS could be that vit D-suppl should have been started in the prodroma phase. The risk factor BMI was reported by the PwMS themselves and was on average 28.8 (SD 7.1). Capsules and no Oily Suspension were used for Vit D Suppl [215].

In the study by Cassard et al. for clinical relapse activity, a daily vit D administration of 5000 IU/day in addition to the daily glatiramer acetate is described as "high-dose" [216]. They may interpret the result of this vit D suppl as not advantageous. However, due to the lack of a second DMT comparison group, this study could not make any direct statements about a possible effect modification [217]. In doing so, they criticize themselves for the fact that a higher dosage of vitamin D could change the therapeutic effect. In other studies, the term "high-dose" is defined for 14,000IU/day or doses of 7,000IU to 20,000IU/day and applied therapeutically [16,55,109].

A study showed that short-term vitamin D supplementation as an adjunct therapy to DMT's led to low efficacy over a period of 6-24 months, although there were indications of improvement in MRI findings [109,218]. There is evidence that more "supraphysiological doses" and confirmation of early Vit D administration are a prerequisite for therapeutic efficacy to achieve serum 1,25(OH)2D3 levels to control neuroinflammatory processes [7].

One explanation for negative studies in Vit D suppl could be the lack of a therapy strategy tailored to the individual patient. The landmark studies that MS has three distinct manifestations at the cellular level may be an amount that explains the discrepancy between confirmed pathophysiological mechanisms on innate and acquired immunity and negative Vit D suppl studies. Therapeutic success of vit D suppl could be improved by immunophenotyping in routine clinical practice by blood tests [25].

For example, the endophenotype E1 with damaging cytokines of the type Th 17 (Il-17A, IL-22) could respond to a 1,25(OH)2D3, Th1 and Th17 cells are considered inhibitory targets for 1,25(OH)2D3 but a therapeutic effect could also be achieved with the "inflammatory E3 type" [16,219-221]. The period of "trial and error" could also be reduced by determining the T cell subgroup (CD8+ lymphocytes), as an increased proportion of CD8+ lymphocytes at the beginning of anti-CD20 therapy indicates a higher probability of later relapse [222].

Vitamin D and Brain Atrophy

For the classification of MS phenotypes, the volume of GM and the volume of white matter lesions are also included [223,224]. Thalamic atrophy occurs early and regularly throughout MS. Preliminary sample size calculations appear feasible, increasing its appeal as MRI markers in the context of neurodegeneration [225].

Disability and cognitive decline have been observed to be significantly related to brain atrophy. Cognitive dysfunction in MS leads to functional impairments of patients' daily activities [226].

Numerous studies have found that higher serum vitamin D levels are associated with a reduction in new active cortical and subcortical lesions and lower lesion volume [227].

In the general population, Vit D deficiency is associated with accelerated brain aging and s25(OH)D levels were positively associated with total brain and GM volume [196]. PwMS and RRMS showed thalamic atrophy and dysconnectivity associated with cognitive impairment [228]. Because 1,25(OH)2D3 is produced in the human brain and acts on the thalamus, but also on various structures, including the prefrontal cortex, hippocampus, gyrus cinguli, hypothalamus and substantia nigra it is pathophysiologically appropriate to bring the s25(OH)D level

to optimal values by vit D [197].

The 90 percent incidence of vit D deficiency in PwMS, as well as the significant association of optimal vit D status with the absence of fatigue and improved physical and functional well-being, indicate that vit D suppl is a potential therapy to improve the patient's quality of life [115,125,229]. In negative vitamin D supplementary studies, only low daily doses (around 600 IU/day) were administered in some cases due to concerns of toxic s25(OH) mirror [230].

Influence on Infections and Adverse Effects of DMTs

A proactive action for infection prevention can be achieved by permanent substitution with Vit D. The laboratory discovery of secondary hypogammaglobulinemia by anti-CD-20 therapies is no guarantee of infection prophylaxis in years of therapy, as the infections occurred before IgG (Immunoglobulin G) levels had dropped, as an indication of the multifactorial nature of the risk of infection [90,231].

Mathias et al. observed under ocelizumab therapy a loss in memory CD8+CD20+ and central memory CD8+ T cells [232]. The loss of memory CD8+T cells correlated with lower CXCR expression and CNS-related LFA-1 integrin expression as well as a reduced antiviral cellular immune response. This constellation could be the cause of infection in 18.4% of ocrelizumab-treated patients [232]. This "gap" in the immunological defense could be closed by vitD suppl Avoiding infections could also promote long-term adherence to therapy with DMTs in PwMS.

The current continuing risk of severe infection from COVID-19 (Cronarvirus disease) infection should be a dual motivation for daily high-dose vitamin D administration [28,233]. An s25(OH)D level of 40-60ng/mL should be achieved by dosing up to 6000IU/day [234]. A daily intake of 10,000IU/day vitD for 4 weeks would result in a more rapid optimal s25(OH)D level in "status nascendi" infection [235]. The further daily VitD dose will depend on the s25(OH) values. However, in the case of severe respiratory infections (COVID-19) or sepsis, a single oral bolus dose (100,000 to 500,000IU) or divided dosis of 50,000IU are administered to ensure rapid (within 3-5 days) adequate intracellular supply of calcitrol to he to make available [148]. A potential role of vit D suppl on the course of Long-Covid should be exploited [145, 236-238].

In older PwMS, special attention must be paid to immune senescence (age-related changes in the immune system) in order to avoid infections with anti-CD20 therapy, as the infection rate was 16.8% with ocrelizumab or ofatumab who developed hypogammaglobulinemia (HGG) [91]. HHG was observed in 9.8% with ocrelizumab or ofatumumab, and severe infection in 8%. Therefore, risk monitoring should be carried out carefully in PwMS ≥ 50 years, Caucasian race and with a therapy period ≥ 3 years [239-241].

In PwMS over 50 years of age, HGG and severe infections occurred more frequently than in younger people. 241 It was confirmed that the risks increase in patients who have been treated for the longest time and have a higher degree of disability [90]. In a study with 150 PwMS, a higher percentage of CD4 T cells were registered with DMTs in immunophenotyping with a higher probability of infections in the follow-up examination [222].

1,25(OH)2D3 suppresses the proliferation of CD4 + T lymphocytes and increased the proportion of CD4 + CD25 + FoxP3 + T-regs. To prevent older PwMS (> 50 years) from being deprived of DMTs during disease activity additive therapy with Vit D suppl should be offered in the informed consent conversation in order to minimize the risk of infection and the fear of it [7,23,41,242-244].

International Consensus on Vitamin D Supplementation for the Benefit of PwMS is Urgently Needed

There is a consensus that delayed onset of DMT leads to adverse outcomes in PwMS as well as relapse and disability in childhood [35].

There is an international consensus that the adaptive immune system is downregulated by 1,25(OH)2D3 and can promote hypovitaminosis D autoimmune diseases [18,245,246].

SNfL values correlate with the disease activity of MS (presence of Gd+ lesions on MRI) but also showed longitudinal controls in PwMS Gd+ lesions without an increase in sNfl values [186,247].

Supplementation with high-dose vitamin D3 for 48 weeks was not associated with lower NfL levels. This study does not support any effect of vitamin D3 on this biomarker of neuroaxonal injury [248,249].

Further studies in patient populations with high disease activity or a larger sample for populations with low disease activity are required to draw a clear conclusion for or against an effect of vitamin D supplements on serum NFL [248-256].

One of many causes of negative supplementation studies could be the lack of attention paid to obesity as a risk factor for MS. (Table).

Table: Relevant, Multifactorial Influences/Potential Confounding Factors in MS Studies on the Results a Vitamin D Supplementation Factors References

Lack of internationally agreed optimal target values for serum 25(OH)D values [s25OH) D] without agreement on the definition of "very severe deficiency", "deficiency", "normal values" and "optimal dose" in autoimmune diseases	Giustina A et al, [246].
No agreement on normal values of s25(OH)D in healthy individuals and in patients with autoimmune diseases, which must be different.	Giustina a et al, [246].
Vit D shows a differential and reduced response to metabolic processes of CD4+, CD8+ T cells in PwMS.	Yeh, W.Z et al, [257].
30 to 100ng/mL s25(OH)D values are proposed to influence immunological imbalance in autoimmune disease [142].	Holick MF et al, [142].
Lack of consensus on the form of oral vitamin D suppl (daily/weekly monthly). Daily administration is preferred.	Giustina A et al, [246].

Lack of discussion of s25(OH) D in pharmacokinetics at daily or bolus doses as to when effective values are reached to exert immunomodulatory effect. "Saturation dose" and "maintenance dose".	Adami S et al, [144].
Achievement of steady-state levels in healthy people, obese people (pharmacokinetic variability) and in patients with autoimmune diseases not comparable. (e.g. 10,000 IU/ day) [246, 258-263].	Giustina A et al, [246]. Wylon K et al, [258]. Meekins ME et al, [259]. Rahme et al, [260]. De Oliveira LF et al, [261]. Duan L et al, [262]. Lemke D et al, [263].
No consideration of individual absorption rates "low, medium, high" in vit D suppl/personal Vit D response index in studies due to genetic variants of Vit D binding protein (VDBP) and genetic polymorphism (CYP27B1). PwMS decreased serological response to Vit D supp.	Bivona G et al, [264]. Carlberg C et al, [265]. Malhotra S et al, [266]. Jassil NK et al, [267]. Jiang T et al, [268]. Bhargava P et al, [269].
Impact of vit D3 Dietary Supplement Matrix on Clinical Response: Oil-emulsified vitamin D supplements resulted in better s25(OH)D levels.	Traub Ml et al, [270].
Rare correlation of the daily dose of vit D to BMI, and (based on waist circumference [WC] (abdominal obesity based on WC is associated with a higher risk of combined vitamin D deficiency and insufficiency). The BMI unteresetimates the "real" obesity, which was determined by DEXA scan in obese.	Zittermann a et al, [271]. Li X et al, [272]. Hajhashemy et al, [273]. Bachmann KN [274]. Larsson SC et al, [275]. Visaria A et al, [276].
Lack of consideration of reduced absorption in PwMS at different degrees of MS severity and comorbidities and adverse events (AE) (e.g., colitis).	Bhargava P et al, [269].
Vit D suppl doses depend on the duration of the disease and the severity of MS.	Agnello L et al, [277].
RCTs of pharmaceuticals cannot be compared to RCTs of dietary supplements. Problems with RCT's with dietary supplements.	Boucher BJ et al, [278]. Föcker M et al [279]. Pierrot-Deseilligny [280].
No standardization of study designs with the consequence of a lack of comparability of studies.	Wimalawansa SJ [236]. Giustina a et al, [246].
Ambitious goals in the primary goals of RCTs, and neglect in the secondary goals achieved in the assessment (e.g., 32% reduction in the number of new gadolinium (Gd+)-enriching or new/enlarging T2 lesions on MRI).	Hupperts R et al, [143].
25(OH)D determination assays show mixed results.	Ziael A et al, [281].
Lack of central laboratories	Ziaei A et al, [282].
Lack of quantification of metabolites of D2 and D3 that show effects on the immune system. No routine determination o free 25(OH) D (fD3) and vitamin D-binding protein (VDBP) or its index.	Grut V et al, [183]. Qu F et al, [283]. Grut V. et al, [210].
Negative RCT results may reflect technical deficiencies.	Lincoln MR et al, [284].
Lack of evaluation of the dose-response aspects of the cause of failed vitamin D suppl studies in the area relevant to the disease.	Hanwell HE et al, [209].

In a study with 1066 PwMS, 14.9% showed a BMI of ≥ 30kg/m² [250]. Adipose tissue is recognized as an active endocrine organ that can trigger chronic inflammation through adipokines [251]. Low vitamin D levels in obese people are a consistent finding regardless of age, ethnicity, and geographic location. Obese people need higher doses of vitamin D to achieve the same s25(OH)D levels as normal-weight people [252]. Six theories have been put forward to explain the underlying immune mechanisms that promote MS through obesity [251].

In the obese phenotype, proinflammatory T cells (e.g., Th1 and Th17) predominate, causing increased inflammation in the blood-brain barrier (BBB), leading to a decrease in tight junction proteins and the process of transcytosis [253-255]. This chronic, mild inflammation is caused by the overproduction of pro-inflammatory adipokines (leptin, resistin, visfatin) and reduction of anti-inflammatory adipokines (adiponectin, Apelin) [251].

Studies on the pharmacokinectics of oral vitamin D suppl in obese children showed that at a saturation dose of 50,000 IU and a 16-week administration of 8,000 IU, 25(OH)D values of over 40 ng/mL were achieved and concentrations >100 ng/mL were avoided [256].

By 2024, there is strong evidence of a direct causal relationship between baseline vitamin D levels and the risk of disease activity in PwMS starting DMT. Genetic predisposition to higher vitamin D levels reduces the risk of disease activity and is associated with delayed MS onset [285]. The potential to explain low vitamin D levels and their association with MS by reverse causality and possible confounding factors is diminished by the detection of variants in VDR binding at a locus relevant to MS risk that is also relevant for other autoimmune diseases [286].

It is biologically plausible that PwMS who do not have this genetic predisposition should be guided to optimal s25(OH) levels before DMT use in order to reduce the risk of disease activity.

The finding that variants in allele-specific vitamin D receptor binding contribute to MS risk in PwMS underpins the causal relationship between s25(OH)D-values and MS [286]. A dose-dependent VitD suppl (5000-10,000IU/ day) modulated the transcriptome of immune cells in PwMS with induction of anti-inflammatory gene expression profiles [287]. The downregulation of Il-17 and TNF-alpha signaling with the resulting inhibition of inflammation would be the basis for therapy in endophenotype 1 (described above). There is cumulative evidence that VitD can modulate the phenotype and function of immune cells as well as MS risk and disease activity through its in vivo effect on mitochondrial gene expression and function [287]. In addition, the clearance of pathogens is facilitated, which promises a protective function against acute respiratory infections [287]. Numerous studies confirm that PwMS respond less well to VitD than control subjects. suppl , which is why high-dose long-term vitD supplementation is a conditio sine qua non [269].

The cytokine IL-27, which has anti-inflammatory, pro-inflammatory and immunoregulatory functions in the pathophysiology of MS, is considered to be of central importance in connection with the autoimmunity caused by the Epstein-Barr virus. IL-27 could be the target of a VitD suppl [288]. A vitD suppl with 50,000IU/ week over a period of 8 weeks led to an increase in the anti-inflammatory IL-27, TGF-ß1 and IL-10 and a reduction in the proinflammatory cytokines IL-17 and IL- 6 [289].

By 2024, so much evidence has also accumulated on various neuroprotective factors of 1,25(OH)2D3 that PwMS may benefit from nutritional supplementation [290].

An important goal of Vit D suppl is the (recognized) influence on reduced Treg cell function, which is also dysfunctional in other autoimmune diseases [41,291]. In the future, improving the dysregulation of Treg cells may be supported by autologous regulatory T cell therapy with ABA-101. The FDA (U.S. Food and Drug Administration) has granted Fast Track status for the treatment of PwMS with progressive MS [292]. An undisputed goal of Vit D suppl is to reduce the pro-inflammatory TNF serum level (see above). Having observed upregulation of TNF expression in both acute and chronic active MS brain lesions in several studies, lowering TNF may also be beneficial in PIRA (relapse activity independent progression) [293].

In a recent systematic review and meta-analysis, the connection between vitamin D status or s25(OH)D concentration and the risk of MS was confirmed. PwMS who did not perform vit D suppl also had a higher risk of vit D deficiency (<20ng/mL) [294]. Maintaining adequate s25(OH)D levels may be an important element in reducing the risk of MS, especially in first-degree relatives of PwMS [289, 294]. Susceptibility to multiple sclerosis show strong genetic associations with HLA alleles and haplotypes [295]. However, the estimation of heritability is still controversial today [296]. The genetic contribution to the risk of developing MS is now estimated to be about 50%, with the genes involved mainly located within the major histocompatibility complex. Familial MS represents 12.6% of all MS cases, with the risk depending on the degree of genetic proximity to the index case [296]. Risk of MS increases by several folds in those with a relative with MS [297].

Women with MS should be recommended to take 1000 IU to 5000 IU of Vit D daily before and during pregnancy to maintain an s25(OH)D level between 30 and 100 ng/mL [298].

The risk of MS in the offspring is reduced by vit D suppl. Hypovitaminosis in early pregnancy doubles the risk [298, 299].

Vit D suppl also enables early treatment intervention to influence disease-related/secondary sarcopenia. It was observed in approximately 20% of PwMS [300]. Low s25(OH)D levels have been identified as a significant risk factor for the development of sarcopenia, particularly in older individuals [301]. Smoldering chronic inflammation in MS exacerbates muscle cell damage and apoptosis in the pathological process of sarcopenia, which vit D suppl can counteract. Vit D also regulates muscle cell proliferation and differentiation, mitochondrial function and other mechanisms details in [301].

In particular, PwMS with higher EDSS values may be at increased risk of falls and fractures due to instability. Muscle loss correlates with disability later in life Hypovitaminosis D and loss of muscle strength show a positive connection [302].

Attention is currently being drawn to the higher risks of disability progression due to the reduction in brain reserve [303].

Increased brain reserve is associated with reduced progression of physical disability in both relapsing-remitting MS and secondary progressive MS. The focus is on neurogenesis and plasticity in certain areas, in particular the hippocampus and the subventricular regions [303].

Hypovitaminosis D is a potential risk factor for accelerated ageing, impaired hippocampal neurogenesis and cognitive decline [304].

Vit D deficiency can be considered a predictor of physical and cognitive disability in PwMS [305, 306].

The current findings could encourage health care providers to consider vitamin D supplements as a piece of the mosaic in the MS clinical picture.

Conclusion

On the basis of pathophysiological findings, the practicing neurologists are presented with the potential therapeutic benefits of early, permanent, daily high-dose vitamin D supplementation in multiple sclerosis. The broad spectrum of activity of 1,25(OH)2D3 on the course of the disease by influencing immune dysregulation can be offered synergistically to DMTs without significant risk to all patients with multiple sclerosis worldwide at low cost and is ethically justifiable. The full spectrum of vitamin D immunomodulation could lead to personalized precision medicine by identifying three different multiple sclerosis subtypes from peripheral blood in the future.

Vitamin D supplementation would have to take place in the MS prodrome before the pathophysiology begins with all the negative consequences and irreversibilities in the life of PwMS.
These current results could motivate healthcare providers to rapidly translate research findings into clinical practice.

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