SCIENCEHOOD

Review Article

Neurology and Neurological Research

Hans-Klaus Goischke *

Early Vitamin D Supplementation in Multiple Sclerosis: A Crucial Preventive Approach in 2025

Hans-Klaus Goischke

Internal medicine, rehabilitation, social medicine, D-97769 Bad Brückenau, Hochwaldstrasse 2, Bavaria, Germany.

***Corresponding Author: Hans-Klaus Goischke,** Internal medicine, rehabilitation, social medicine, D-97769 Bad Brückenau, Hochwaldstrasse 2, Bavaria, Germany.

Citation: Hans-Klaus Goischke (2025), Early Vitamin D Supplementation in Multiple Sclerosis: A Crucial Preventive Approach in 2025; J. Neurology and Neurological Research, 2(1): DOI: SH-NNR-RW-007.

Review Article

Volume 02; Issue 01

Received Date: January 31, 2025

Accepted Date: February 07, 2025

Published Date: February 25, 2025

DOI: SH-NNR-RW-007

ABSTRACT

Based on current pathobiochemical findings up to 2024, it is urgently recommended to implement early proactive therapy in the prodromal phase of multiple sclerosis (MS).

Even in the “stage nascendi” of MS, there is an imbalance between anti-inflammatory and pro-inflammatory processes. The pro-inflammatory actors predominate. Only optimal serum 25-hydroxy-vitamin D values can influence this dysimmunity because of the dose-response relationship. The entire course of the disease, especially the early phase, should be used for daily vitamin D supplementation.

This review explains the existence of a prodromal stage to all practicing neurologists and general practitioners, including non-MS specialists. The usefulness of very early use of vitamin D supplementation is also exemplified by the fact that elevated Epstein-Barr virus antibodies, as an important player in MS (target of vitamin D), can occur 15-20 years before the clinical onset of this incurable disease. About a decade later, elevated serum neurofilament light chains can be verified as an indication of neuroaxonal damage. Because of these findings, a consensus should be reached to start adequate daily vitamin D supplementation immediately upon initial diagnosis of MS.

If this were recognized as a “biologically rational obligation” by health care providers, the quality of life of people with MS could improve early and long-term.

Relatives of people suffering from MS should also be involved in MS prevention. This includes children, siblings, especially a twin.

In contrast to previous reviews with studies on MS and vitamin D supplementation with contradictory results (influence on relapse rate, MRI results, etc.), in this review the priority is given to comorbidities. The focus is on the results on quality of life. Depression, anxiety, fatigue, cognition, suicidality, pregnancy, infection prophylaxis (Covid-19), aspects of childhood MS, adjuvant therapy for disease modifying therapies, cancer prevention, influence on intestinal dysbiosis and osteoporosis are taken into account.

The statements of this non-systematic review are based on clinical studies, meta-analyses, observational studies and the current contributions from ECTRIMS 2024 (The 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, September 18-20, 2024) Copenhagen.

KEYWORDS:

multiple sclerosis, immunopathological mechanisms, comorbidities, vitamin D supplementation, prevention

INTRODUCTION

Multiple sclerosis (MS) is a complex, autoimmune-mediated disease of the central nervous system characterized by inflammatory demyelination and axonal/neuronal damage [1]. It is a leading cause of disability in young adults, but also in children and adolescents, and affects approximately 2.8 million people worldwide (35.9 per 100,000 population) [2]. The risk for MS is approximately 25% heritable in identical twins, with the remaining susceptibility being due to environmental, epigenetic, and gene-gene or gene-environment interactions [3-5].

People with MS (PwMS) experience a very heterogeneous clinical course (relapsing-remitting, primary progressive, secondary progressive) and a key goal of treatment is to slow down disability at an *early stage*, particularly in young PwMS and pediatric-onset multiple sclerosis (POMS) [1,6]. Motor and cognitive changes are present in 80% of MS patients and most commonly include loss of balance and walking speed, loss of hand and foot dexterity, slower information processing and poorer episodic memory [7]. Relapses contribute to the accumulation of disability, especially in the early stages of MS.

Even in the *earliest* stages of MS, a smoldering inflammatory activity is present that progresses inexorably and independently of clinical and radiological relapses. This PIRA (progression independent of relapse activity) begins *early* in relapsing-remitting MS and becomes the dominant factor for the accumulation of disability as the disease progresses [8,9]. PwMS characterized by PIRA and superimposed relapses showed the most rapid transition to disability, EDSS 6 (Expanded Disability Status Scale) [8].

The strategy that should be pursued worldwide is to use highly effective therapeutics to reduce disease activity early or as early as possible. This is the only way to achieve the best possible disease control and the best possible quality of life [10].

In holistic management, alternative strategies including vitamin D supplementation (Vit D suppl) must also be introduced into practice in order to influence systemic disease processes that improve treatment outcomes [11]. Vitamin D deficiency is a worldwide epidemic [12]. Vitamin D (Vit D) plays a role in the primary prevention of MS [13]. In addition to the acute attacks and relapse activity in RRMS (relapsing-remitting MS), diffuse smoldering pathological processes throughout the CNS (smoldering multiple sclerosis) contribute to the slow loss of neurological functions in PwMS [14].
All possible mechanisms must be investigated to halt chronic progressive deterioration of disability in order to enable an adequate quality of life [15]. Hypovitaminosis D was significantly associated with more severe disability [16].

Based on the pathophysiological/pathoimmunological findings, early, high-dose and long-term VitD suppl has been shown to have a broad spectrum of benefits for PwMS. Increased serum 25(OH)D levels have been identified as protective against MS risk and are associated with the risk of relapse [15,17]. Only selected therapeutic areas of Vit D suppl in MS are discussed.

“Proponents of heterodox views” on this add - on therapy are offered the accumulated knowledge on selected topics in order to provide a therapeutic *impitus*. The greatest potential for gaining time and postponing disability as far as possible exists among the youngest, least disabled PwMS [8].

Immunological background

Although the etiology of MS is still unknown, immunological factors (dysimmunity), environmental factors (vitamin D deficiency), Epstein-Barr virus infections and genetic associations are at the center of research [18-21].
These include inflammation and neurodegeneration, both of which are present early in the disease onset [22-26]. Comprehensive recent review and details in [Perdaens 27].

2.1 Persistent, acute inflammation caused by proinflammatory cytokines - one of the causes of MS

Neuroinflammation in MS results from a complex interplay of adaptive and innate immune cells. Inflammatory damage to the semipermeable blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCFSB) allows infiltration of peripheral immune cells (activation of autoreactive lymphocytes from secondary lymphoid tissue, monocytes) and

factors into the CNS that interact with resident immune cells in the central nervous system (CNS) [28-31]. 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 [32,33].

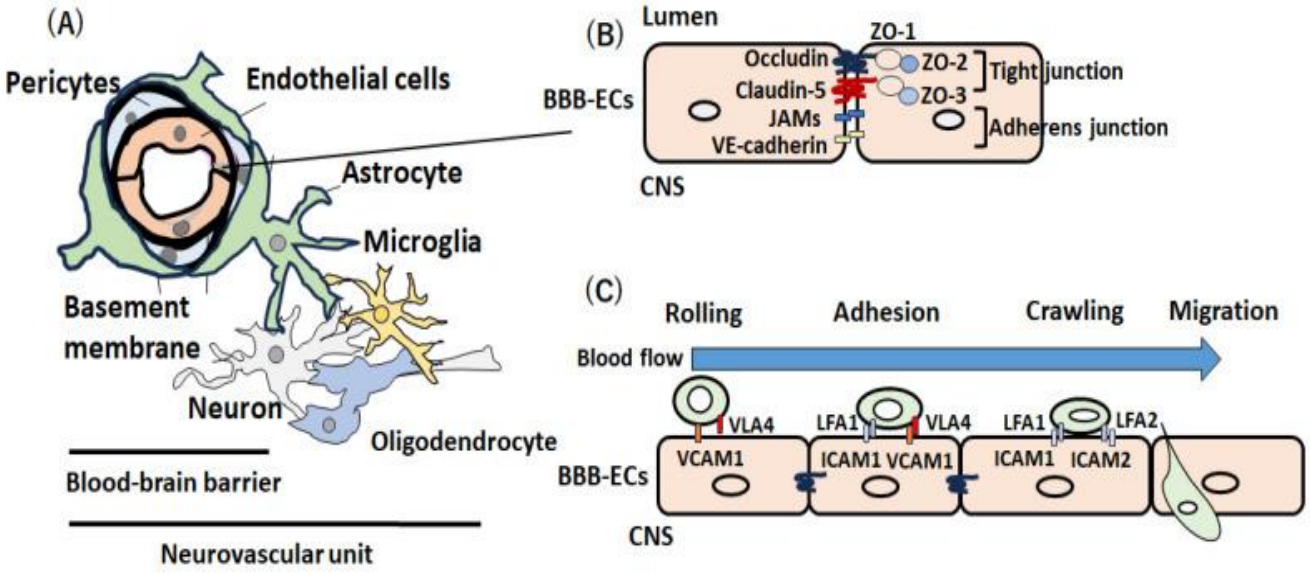


Figure 1: Structure of the blood–brain barrier (BBB). (A) The blood–brain barrier (BBB) consists of endothelial cells, pericytes, astrocytes, and the basement membrane. The neurovascular unit (NVU) is composed of endothelial cells, pericytes, and astrocytes of the BBB and neurons, oligodendrocytes, and microglia, which closely communicate with each other in order to regulate brain homeostasis. (B) Tight junctions (claudin-5, occludin, ZO-1, ZO-2, and ZO-3) and adhesion junctions (JAMs and VE-cadherin) between BBB endothelial cells (BBB-ECs) form the BBB. (C) Transcellular migration of lymphocytes involves the following 4 steps: (1) in the rolling process, activated lymphocytes slow their flow speed due to the interaction of VLA-4 from the surface of lymphocytes with vascular cell adhesion molecules 1 (VCAM-1) on BBB-ECs; (2) in adhesion pathways, the lymphocytes adhere to endothelial cells and transverse the BBB by coupling the VLA-4 and LFA-1 expressed on lymphocytes with the endothelial cell receptor (VCAM-1 and intracellular adhesion molecules (ICAM-1); (3) during adhesion, interaction between VCAM-1 and ICAM on BBB-ECs and their ligands (LFA-1 and VLA-4) on leukocytes induces the arrest of immune cells from the blood by the brain endothelial cells; and (4) interaction between ICAM-1 and ICAM-2 and their ligands (LFA-1 and LFA-2) is involved in crawling and migration.

{Original illustration from: Shimizu F et al. Blood-Brain-Barrier Disruption in Neuroimmunological Disease. Int J Mol Sci. 2024;25(19):10625 [31].}

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 [34].

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 light chains) concentrations and intrathecal IgM concentrations [34]. Serum of concentrations NfL have been shown to be biomarkers of acute axonal injury and neurological disease activity.

Immune Signature E2

Changes in the natural killer cells (NK) cell compartment with pro - inflammatory features [34].

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 [34].

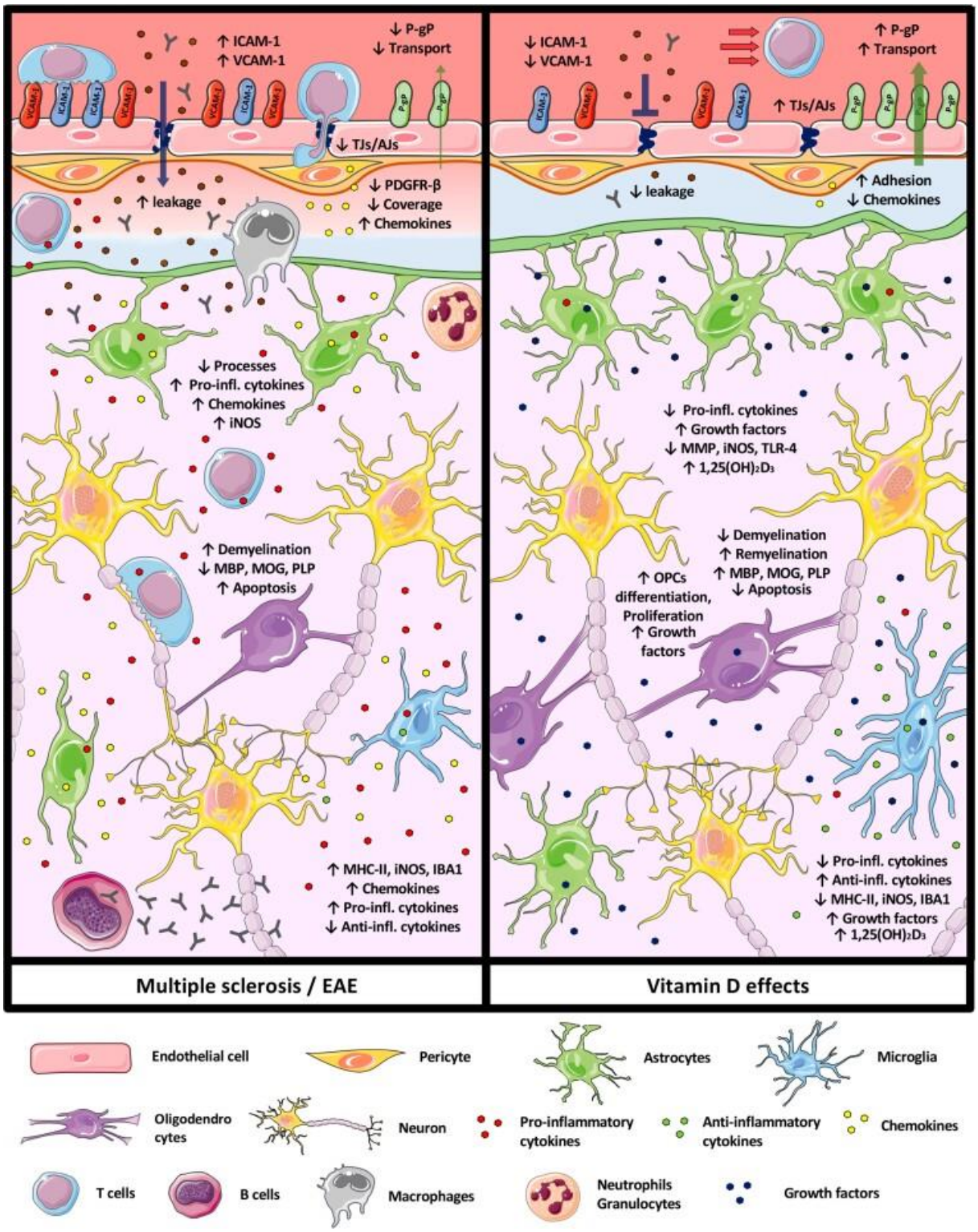


Figure 2: VitD modulates different cellular and molecular mechanisms of CNS-resident cells and of the blood – brain barrier involved in multiple sclerosis pathology. (Left) Schematic representation of the cellular and molecular mechanisms involved in multiple sclerosis /EAE pathology at the level of 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 cells types were adapted from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Common Attribution 3.0 Generic License.

{Original illustration from : Gallopin et al. [35], Oxford University Press}

The interleukins (IL) IL-1, IL-2, IL-4, IL-6, IL-13, IL-17, IL-21, IL-22 and IL-33 are particularly involved in the active phase of MS [35,36, 37]. [Figure 2]. The synergistic cytokine combination IL-17A/TNFα has been identified as a major neurodegenerative trigger [38]. High TNF levels in the cerebrospinal fluid and serum are responsible for damage to the gray matter (GM) even in the early stages of the disease and could play a role in PIRA [39]. The pathogenesis and progression of MS is influenced by other factors such as chemokines, nitric oxide, reactive oxygen species (ROS), glutamate and free radicals [40].

PwMS who develop so-called paramagnetic marginal zone lesions (PRLs) and are diagnosed by MRI tend to have more brain lesions due to more relapses, more severe brain atrophy and progressive disability. There was also a significant association between the increased likelihood of developing PIRA and the number of persistent PRLs [41]. *Early* treatment with highly effective disease-modifying therapies (DMTs) may attempt to prevent the occurrence of PRLs [41]. On the other hand, resolution of existing PRLs and the absence of new PRLs has been shown to be associated with improved clinical outcomes.

These chronic active lesions (CALs) consist of iron-rich inflammatory-type microglia (MG) [41,42].

2.2 Key role: Microglia, dendritic cells

Microglia and macrophages, the main components of the innate immune system, are considered important mediators of smoldering neuroinflammation and are found not only in focal demyelinating lesions but also diffusely in the normal-appearing white and gray matter. In addition to peripherally triggered inflammation in combination with an open blood-brain-barrier (BBB), persistent neuroinflammation occurs behind the relatively intact BBB [42].

Activation of MG is the earliest biomarker of central nervous system (CNS) inflammatory processes in MS [43]. Activated microglia are required for demyelination and can directly promote it [44-47]. Activated microglia release TNF-α and IL-1β and reduced the expression of occludin and ZO-1 and increased thereby increasing the permeability of the BBB [48-50]. In addition, TNF-α and IL-1β influenced immune cells by promoting paracellular and transcellular migration across the BBB, respectively [51].

Brain-resident microglia are also a target for calcitriol [33,51,52,53]. MG themselves can convert circulating Vit D into its active form. Activated microglia exposed to vitamin D3 showed reduced expression of the proinflammatory cytokines IL-6, IL-12 and TNFα and increased expression of IL-10 [54].

Dendritic cells (DCs) are professional antigen-presenting cells that play a key role in initiating immune responses and immune tolerance. There is evidence that DCs contribute to the pathogenesis of MS. DCs are present in MS lesions and exhibit abnormal function in PwMS [55].

DC may also be among the target cells of 1,25(O)2D3. By reducing proinflammatory cytokines and chemokines, calcitriol reduces differentiation, maturation, MHC class II expression, antigen presentation and promotes apoptosis [55,56]. 1,25(OH) 2D3 -induced tolerogenic DC are currently being tested in a clinical trial [55].

2.3 Early immunological and metabolic dysregulation of CD8+ T cells in MS as an early warning sign

CD8+ T cells are present in large numbers in MS lesions and increased migratory, proinflammatory and activating CD8+ T cell phenotypes have been detected. These special CD8+ cells were found in both the blood and the cerebrospinal fluid, and they also migrate to the central nervous system (CNS) and are found there again [5]. Studies on identical twins showed that this CD8+ T cell phenotype occurred not only in people who had already been diagnosed with MS, but also in people who did not yet show clear clinical symptoms [5]. Some of the clinically healthy twin children showed signs of subclinical neuroinflammation in MRI and/or CSF without fulfilling the clinical radiological criteria of MS, which represents the *earliest* recognizable prodromal

stage of the disease (see later) [5,57,58).

Since the healthy twin has an up to 25% increased risk of also developing MS, preventive measures in the *early* stages by means of Vit D suppl are definitely justified.
CD8 + T cells express higher levels of VDR than CD4 + T cells [59]. Lysandropulos et al. found that CD8 + T cells treated with 1,25(OH)2D3 secreted lower levels of the proinflammatory cytokines IFN-γ and TNF-α and increased levels of anti-inflammatory cytokines such as IL-5 and TGF-β [60,61].

2.4 Treg cells - Central role in preventing autoimmunity and target for 1,25(OH)2D3

CD4+CD25+ regulatory T cells contribute to the maintenance of peripheral tolerance through active suppression [62]. For over two decades, we have known that Treg cells (T regulatory cells [CD4+FOXP3+ regulatory T cells]) exhibit a broad spectrum of functions by modulating the activities of various cell types, including CD4+ T helper cells, cytotoxic CD8+ T cells, B cells, and dendritic cells [63]. In addition, Treg cells play an important role in maintaining tissue homeostasis and regeneration [64,65]. Treg cell dysfunction in autoimmune diseases, including MS, is very complex [66]. The fine-tuning of Treg cell function is probably not only dependent on the transcription factor FOXP3. Recent research has found additional factors for the fine-tuning of Treg cell function. Full details on the complexity of regulatory T cell regulation and differentiation in MS can be found in [Somuda]. [67]. 1,25(OH)2D3 induces Treg cell differentiation, particularly Treg cells expressing CTLA-4 and FOXP3 [56,68,69,70]. S25(OH)D levels correlate positively with the ability of Treg cells to inhibit T cell proliferation in RRMS [71,72].

2.4 Breg cells

The discovery of regulatory B cells (Breg) and their important role in maintaining immune homeostasis and limiting pathology in autoimmune diseases demonstrates the complexity of MS. Numerical and defective Breg cells can promote autoimmunity, including through reduced IL-10 secretion [73,74,75]. There is evidence for a positive regulatory role of a subset of B cells in MS disease that can release several inhibitory cytokines such as IL-10, TGF-β and IL-35 [76]. In addition, it has been shown that functional Breg cells can impair the production of proinflammatory cytokines by dendritic cells, promote Treg cell expansion and inhibit the development of T effector cells [61,77]. Data from in vitro studies showed that vitamin D enables an increase in Breg cell activity [78].

2.5 Dysregulation of hnRNP A1 in MS pathogenesis

Dysfunction of the RNA-binding protein (RBP) heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) is one of the causes of neurodegeneration/MS [79,80] and can be exacerbated by smoldering/slow-growing proteins (SELs) in progressive MS [81,82]. hnRNP are a family of > 20 proteins that contribute to the complex surrounding nascent pre-mRNA [83]. hnRNP A1 is a multifunctional protein and is required for the maintenance of healthy nerves [80,84]. MS cases could be differentiated according to the severity of hnRNP A1 pathology. PwMS with high hnRNP A1 pathology showed increased markers of neurodegeneration, such as neuronal loss and injury, brain atrophy, axon loss , and axon degeneration [81]. hnRNP A1 dysfunction in oligodendrocytes contributes to the pathogenesis of multiple sclerosis [85]. Autoantibodies against hnRNP A1 are involved in MS pathology [86].

hnRNP in disturbances of vitamin D homeostasis was suggested 20 years ago [87]. hnRNP A1 attenuates transactivation of steroid hormone receptor genes and may contribute to resistance to 1,25(OH)2D3 [83,88,89]. hnRNPC may provide an additional mechanism to fine-tune vitamin D-regulated target gene expression [90].

On the other hand, calcitriol showed a beneficial effect on oligodendrocyte apoptosis by also increasing the expression of growth factors, such as nerve growth factor and BDNF (brain-derived neurotrophic factor), and therefore may maintain cell survival in the CNS [35].

It could therefore be of great interest whether another cause of SELs is resistance to 1,25(OH)2D3, the active form of vitamin D, despite normal expression of the vitamin D receptor (VDR). In previous vitamin D supplementation studies with negative results, one of the reasons could be that PwMS were not divided into "vitamin D-resistant subgroups", so that the benefit of a vitamin D supplement could not be observed [91,92]. An acquired vitamin D resistance as the cause of the lack of effectiveness of a vitamin D supplement in

autoimmune diseases has been hypothesized [93]. Details in [94,95].

Recognizing the prodromal stage of MS

A prodromal stage is an early sequence of signs or symptoms that indicate the onset of a disease before typical symptoms develop [96]. Serum neurofilament light chains (sNfL) were elevated 6 years before the clinical onset of MS, supporting a prodromal phase lasting several years [97].

Immunological processes are probably initiated already in the prodromal phase of MS (5 years or more [10 years] before clinical symptoms or the first demyelinating event) [98,99,100]. Immune-mediated skin diseases in individuals who later developed MS may indicate generalized immune dysregulation [101]. In autoimmune rheumatoid arthritis, autoantibodies have been verified in the prodromal phase [99,102]. Frequent ENT care in the prodrome may be linked to chronic rhinosinusitis in PwMS [99,103]. There is a significant association between premorbid autoimmune diseases and chronic rhinosinusitis with and without polyps [104].

The aim of a future preventive strategy should be to enable a possible delay in the onset of the disease/disability progression and/or the prevention of long-term complications through high-dose Vit D supplementation in the prodromal phase. Only by identifying PwMS who are likely to develop disability more quickly can personalized therapy be carried out in practice.

In the future, the determination of genetic variants, homozygous carriers of single nucleotide polymorphisms (SNPs) (rs10191329 AA) in PwMS could be helpful. Homozygous carriers of the risk allele showed increased sNfL values in the early stages of MS, an increasingly higher EDSS (Expanded Disability Status) in the next few years, higher disability rates and a higher probability of developing SPMS (secondary progressive MS) [105]. Achieving high s25(OH)D values (dose-response effect) in this group of people in particular is not only associated with a reduction in axonal injury in MS but also with an improvement in cognitive performance [106,107,108].

3.1 Calcitriol is essential in the early stages

By 2025, it will be recognized that the circulating as well as the biologically active forms of vitamin D (25(OH)D or 1,25(OH)2 D3 can cross the BBB and thus enter the CNS. The target cells are various neuronal and glial cells [109,110]. A key pathological hallmark of early MS is increased BBB permeability. 1,25(OH)2D3 reduces BBB permeability, prevents neuroinflammation, and local macrophage/microglia activation [28,33,35,111,112].

From the results of the study, where serum increased NfL levels (axon damage is indicated by neurofilament light chain [NFL] elevation) during the first demyelinating event of MS were associated with greater impairment of BBB integrity, immune cell extravasation, and brain lesion activity on MRI, early high-dose vit D supplementation is justified [113].

3.2. Problems in children with MS (POMS)

There are calls to increase the capacity for early detection of MS in the pediatric population [114]. It has been demonstrated that children and adolescents with MS are presented with various metabolic, ocular, musculoskeletal, gastrointestinal and cardiovascular symptoms, signs or diagnoses within 5 years before their first MS diagnosis [115]. Better characterization of early symptoms and/or risk factors, comorbid conditions and possible prodromal features of MS may have significant impact on early detection and subsequent disease course.

Recent results from studies on the involvement of the choroid plexus (PC) in children with multiple sclerosis (POMS) indicate that the PC plays an inflammatory role in the pathophysiology of MS [116]. Because POMS are characterized by a high inflammatory burden and the BCSFB is also a site of immune cell leakage from the blood into the cerebrospinal fluid, early sealing with calcitriol through the formation of tight Junctions (e.g. claudin-5, occludin and ZO-1), gap junctions may be beneficial in the *earliest* stages of disease development [33,35,117,118,119]. Neurons, microglia and astrocytes express 1α-hydroxylase (CYP27B1), the enzyme responsible for the conversion of 25(OH)D to 1,25(OH)2 D3 and acts locally [120-123].

Together with oligodendrocytes, all of these cells also express the vitamin D receptor (VDR) [124,125,126].
The M1 microglia phenotype is considered to be pro-inflammatory and neurotoxic, while the M2 microglia phenotype is considered to be anti-inflammatory and neuroregenerative. Increased vitamin D exposure leads to a weakening of the M1 phenotype. Vitamin D helps mediate a microglial shift towards the M2 phenotype [35]. The alternative M2 phenotype is neuroprotective in nature as it is associated with an increased secretion of anti-inflammatory cytokines [127].

A study of children and adolescents (10 to 19 years) in a region with plenty of sunshine shows that sun exposure alone is not sufficient to produce adequate vitamin D levels. 92% had a vitamin D deficiency, with a higher percentage in boys than in girls. Hypovitaminosis D was more common in overweight (obese) patients [128]. A suggestion to achieve sufficient s25(OH)D levels through moderate sun exposure and diet and to recommend this as a balanced and advisable strategy for PwMS [129] is refuted by this study. In addition, the risk of acute respiratory infections and COVID-19 in children and adolescents can be reduced by Vit D suppl [130]. There is an inverse relationship between s25(OH)D levels and hsCRP (high-sensitivity c-reactive protein) in children [131].

3.2.1 Advanced aspects of POMS

In approximately 2 to 10% of PwMS, the *first* clinical symptoms appear in childhood or adolescence [132-135]. The inflammatory pathology in POMS is characterized by higher proportions of naive T cells and a higher capacity of B cells, resulting in stronger immune reactions to antigens than adults [136,137]. Even before clinical manifestation, cognitive and volumetric differences in brain volume were verified [138]. Poorer school performance had been observed in the preclinical phase of MS (preclinical cognitive endotype) [139]. In addition, Vit D plays an essential role in brain maturation and promotes neurotrophic factors (12,140,141,142). Higher s25(OH)D levels in younger years show a positive association with neurodevelopmental outcomes [141].

Mainly RRMS with high activity and two to three times higher relapse rate and larger lesions on MRI are observed with the risk of cognitive and physical impairment, despite the more robust repair mechanisms in children and adolescents [143,144]. In Canadian children, a low s25(OH)D level has been associated with the risk of a later MS diagnosis [145].

Further studies have shown a link to hypovitaminosis D and obesity [146,147]. While viral exposure (EBV), obesity (with the risk of a low s25(OH)D level), genetic factors (HLA-DRB1*15:01 allele), passive smoking and maternal illness during pregnancy (including stress) represent a risk for MS [135], stress in early childhood as a cause of chronic inflammation is given too little attention in therapy management. Chronic stress is associated with altered cytokine levels (IL-1ß, IL-6, TNF alpha, CRP) [148].

If chronic stress in early life leads to an increase in inflammation, is linked to autoimmune diseases and MS in children and adolescents causes chronic stress per se, a targeted intervention to reduce inflammation with Vit D suppl is indicated [69,149,150]. For detailed details on early life stress and a proinflammatory phenotype see Entringer S et Heim Ch . [151]. Exposure to adverse living conditions in early childhood showed increased inflammatory markers in adulthood such as C-reactive protein (CRP), IL-6, TNF-alpha, IL-1ß [152-155].

3.2 Prodromal stage - Early monitoring of s25(OH)D serum levels and sNfL

Early therapeutic measures aim to prevent disease progression in MS. Physical and mental neurological disability have been observed in the earliest stages of MS and radiologically isolated syndrome (RIS) [29]. However, low serum 25-hydroxy-vitamin D (s25(OH)D) levels are associated with cognitive impairment and disability [156]. In addition, attention, work performance and verbal memory are most strongly correlated with s25 (OH)D levels [108]. Control of s25(OH)D levels could be established to monitor cognitive performance and the neuroprotective effect of 1,25(OH)2D3 could be exploited by early Vit D supplementation [33,157,158,159].

The realization that PwMS were visiting physicians or hospitals and taking prescription medications 5 years before the onset of clinical MS symptoms led to the acceptance of the existence of an MS prodromal stage [160,161]. Following primary axonal damage, neurofilament light chain (NfL), a cytoskeletal protein , is released into the interstitial space and subsequently enters the cerebrospinal fluid and peripheral blood. Using this biomarker in routine practice is a milestone

in the care of PwMS , because sNfL concentration is directly associated with relapse and clinical progression [162].

SNfL will probably be important in daily practice as a prognostic biomarker and will be widely available to monitor MS patients for progression, disease activity and treatment effectiveness [163,164]. Glial fibrillary acidic protein (GFAP) (astroglial damage) in serum has also been established as a potential biomarker for smoldering MS/PIRA in early stages [165,166]. The future will show to what extent ubiquitin C-terminal hydrolase (UCHL1) and glial protein with the calcium-binding domain (S100B) will be added [167]. A negative correlation between s25(OH)D values and GFAP values, heavy neurofilaments and S100B in the cerebrospinal fluid could be verified [167]. An anti-inflammatory effect was demonstrated by increased 25(OH)D levels and subsequently by reduced GFAP levels [168].

3.3 Revised McDonald criteria 2024/2025 promote early treatment strategies 2025

The future McDonald revision 2024/2025 with new MS diagnostic criteria favors early therapy by stating that the diagnosis of a radiologically isolated syndrome (RIS) including additional criteria already justifies making an MS diagnosis and starting effective medication [169].

It is generally accepted that MS progresses independently of relapse activity and is defined as “Progression Independent of Relapse Activity (PIRA)” [14]. This smoldering inflammatory activity in combination with acute inflammation (relapses) leads to the accumulation of disability [8]. PIRA can be present in the earliest stages of MS and has been recorded after the second year after disease onset and contributes more significantly to deterioration than “relapse-associated deterioration” [8,170,171,172].

3.4 Targeted effect of vitamin D on different MS phenotypes

By verifying three immunologically different endophenotypes (E 1, E 2, E3) of MS immediately after diagnosis, for example, the E1 immune signature revealed changes in the CD4 T cell compartment with increased proportions of CD4 memory subsets that produce T helper 17 (Th17) associated cytokines (interleukin-17A [IL-17], IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF)) [34].

The hormonal form of vitamin D 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 [172].

High-dose VitD supplementation reduces IL-17-producing CD4+ T cells and effector memory CD4+ T cells in PwMS when they exhibit a significant increase in s25(OH)D levels [173]. If 1,25-dihydroxyvitamin D3 reduces the pro-inflammatory cytokines IL-17 and IL-21, promotes the migration ability of regulatory T cells into the CNS and increases anti-inflammatory IL-10 production [68,172,174], the therapeutic efficiency is increased by additional therapy with VitD.

3.5 Years of controversial discussions on Vit D suppl - brake blocks to implement new findings in practice

There are numerous international efforts to favor therapies that definitively delay the progression of MS [29]. Among the multitude of factors that lead to the onset, heterogeneity and extent of progression of MS, one of them is the effect of Vit D on the immune system [175]. In the last decade, numerous studies on vit D supplementation have been conducted, some with controversial results.

Two "pro" and "contra" camps have been established in the neurological community, to the detriment of PwMS. Due to differing results in Vit D supplementation studies, the transmission of proven pathophysiological and pathoimmunological findings of MS into the daily practice of health care providers is partially blocked. The use of the early pluripotent effect of calcitriol for women with MS promises a benefit.

Early Vit D suppl in women with MS and impact on their children

In women who wish to have children, the presence of a Vit D supplement before conception and during pregnancy as well as in the lactation period is recommended, since in very few countries national

prenatal Vit D supplementation programs are offered to protect the newborn from Vit D deficiency [176].

Newborns from ethnic minority groups and dark-skinned people are particularly at risk [177]. Vitamin D plays an essential role in the development of children's brains, even in utero [178]. Children who were exposed to long-term hypovitaminosis D from mid-pregnancy to delivery had less volume of gray and white brain matter, less surface area, and less gyrification after 10 years compared to children with sufficient s25(OH)D levels [179]. Vitamin D has a decisive influence on initial embryo implantation, early trophoblast invasion, and decidualization of the endometrium. Infertile patients have been shown to achieve better reproductive outcomes when they receive vitamin D (1,000–10,000 IU) daily for more than 30 days [180,181].

Hypovitaminosis during *early* pregnancy is associated with a two-fold increased risk of MS in the offspring. An increase in s25(OH)D of 50 nmol/L (20 ng/ mL) was associated with a 39% reduced risk of MS (p=0.003) [182-184]. Neonatal s25(OH) levels were inversely related to the risk of developing MS, supporting the notion that maternal Vit D levels may be important for preventing MS in children [69,185]. If the Endocrine Society 2024 already recommends that women without MS who wish to have children take a Vit D supplement during pregnancy to reduce the risk of preeclampsia, intrauterine mortality, premature births, small births and neonatal mortality [186], it would be biologically plausible to provide this supplement even more in PwMS. In addition, for PwMS and high prediabetes risk, such as obesity, the development of diabetes mellitus as a comorbidity could be reduced [187]. The s25(OH)D values should be at least between 40-60 ng/ml. In healthy pregnant women, at least 4000 IU/ day Vit D is required [188,189]. This dose is currently accepted as the upper tolerable limit (EFSA) [190]. Because of the continuing uncertainty of the controversial classification of s25(OH)D levels (deficiency/insufficiency/sufficient) in healthy individuals, empirical vitamin D supplementation should generally be carried out without regard to the baseline s25(OH)D levels [191,192]. A low daily vitamin D supplement of 1000 IU/ day during pregnancy led to higher bone density and muscle mass in middle childhood (6-7 years) [193].

How little Vit D therapy is integrated into adjuvant therapy during the lactation period is shown by a recent study that does not even mention this possibility [194,195].

4.1 Early vitamin D supplementation during pregnancy

Women who wish to have children and who are taking DMTs (or therapists) are concerned that the continued use of these highly effective therapeutic agents on the fetus and mother before conception, during pregnancy and postpartum during breastfeeding could lead to harm of various kinds [196]. The risk of MS relapse when discontinuing DMDs (disease modifying drugs) and is not offset by the relative protection during pregnancy [197].

Because phases of immune deficiency increase the risk of viral and bacterial infections, the third trimester shows phases of an inflammatory immune state, which also affects the course of MS [198]. To strengthen the bacterial and viral defense mechanisms as part of a holistic approach, a vit D suppl before conception, during pregnancy and after birth as well as during breastfeeding could offer possible protection.

There is still no reliable concept for preventing early postpartum (PP) MS relapses, as the indication of early DMT is complicated by various variables [199]. In addition to breastfeeding, Vit D supplementation is recommended for an effective reduction of very early PP relapses in women with active MS, as this does not require a break in therapy compared to DMDs and adverse effects are not to be expected [69]. The therapeutic effect depends on the amount of daily vitamin D administration [200]. In addition, the potential to prevent childhood MS could be exploited [201].

Vit D suppl has the potency to prevent infectious diseases (burden with pathogens) in pregnant women, since diseases were associated with a 2.3-fold increase in the probability of MS in the offspring and also to improve the outcome for the offspring in general [202-206].

Furthermore, relative protection to mitigate SARS-CoV-2 infection during pregnancy could be provided by Vit D supplementation [207].

SARS-CoV-2 infection and autoimmune reactions

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2. The coronavirus family is neurotropic and enters the central nervous system mainly via the BBB and neuronal pathways [208]. SARS-CoV-2 causes disruption of tight junction and adhesion proteins and consequently permeability in the BBB; but also, in the respiratory epithelium and intestinal epithelium [209,210]. 1,25(OH)2D3 protects the epithelial barrier of the intestine, lung and BBB [111,127,211,212,213]. Demyelination induced by neurotropic viruses appears to be mediated by adaptive immunity [212] rather than by direct viral infection [214].

PwMS have an increased risk of general infections and consequently an increased hospital stay due to infections [215,216]. An increased risk of severe COVID-19 outcomes (hospitalization, admission to intensive care unit , death) was observed in patients with higher disability level , progressive disease course and under specific treatments (i.e. some anti-CD20 agents) [217,218]. The cause of death in severely ill PwMS is largely due to respiratory complications [219]. The occurrence of infections in the prodromal phase of MS as a comorbidity confirms an early disruption of immunological homeostasis [216,220]. In persons with POMS and B cell depleting therapy (DMTs), the overall percentage of COVID-19 positive children increased. In addition, obesity has been identified as a risk factor, also for the manifestation of MS (221,222,223], and vit D suppl allows for attenuation of the disease [224].

5.1 Aspects of Long-COVID

Cytokine storm observed in acute disease with increased circulating concentrations of cytokines is also found in a weakened form in patients with long-COVID. Higher concentrations of proinflammatory cytokines such as IL-6, IL1-ß, IL-13, IL-17A, IFN-alpha, IFN-beta, NF-gamma TNF-alpha and G-CSF were found. Most of these cellular immune components had not returned to baseline levels even 7 to 9 months after infection [225,226]. After 18 months, proinflammatory cytokines were still detected [227].

Postmortem studies showed that pathological changes in the CNS, especially in the brain stem, occurred as a result of parainfectious and/or post-infectious immune reactions. Quantitative susceptibility mapping (QSM/7 Tesla MRI) provided evidence that inflammatory reactions were also found in long-COVID. QSM can detect iron molecules. Inflammatory reactions lead to an increase in iron concentrations in macrophages, which are inflammatory cells, and there was a particular correlation with high CRP (C-reactive protein) levels in the acute phase [228].

Data suggests that persistent systemic inflammation and persistent localized BBB dysfunction are a major feature of Long-COVID-associated brain fog [229]. A study on Long-COVID in pediatric patients showed that symptoms can persist for a long time [230].

7.1% showed symptoms 24 months after acute infection and a few even after 36 months.
1.1% developed autoimmune diseases such as Hashimoto's thyroiditis, celiac disease, systemic lupus erythematosus, autoimmune urticaria and autoimmune connective tissue diseases [230,231]. Case reports have been reported of newly diagnosed multiple sclerosis occurring concurrently with active COVID-19 infection [232,233].

Because long COVID has been observed in 50-70% of COVID-19 survivors, an accentuated role of vitamin D supplementation as a prevention strategy in PwMS should be prioritized. This demand is reinforced by the observation that hypovitaminosis D has been registered as a modifiable risk factor for SARS-CoV-2 infection and a worse acute COVID-19 course and that hypovitaminosis D also exists in long COVID syndrome [234-237]. Vit D also improves Covid-19 vaccination [235].

Controversies about the clinical results of Vit D supplementation may be caused not only by genetic polymorphisms of vitamin D metabolism (e.g., VDR [Vit D receptor] polymorphisms, DBP gene polymorphisms [Vit D binding protein]), but also by the lack of immunologically effective s25(OH)D values and the too low daily dose of Vit D [237]. In addition, long-COVID-19 also affects bone health, which also requires prophylaxis in MS, which strengthens the indication for Vit D suppl [238,239,240]. Reduced bone mineral density was already evident in early MS as well as in CIS [241,242].

In a systematic review, the prevalence of osteopenia, osteoporosis, and total fractures in PwMS was 41.4%,

14.2%, and 12.8%, respectively, and the combined prevalence of all fractures was 12.8% [243].

5.2 Pathoimmunological similarities between MS and Covid-19

The risk of MS relapse or worsening disability after COVID-19 is controversial [244,245]. One study found that both the occurrence and severity of COVID-19 were associated with worsening clinical disability in patients with MS [246]. A large multinational observational cohort study showed that MS patients infected with COVID-19 have a significantly increased relapse rate and a shorter time to first relapse than comparable control subjects without COVID-19 infection [247]. The risk of relapse increases because the impaired BBB makes it easier for the leukocytes and cytokines that promote inflammation caused by COVID-19 to penetrate the CNS [247, 248]. The hematogenous spread of the COVID-19 virus also suggests that the virus spreads in the bloodstream and can reach the brain and cause inflammation via the BBB. COVID-19 and MS are associated with several immunological disorders and may influence each other's disease onset or progression [249].

Due to the detection of SARS-CoV-2 spike protein in the meninges and bone marrow of the skull and persistence over several years as well as increased plasma cytokine levels, chronic inflammation must be stopped [250]. Neurological manifestations of the post-acute consequences of SARS-CoV-2 infection have also been observed predominantly in younger (18-44 years) and middle-aged patients (45-64 years) [251].

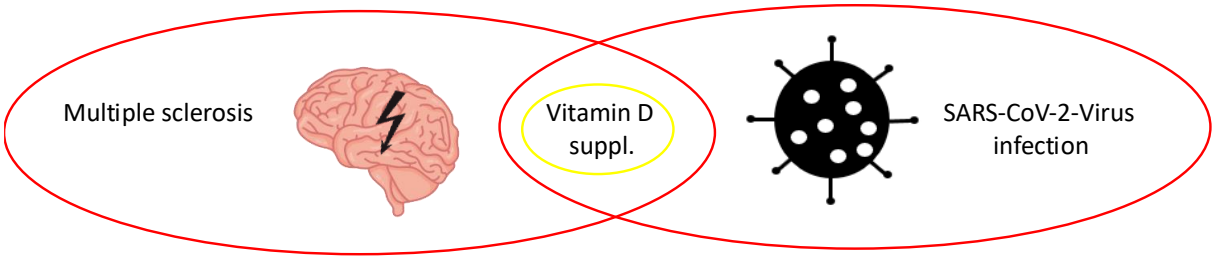
If BBB disruption could be responsible for the severe neurological symptoms in COVID-19 [252], the potency of 1,25(OH)2D3 to seal the BBB and reduce proinflammatory cytokines and neuroprotective properties should be exploited to reduce disease severity with long-term consequences [111,127,253]. Interfaces between COVID-19 infection and MS are described in detail in [254]. [Graphical abstract 1]

Neurology and Neurological Research

Graphical Abstract

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

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



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

PwMS who survived a COVID-19 infection showed a worse long-term course, measured by treatment of relapses, hospitalization and mortality. In particular, comorbidities and high-dose glucocorticoid therapies risk factors for relapses. Optic neuritis occurred more frequently after infection with "COVID-19" [255]. During the COVID-19 pandemic and ocrelizumab therapy, 262 patients suffered 275 COVID-19 infections [256]. Women with MS and pregnancy or pregnancy planning should be proactively monitored by daily vit D supply careful prevention can be achieved by achieving sufficient s25(OH)D levels [257].

Risk of relapse after Covid-19 vaccination

A recent study provides class III evidence that COVID-19 vaccination does not increase the risk of severe relapse in PwMS. However, the risk of relapse was only assessed over a period of 45 days after vaccination [258]. Vaccination with mRNA COVID-19 vaccine (BioNTech/Pfizer) was able to reduce the accumulation of the spike protein by 50%, so that a residual spike protein still poses a toxic risk to the brain and long-term VitD supplementation could be justified [250].

Vitamin D supplementation and antibodies against the Epstein-Barr virus (EBV)

Increasing evidence suggests that vitamin D deficiency and EBV virus infection are important environmental factors in MS [259]. Vitamin D receptors (VDR) are expressed in EBV-infected B cells, antigen-presenting cells (APCs), and activated lymphocytes. 1,25(OH)2D3, the bioactive metabolite, suppresses antibody production and T cell proliferation and shifts T cells toward a less harmful Th2 phenotype [260].

Data to date have shown that almost all PwMS are infected with EBV, and high anti-EBV antibody titers increase the risk of developing MS [261,262]. The underlying mechanism or mechanisms by which EBV-induced immune dysregulation causes MS in susceptible individuals are not yet fully understood [263].

The risk of MS increased 32-fold after infection with EBV, but was not increased after infection with other viruses, including the similarly transmissible cytomegalovirus [264]. Serum levels of neurofilament light chains (sNfL), a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These results cannot be explained by any known risk factor for MS and suggest EBV as the main cause of MS. EBV not only causes MS but also contributes to the clinical course of MS, which could therefore potentially be influenced by antiviral agents [264].

Elevation of sNfL levels is preceded by EBV infection prior to the onset of MS. Furthermore, MS is not only preceded by EBV infection but is also associated with broader EBV-specific TCR (T cell receptor β chain (TCRβ)) repertoires, consistent with a sustained anti-EBV immune response in MS [265].

A positive correlation between antibodies (AB) against the EBV antigen EBNA 1 and the risk of developing MS was discovered years ago. Additional studies over the last 30 years have also shown a correlation between circulating AB against EBV and vitamin D. There was an inverse correlation between anti-EBNA1 AB and s25(OH)D values [266,267,268]. Low s25(OH)D levels and advanced EBV infection may be associated with clinical MS breakthrough within 2–3 years [269]. Immunoglobulin G (IgG) against EBNA-1 were elevated during the 36-month pre -CIS interval. Low s25(OH)D levels were observed during the 24-month pre -CIS interval [269].

Since it is generally accepted that poor vitamin D status is associated with an increased risk of MS, the association between vitamin D deficiency and EBV infection was also investigated. PwMS and RRMS received 20,000IU/ day of vitamin D3 daily for 12 weeks and circulating antibody levels against EBNA 1 decreased significantly, especially in PwMS with higher antibody levels. There was a positive correlation between antibody levels before vitamin D supplementation and their decrease after vit D suppl [270].

PwMS and RRMS received a Vit D supplement for 48 weeks (14,000IU/ day) and this high-dose vitamin D supplementation selectively reduced anti-EBNA-1 antibody levels [271]. Arguments for a vit D suppl also provides the results of a study in PPMS, which showed increased humoral immune responses to the EBV-encoded nuclear antigen-1 (EBNA1) [273].

Since EBV infection is predominantly asymptomatic in childhood and is associated with an increased risk of developing MS [271], prevention should be targeted in childhood by achieving sufficient s25(OH)D levels. Anti-EBV antibodies against nuclear antigen-1, however, persist in the host throughout life [274]. An interaction between Vit D, EBV, and endogenous retrovirus (ERV) seems likely, and the pro-inflammatory milieu in MS could restore the disturbed homeostasis between anti-inflammatory and pro-inflammatory immune reactions through the effect of 1,25(OH)2D3 [275].

It is discussed that a higher Vit D level causes an induction of apoptosis of autoreactive B cells [78]. A new aspect for initiating vitamin D prevention is provided by studies in patients with long-COVID disease and reactivation of chronic viral co-infections, especially in PwMS. During the period of long -COVID symptoms (fatigue, neurocognitive disorder), EBV reactivation could be demonstrated by early antigen-diffuse IgG positivity and high nuclear (EBNA) IgG values [276,277].

Current background- choroid plexus

Inflammation of the choroid plexus (CP) can be quantified in vivo using MRI in PwMS [116]. It has also been shown in pediatric MS patients that CP changes are an early symptom of MS and that the CP can be seen as an entry point for inflammatory cells into the CNS [166,278]. Anti-EBNA-1 IgG antibodies and anti-EBV capsid antigen (VCA) IgG antibodies were measured in correlation with CP volumes and CP pseudo-T2, a relaxation time that indicates edema and neuroinflammation. An increased humoral anti-EBV response can be associated with increased neuroinflammatory CP changes. These new results would also hypothetically be an expanded goal of Vit D supplementation [279].

In a groundbreaking study by Vietzen et al. on the causal significance of EBV for the development of MS, the role of EBV- specific HLA-E restricted CD8+ T cells in the defense against MS was investigated [19]. Specific cytotoxic T cell responses can control EBV- infected GlialCAM-specific B cells. EBV- specific and HLA-E are restricted Tc - cell levels at high EBV- specific IgG healthy controls, while in people with multiple sclerosis (PwMS) they show low levels [19].

In addition to these mechanisms, interleukin 27 (IL-27) is thought to play an increased role in the pathogenesis of MS because increased IL-27 expression was observed in EBV-infected GlialCAM370-368-specific B cells of PwMS [19]. In addition, an increased IL-27 expression level was observed in the serum and CNS of PwMS [280]. IL-27 has both pro-inflammatory and anti-inflammatory and neuroprotective effects as well as immunoregulatory functions [19,281].

An anti-inflammatory function is attributed to Vit D in numerous studies and a Vit D supplement with 50,000 IU/week for 8 weeks was able to demonstrate an increase in anti-inflammatory cytokines (IL-27, TGF-ß1 and IL-10) in PwMS. The plasma levels of proinflammatory cytokines (IL-17A and IL-6) decreased [282]. Because IL-27 additionally increases the effector function of the natural killer cells (NK) and promotes the differentiation and function of T-regulatory cells in PwMS, a daily Vit D supplement could make a therapeutic contribution to the suppression of autoimmunity by IL-27, achieving a s25(OH)D level of 40-100ng/ mL. However, if an upregulation of HLA-E by IL-27 in conjunction with a further inhibition of NKG2A-expressing NK cells influences the development of MS [19], it would have to be investigated whether the achievement of physiological 25(OH)-D serum levels produce a higher HLA-E expression level.

Cognition and MS -factor for quality of life

The prevalence of cognitive impairment in MS has been reported to be between 40 and 70% depending on the country and type of study and has a serious impact on PwMS as it occurs during the most productive phase of their lives [283].

Early detection may contribute to decision-making and individual treatment planning for PwMS [284]. MRI can demonstrate damage in white and gray matter [285]. A stronger association between cognitive impairment and deep GM atrophy was observed in PwMS. Fatigue, anxiety, and depression were more strongly correlated with cerebellar atrophy. In addition, the accumulation of cognitive impairment, fatigue, anxiety, and depression is associated with increasing global cortical and deep gray matter atrophy [286]. Cognitive deficits are associated with microglia, possibly triggered by direct or indirect stimulation by CD8+ T cells [287].

Cognitive impairments have been observed in the earliest stages of MS (CIS) [288-292]. One in seven

PwMS experienced isolated cognitive decline in stable MS [293]. Four cognitive phenotypes have been defined in PwMS. Details in [284].

Due to the negative impact on the work situation, social contacts and self-care of MS patients, all therapeutic measures must be taken early [294]. In analogy to PIRA, the existence of a "cognitive PIRA" should be included in clinical care and brought to the therapist's attention [295].

It is suggested that a cognitive evaluation should be included in the combined measures for the detection and progression of PIRA, which underlines the importance of cognition in disability accumulation [9,172].

Alexithymia (characterized by difficulties in identifying and describing one's feelings, and externally oriented thinking) as part of a cognitive disorder, the prevalence in PwMS can be up to 53% [294,296]. In patients with RIS (radiologically isolated syndrome), signs of alexithymia were observed in one third [296]. Regardless of the phenotype of MS, alexithymia is associated with atrophy of cerebral and cerebellar white matter, brainstem, corpus callosum, and thalami [297,298].

In RIS patients, alexithymia was strongly associated with the level of depression and cognitive fatigue and reduced mental quality of life [296]. Alexithymia, depression and anxiety are closely associated in PwMS [299,300].

Low vitamin D levels may be involved in the pathophysiology of alexithymia [301]. Data have been presented suggesting a link between impaired emotional processing and low vitamin D levels [302].
There is considerable evidence that VitD plays a crucial role in overall brain health and morphology, and its deficiency is associated with neurological disorders due to impairment of essential brain functions [303].

Higher s25(OH)D3 concentrations in the brain (neuropathology) were associated with a 25% to 33% lower likelihood of dementia or mild cognitive impairment before death [156]. It was also shown that low s25(OH) levels were associated with a reduction in brain volume of the olfactory functional areas [303].
Furthermore, patients with CIS and low serum s25(OH)D levels were found to have poorer cognitive performance and neuronal integrity over 11 years of follow-up [304]. There was an association with serum neurofilament light chains (sNfL), which are a biomarker for neuroaxonal damage. High or increasing NfL levels in longitudinal studies are an indication of active disease or impending MS relapses [305]. Higher serum calcidiol levels predicted better cognitive performance. A 50 nmol /L higher mean s25(OH)D level in the first 2 years was associated with a 65% lower likelihood of poorer PASAT-3 (Auditory Serial Addition Test) performance in year 11. NfL concentrations in the 11th year of observation showed that a 50 nmol /L higher mean 25(OH)D level in the first 2 years was also associated with a 20% lower NfL [304].

In a systematic review and meta-analysis, a correlation was found between the biomarkers sNfL and vitamin D and cognitive impairment (IPS: slower information processing speed) [157].

For 10 years, there has been evidence that there is a link between s25(OH)D and IPS. Higher calcidiol levels through supplementation led to long-term neuroprotection and consequently to an inhibition of cognitive impairment [290,306,307]. The brain reserve hypothesis states that higher maximum lifelong brain growth is associated with protection against cognitive impairment and physical disability even in the early stages of MS [308]. Hypovitaminosis D would prevent this protection [309]. Fatigue and cognitive impairment are not sufficiently taken into account in treatment and in studies from Germany 65% and 81% of patients were not treated for fatigue and 73% and <70% for cognitive symptoms [310,311,312].

Fatigue - use all therapeutic options

Fatigue is one of the most disabling symptoms reported by PwMS [313]. Over 80% (55-95%) of patients with MS suffer from this symptomatology [312,314]. It often occurs at the onset of the disease, may precede other clinical symptoms, and persists throughout the disease phase [315,316]. It has been demonstrated that fatigue and health-related quality of life have been observed early in RIS and CIS [317]. There are no doubt that immune-mediated processes are involved in the pathogenesis of fatigue [318]. There is a link between MS-related choroid plexus volume and fatigue [318].

On the other hand, a higher anti-EBV response in PwMS may be associated with increased choroid plexus neuroinflammatory activity in progressive MS [279] and Vit D supplementation may reduce anti-EBV nucleic antigen-1 (EBNA-1) IgG antibodies [271]. Vitamin D3 supplementation may limit the increase in these titers in MS patients [319,320]. Since fatigue did not improve even with highly effective DMT therapy or even increased it and affected the quality of life [315], Vit D supplementation could be justified as an add -on therapy [315]. Up to 90% of PwMS have a Vit D deficiency and Vit D supplementation could improve the quality of life through immune modulation and neuroprotection [321,322].

Depression and anxiety

Depressive and anxiety symptoms occur early in CIS and early MS [323] and are observed as prodromal signs of MS [100]. The prevalence is up to 25% in PwMS [324,325]. The lifetime prevalence is between 24 and 54% and can be considered as prodromal signs of early MS [100,326,327]. The comorbidity of depression is associated with a faster progression of disability [328]. Early treatment is therefore urgently needed [329].

There is a wealth of evidence that underlines the therapeutic potential of vitamin D in the treatment of depression and anxiety disorders. The involvement of immunological mechanisms in the pathophysiology of psychiatric disorders is no longer in doubt [330]. The goal is to reduce elevated inflammatory biomarkers [331-335].

In patients with difficult-to-treat depression, the s25(OH)D level is reduced [336]. In a German Nation MS cohort, PwMS and depression had a 25-OH-VD deficiency in 51.0%, 15.9% and a severe deficiency (<10 ng /ml) [337]. Neuroinflammation is considered a central pathophysiological mechanism of mood disorders [104,338,339]. Significantly increased sNfL levels were observed in depression and corresponded with reduced cognitive performance. The increase in sNfL levels also correlated with neuroimaging studies that showed subtle, widespread changes in white matter and reduced brain volumes in patients with depression. In addition, chronic stress may be associated with the pathophysiology of depression [340-345].

If patients with depression are divided into two subgroups, "inflammatory depression" and "non-inflammatory depression" [346], a Vit D supplement could lead to different results. A accumulation of evidence shows that vitamin D has antioxidant, anti-inflammatory, proneurogenic and neuromodulatory properties and may therefore act in a similar way to classic antidepressants or serve as a co-adjuvant [334,347]. Because the upregulation of proinflammatory cytokines in the brain may be associated with depression, Vit D supplement could be a safe, widely accepted, readily available and inexpensive treatment for depression. A recent study shows that depression impairs the integrity of white matter and in this way permanently reduces cognitive performance because frequent depressive phases continuously damage the brain and early prevention is necessary.[348]. Depression in children/adolescents could be improved by a Vit D supplement. High doses of vitamin D (50,000IU/ day for 9 weeks) were able to demonstrate a significant reduction in depression scores in girls and ensure a therapeutic benefit [349,350,351].

9.1 1,25(OH)2D3 in critical situations in the life of PwMS

PwMS experience severe psychological distress, and suicidal thoughts are more common than in the general population [352,353]. Suicide is the third leading cause of death in children and adolescents without MS (10-24 years) and the second leading cause of death in the 15-20 year age group [354-358].

Suicides are far too common among PwMS and have a significant association [353,359]. Multiple factors may contribute to the risk of suicide. In MS, depression is one of the strongest risk factors for suicidal ideation [360] and depression is where- to threefold more common than in the general population [361] but remains undertreated [362].

Suicides can and must be prevented [363] and special attention must be paid to prevention [357,325,363]. Approximately 13-28% have had suicidal thoughts since their MS diagnosis [364,365].

The prevalence of depression and increased suicide risk in MS patients must be aware of any clinician who treats these patients and must be prepared to recognize and respond to potential warning signs [364].

Predicting suicidal behavior in PwMS is complex [366]. Biomarkers such as proinflammatory cytokines (IL-1 beta; IL-6), C-reactive protein (CRP), TNF- alpha and s25(OH)D levels can be helpful in the extremely difficult diagnosis [367]. By 2025, there is accumulating evidence in the field of psychoneuroimmunology that anti-inflammatory drugs in psychiatric disorders have a positive impact on treatment due to the involvement of the immune system [330]. Low s25(OH)D levels are associated with increased suicide risk [368].

Studies have shown that hypovitaminosis D reduces immune modulation of inflammation and serotonin synthesis, two processes associated with depression and suicide attempts, thus supporting the potential benefit of Vit D supplementation in reducing depression symptoms and a possible indirect effect in the prevention of suicide and suicide attempts [369]. Higher doses of Vit D supplementation were associated with up to a 48% lower risk of suicide attempt injuries [367,370,371].

In impending suicide situations, a rapid high-dose daily Vit D saturation dose could be considered as an additional therapy, and the fear of Vit D intoxication could be removed. 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. This allows values above 30 ng/ mL to be reached quickly (cumulative dose 1,000,000 IU at <10 ng/ mL; 10-20 ng/ mL 600,000 IU/L; 20-30 ng/ml 300,000 IU [372].

Obesity – Association with the severity of MS

A specific factor that accelerates disability is the comorbidity of obesity, and there is a positive correlation between the severity of obesity and MS severity [373,374]. Childhood obesity may lead to increased morbidity of MS/CIS, especially in adolescent girls [375-377]. Levels of hsCRP were significantly elevated in overweight and obese children as compared to non- obese children [378]. In addition, severe obesity is associated with increased inflammatory cytokines and chemokines [379-381].

This group of people should especially avoid high-dose receive vit D suppl, as the BMI reacts with an altered response to Vit D administration and could partly explain the reduced results of suppl studies [382]. BMI is not sufficient for assessing obesity and additional obesity mass should be considered, especially in studies [373]. A change in pharmacokinetics has also been observed in first-line therapy for obese POMS, so that adjusting the dose according to BMI increases the therapeutic success [383]. Because there is an inverse correlation between 25(OH)D values and hs-CRP (highly sensitive), systemic, mild inflammation in autoimmunity could be abolished [384].

Comorbidity - chronic sinusitis with and without polyposis

The presence of 3 or more comorbidities was associated with an increased risk of increased MS disease activity [385]. The presence of 2 or more cardiometabolic disorders was also associated with an increased risk of MS activity. Likewise, psychiatric disorders were associated with an increased risk of disease activity. Clinically, cardiovascular disease, mental illness and chronic lung disease are the most common comorbidities affecting people with MS over the course of their disease. While mental illness is consistently common at all ages, the prevalence of cardiovascular and chronic lung disease increases with age (details in Salter [385].

While the negative connections between comorbidities and disease activity are no longer in doubt, the focus should be on the prevention and treatment of previously little-noticed comorbidities in PwMS that impaired quality of life. In the early stages of MS, alterations in the nasal microbiota flora because of chronic nasal and paranasal sinus disease may indirectly influence neuroinflammation [386]. Regular monitoring of the course of MS by cranial MRI automatically detects the paranasal sinuses (PS), and chronic sinusitis in PwMS and acute optic neuritis has been verified in up to 53% of cases, sometimes bilateral and asymptomatic [103,387,388,389].

Autoimmune diseases are considered risk factors for chronic rhinosinusitis (CRS) [390]. There is a bidirectional relationship between CRS and autoimmune diseases [391,392]. Pathoimmunology shows intersections with MS. In patients with CRS, the expression of Th-17 cells and their secreted cytokine IL-17A is upregulated in the paranasal sinus mucosa, leading to increased inflammatory reactions, subsequent mucosal damage and pathological remodeling. The imbalance between Th-17 cells and regulatory T cells (Tregs) in the body of patients with CRS may contribute to the persistence of inflammation

and the chronic nature of the disease [393].

The prevalence of CRS overall and its two phenotypic variants, CRS with and without polyposis (NP), has been observed in patients with early autoimmune diseases, involving both T-helper 1 responses (as in MS) and T-helper 2 responses [104,394]. It is likely that the underlying Th1/Th2 status is only one of several factors influencing the phenotypic presentation of comorbid CRS [394]. MS, like CRS, are multifactorial diseases and have a wide spectrum of associations ranging from genetics, environmental factors and comorbidities [104].

Three endophenotypes have been identified in early MS (see above) [34] and three endotypes are also evident in CRS based on cytokine patterns:

Type1 (Th1 cytokine, IFN-gamma); Type2 (Th2 cytokines IL-4, IL-5, Il- 13, IL-9); Type3: (Th17 cytokines Il-17. Il-22) [393-396]. Further interfaces are the disturbances tight junction (TJ) as a physical-mechanistic barrier with reduced expression of ZO-1, occludin, claudin-1, which occur both in the BBB in MS and in the epithelial barrier CRS. TJ proteins between the epithelial cells of the nasal cavities play a central role in the integrity of the epithelial barrier [397-400].

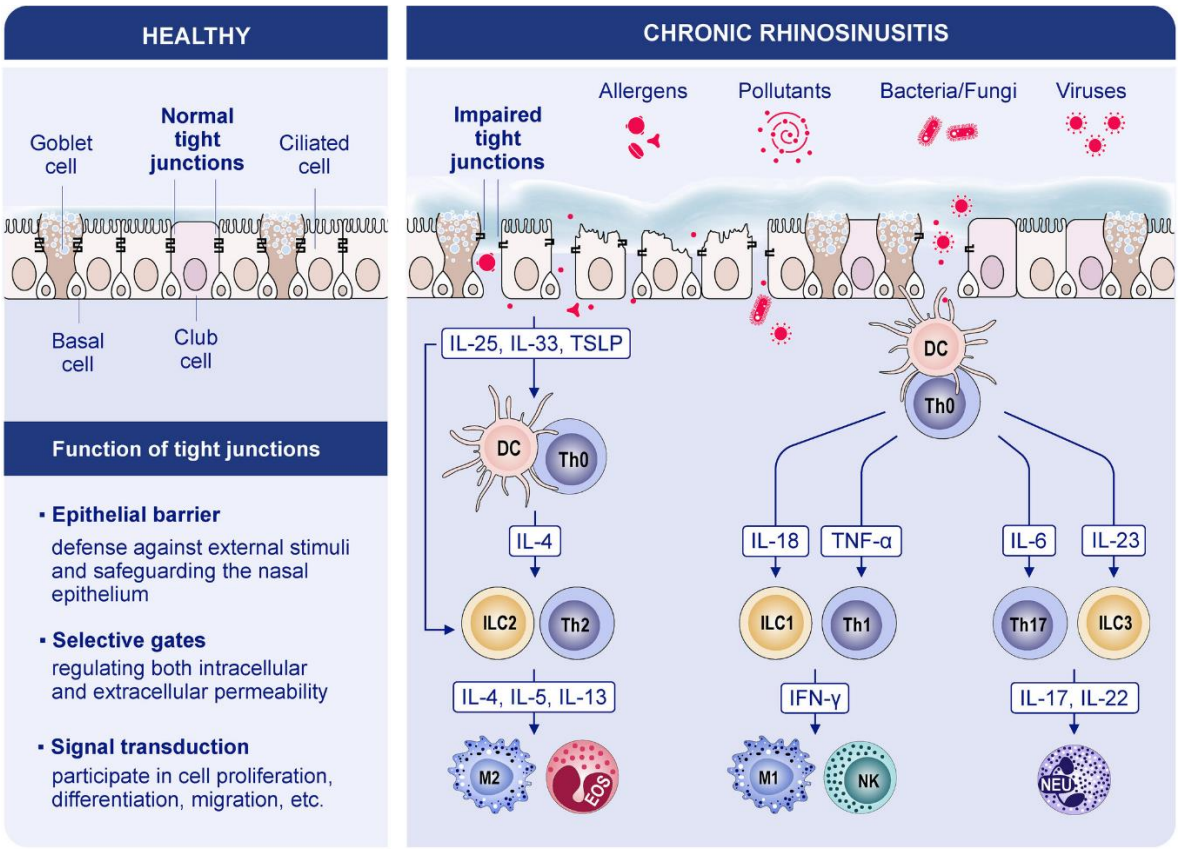


Figure 3: Overview the nasal epithelial abnormalities in the pathogenesis of CRS. In health state, intact TJ proteins effectively resist various stimuli from the external environment . However, persistent and rigorous environmental factors impair the integrity of epithelial barrier , resulting in an imbalance of epithelium immune response , dysfunction of mucociliary clearance , and excessive tissue remodeling in CRS. CRS, chronic rhinosinusitis; DC, dendritic cells ; EOS, eosinophils ; IFN-γ, interferon gamma ; IL, interleukin ; ILC, innate lymphoid cells ; M, macrophages ; NEW, neutrophils ; NK, of course killer cells ; Th, T helper ; TJ, tight junction ; TNF-α, tumor necrosis factor alpha ; TSLP, thymic stromal lymphopoietin .
{Original figure from Allergy. 2024;79:1146 –1165: Zhi- Qun Huang,| Jing Liu, Li-Ying Sun, Hsiao Hui Ong, Jing Ye , Yu Xu1,De-Yun Wang [398]. Wiley online library.}

It has been discussed in the past whether alterations in the nasal microbiota (microbial dysbiosis) and their metabolites pass the BBB and contribute to neuroinflammation and neurodegeneration [401]. Three possible main routes have been identified through which microbiota enter the CNS: the olfactory route, the trigeminal pathway and the systemic pathway. The last pathway is characterized by the microbiota penetrating the rich vascular network of the nasal mucosa and being carried to the CNS via the systemic pathway across the BBB [386].

11.1 Chronic sinusitis- microbial factors

Over 30 years ago, it was discussed whether microbial factors are involved in the pathogenesis of MS. Antibodies (AB) against Acinetobacter species in infections of the paranasal sinuses could be formed in PwMS. Due to existing molecular similarities between microbes and brain antigens, these cross-reactive AB, which are mostly of the IgG isotype, could cross the BBB and thereby cause demyelination through the process of antibody-dependent, cell-mediated cytotoxicity [402].
Mast cells (MC) also belong to the complex series of etiopathogenetic components of MS.

MC are important immune cells and players involved in tissue inflammation and remodeling. Particularly in CRS with polyps [403]. In MC, 1,25(OH)2D3 can increase VDRs, upregulate IL-10 mRNA and induce the secretion of anti-inflammatory IL -10 [404]. CRS and MS show clinical and epidemiological similarities with phases of exacerbation and remission. Likewise, these two diseases show identical disease age curves, with the prevalence being in women (2:1; women-men) [386].
Hypersensitivity of the MC in PwMS can cause chronic inflammation of the nasal mucosa [405]. Mast cells can act at an early stage and promote demyelination through interactions between mast cells, neurons and other immune cells to mediate neuroinflammation [406]. The findings to date support the hypothesis that CRS in varying degrees and severity can influence the course of MS [386]. In brain samples from PwMS, Proteobacteria were found in the white matter (WM) of patients with progressive MS, associated with an increased expression of inflammatory genes. Inflammatory demyelination with organ-specific dysbiosis in PwMS could contribute to the disease mechanisms to date [407].

11.2 Vitamin D

The prevalence of vitamin D deficiency is higher in CRS patients and a significant association has been found between lower serum vitamin D levels and chronic rhinosinusitis [404,408]. There was also a significant association between vitamin D and disease severity in patients with chronic rhinosinusitis with nasal polyps [409-411]. Low s25(OH)D levels were often associated with increased inflammation [412]. Low s25(OH)D levels were associated with higher radiological severity (Lund -Mackay scale) [409]. Vitamin D supplementation contributed significantly to the relief of symptoms in these patients [410,414]. After nasal polyp surgery, a vitamin D supplement of 4000 IU/ day significantly reduced the recurrence rate [415]. Calcitriol should contribute to the repair of TJs in analogy to the BBB. A reduction in nasal spray, steroids or antibiotics, which have a negative effect on the nasal flora [386] and are used symptomatically by PwMS, could be achieved by a vitamin D supplement [416].

Important inflammatory mediators such as IL-4, IL-5, IL-6, IL-8 and IL- 13 and anti-inflammatory IL-10 are influenced by 1,25(OH)2D3, also in obesity [417-419].
Calcitriol reduces the expression of the cytokines IL-6 and IL-8 in sinonasal epithelial cells [420].
1,25(OH) 2D3 can act directly on endothelial cells to upregulate tight junction proteins (zonula occluden-1 and claudin-5) [111,421].
Vit D promotes the proliferation, differentiation and repair of epithelial tissue in the nose [398,422].

Calcitriol for the prevention of cancer risks under DMT therapy

Although there is no consensus on the cancer risk in PwMS, there is evidence of a slightly increased risk of up to 30% [423]. In early-stage colorectal cancer, overall survival and cancer-specific survival were lower in PwMS than in people without MS [424]. As early as 2009, it was pointed out that 1,25(OH)2D3 is a hormone with strong anti-cancer and anti-inflammatory effects [425]. In the following years, the molecular mechanisms of the action of 1,25(OH)2D3 on cancer cells were intensively studied and include the regulation of cell proliferation and apoptosis [426-428]. In addition, 1,25(OH)2D3 attenuates the ability of cancer cells to metastasize and inhibits angiogenesis and the

inflammatory process associated with carcinogenesis [429]. Over 40 years ago, it was demonstrated in cell cultures that melanoma cell growth is inhibited by 1,25(OH)2D3 [430]. Active forms of vitamin D can prevent or inhibit the development and progression of melanoma and can be used to treat this disease [431].
Because the different DMDs carry different risks [432], continuous VitD suppl would have another indication area.

In follow-up care for monoclonal antibody therapy, the focus should be on thyroid cancer, in women especially breast cancer and bladder cancer, cancer of the digestive system in men and older age [433]. The pluripotent effect of 1,25(OH)2D3 in young women with MS could significantly reduce the rate of cervical abnormalities under DMT, especially since the risk of cancer is slightly increased in PwMS [213,434-437]. DMTs alter the immune response to eliminate the human papillomavirus (HPV) [438]. A future systematic review and meta-analysis of randomized and nonrandomized trials will provide an updated summary of the cancer risk associated with DMTs for adult patients with multiple sclerosis [439].

Discussion

The findings by 2025 on the CNS effectiveness of vitamin D (1,25(OH)2D3) in MS and their clinical implications should not only be discussed in scientific articles and at conferences. In order to benefit PwMS, implementation in the daily practice of physicians and in patient care is necessary. By 2025, it is generally accepted that an altered balance between pro-inflammatory and regulatory immune cells exists in MS [440]. A 2024 consensus on promoting brain health in PwMS included adequate s25(OH)D levels [441].

Numerous studies have confirmed that increased s25(OH)D protects against MS risk and reduces the risk of relapse, also in combination with DMTs [17, 55,56,69,442-446]. Higher VitD levels (s25(OH)D >30.31 ng /ml) in PwMS, especially in children, may reduce the risk of relapse and disability accumulation [69,447,448].

Internationally, numerous neurological societies support early therapy with highly effective DMTs [449]. To date, the focus has been on suppressing acute inflammatory parameters (relapses and acute MRI lesions). The existence of PIRA and the realization that a significant deterioration in cognition occurs from the earliest stages of the disease [9] make early adjuvant therapy to DMTs necessary. In younger individuals, immunological reactions are mainly controlled by the adaptive system, which strongly characterizes active lesions in relapsing multiple sclerosis [171].

The greatest potential for time gain is in the youngest, least disabled patients with multiple sclerosis [170]. Immunopathological mechanisms include the role of adaptive immunity with a focus on T and B cells and pro-inflammatory cytokines. The role of innate immunity is characterized by activated microglia (MG) and macrophages, and BBB breakdown is another element in the pathology of MS. Further details in [9].
The function of regulatory T cells (Treg) is reduced in the pathophysiology of MS, leading to the frequency of type 1 Th cells (Th1) and Th17 cells or GM-CSF-secreting effector T cells [450-453].

On the other hand, vitamin D can promote the migration ability of regulatory T cells to the CNS [454] and promote Th 2 and Tregs [35]. Early BBB damage causes an influx of peripheral immune cells and factors that interact with resident immune cells in the CNS. Autoreactive CD4+ and CD8+ T cells have been shown to migrate across the destroyed BBB and are also present in active demyelinating lesions [32].

14.1 1 ,25(OH)2D3- reduces pro-inflammatory and increases anti-inflammatory cytokines

The active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1α,25-[OH]2D3), is reported to have protective effects for multiple sclerosis [69,111]. Calcitriol exerts an anti-inflammatory effect by suppressing both the innate and the adaptive immune system [56,61,91]. Calcitriol inhibits neuroinflammation, local activation of macrophages/microglia and astrocytes and has a Influence on the BBB by sealing [28,33,35,61,69,445]. It is postulated that the disruption of the BBB is not only temporary but persists throughout the disease. Both active lesions (“acute demyelinating brain lesion”) and inactive lesions showed disruption of the BBB dysfunction and reduced expression of tight junction proteins [13,455,456].

A positive effect of VitD supplementation on the integrity of the BBB during various neuroinflammatory processes should be initiated as early as possible [33, 35,421,457]. The differentiation and maturation of

oligodendrocytes is promoted, thereby increasing the potential for remyelination and nerve repair [266,458-462]. Vit D deficiency is associated with the onset or progression of autoimmune diseases in general and in MS in particular [463].

Another driver of MS activity may be the "leak gut syndrome". Dysbiosis, disturbances in the gut microbial community, can increase intestinal permeability, increase the production of IL-17A and increase disease activity in MS. Bacterial species that were more common in disease-active, treatment-naive MS were also positively associated with the plasma cytokines IL-22, 1L-17A, INF ß, IL33 and TNF alpha, some of which are targeted by Vit D influence [464]. If BBB integrity is impaired, immune cells (CD4+ cells) can invade the CNS [464-468]. The gut microbiome is also associated with MS activity in children [469]. The composition of the gut microbiota depends on the presence of 1,25(OH)2D3 [470].

An optimal s25(OH)D level showed a higher gut microbiota diversity. A higher Vit D level was associated with increasing levels of beneficial species and lower levels of pathogenic bacteria [471,472]. 1,25(OH)2D3 can improve intestinal epithelial barrier function by increasing expression of some tight junction proteins such as occludin, Zo-1, Zo-2, vinculin and claudins [473-476].

Currently, it can be stated that vitamin D deficiency impairs the microbiome and the immune system and thus may contribute to MS and autoimmune diseases in general [477] and that Vit D supplementation may in the future serve as part of a therapeutic strategy for human autoimmune or infectious diseases with dysfunction of the intestinal barrier (leaky gut phenomenon) [476].
Because of years of controversy regarding Vit D supplementation despite the existence of pathoimmunological knowledge about this fundamental multifactorial effect of vit D, only a few national neurological societies worldwide have recommended early, high-dose concurrent add -on therapy for PwMS [478].

Although the risk of adverse events (AEs) with DMTs may be influenced by Vit D supplementation and disease activity, similar to DMT initiation, therapeutic inertia appears to be a major contributing factor, with herd mentality appearing to play a role among many other causes [273,449,479-481]. The expertise of the individual neurologist will decide whether high-dose Vit D supplementation is offered to PwMS .

14.2 Withholding/rejection of high-dose Vit D suppl due to negative study results

The relevance of the start and duration of Vit D supplementation was demonstrated in a study conducted over only 48 weeks in people with CIS and Vit D doses of 5000IU/ day and 10,000IU/ day. Conversion to clinically confirmed MS was not prevented during this period [482]. However, the result would have to be replicated with a higher daily dosage and s25(OH) values that could be close to 100ng/ml s25(OH)D values in order to achieve an optimal influence on the disturbed immunological homeostasis, which the investigators themselves admit. "Supraphysiological doses" seem to be necessary to control the neuroinflammatory process [33,200]. Because MS can have a prodromal phase lasting several years and neuroaxonal damage has already existed during this period, negative results in supplementation studies can be explained later in the course of MS. Increased sNfl levels had already been observed 6 years before the onset of clinical MS [97]. In addition, there are other confounding factors [Table 1].

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. [527]

No agreement on normal values of s25(OH)D in healthy individuals and in patients with autoimmune diseases, which must be different. Vit D shows a differential and reduced response to metabolic processes of CD4+, CD8+ T cells in PwMS.	Giustina a et al. [527] Yeh, W.Z et al. [199]
30 to 100ng/mL s25(OH)D values are proposed to influence immunological imbalance in autoimmune disease.	Holick MF et al.[528]
Lack of consensus on the form of oral vitamin D suppl (daily/weekly monthly). Daily administration is preferred.	Giustina A et al.[527]
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.[372]
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).	Giustina A et al. [527] Wylon K et al. [529] Meekins ME et al.[530] Rahme et al. [531] De Oliveira LF et al. [532] Duan L et al. [533] Lemke D et al. [94]
No consideration of individual absorption rates "low, medium, high" in vit D suppl-studies, due to genetic variants of vit D-binding protein (VDBP) and genetic polymorphism (CYP27B1). PwMS reduced the serological response to vit D suppl.	Bivona G et al. [534] Carlberg C et al. [95] Malhotra S et al. [535] Jassil NK et al. [536] Jiang T et al. [537] Bhargava P et al. [538]
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. [539]
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. [540] Li X et al. [541] Hajhashemy et al. [542] Bachmann KN [543] Larsson SC et al. [544]. Visaria A et al. [545]
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.[538]

Vit D suppl doses depend on the duration of the disease and the severity of MS.	Agnello L et al. [546]
RCTs of pharmaceuticals cannot be compared to RCTs of dietary supplements. Problems with RCT's with dietary supplements.	Boucher BJ et al. [547] Föcker M et al. [548] Pierrot-Deseilligny [549]
No standardization of study designs with the consequence of a lack of comparability of studies.	Wimalawansa SJ [550] Giustina a et al. [527]
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. [551]
25(OH)D determination assays show mixed results.	Sempos CT et al. [552] Lahoz R et al. [553], Qu F et al.[554]
Lack of central laboratories	
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. [555] Qu F et al. [554]
Negative RCT results may reflect technical deficiencies.	Lincoln MR et al. [556]
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. [495]

Table 1. Relevant, multifactorial influences/potential confounding factors in MS studies on the results a vitamin D supplementation

This study [482] does not refute the clinical benefit of Vit D supplementation in the context of other therapeutic goals [483]. Low bone density appears to occur early in PwMS. This is consistent with common etiological or pathogenic factors in MS and osteoporosis and requires an active approach to optimize bone health in the early stages of MS [483].

Despite all the debates about the individual therapeutic approach, such as the dose level of daily Vit D intake and the target 25(OH)D values, the therapeutic window, the earliest start of therapy, is no longer in question [113,449,484-486]. Patient preferences should be respected when choosing the DMT and adverse events should be taken into account [487]. One of many patient preferences is mainly determined by risk minimization [588,489], which could be reduced by Vit D supplementation [490].

14.3 Early and continuous prevention - conditio sine qua non

Increased cytokine production is associated with the earliest onset of MS and is typical throughout life in PwMS [38]. The classic pleiotropic proinflammatory cytokines such as TNFα and IFNγ as well as more specific Cytokines such as GM-CSF and IL-17A in

serum/cerebrospinal fluid (CSF) are increased. The anti-inflammatory IL-10 with its immunoregulatory properties is reduced and IL-10 production in blood lymphocytes correlates inversely with lesion burden and clinical disability. Serum IL-10 levels have been shown to be a risk factor for further relapses in patients with clinically isolated syndrome [38,491,492].

Despite controversial discussions, most epidemiological observational studies suggest that early and adequate vitamin D levels can reduce the risk of MS onset and modify the course of the disease [457,493]. The earlier the Vit D supplement is given, the higher the therapeutic success, since a " window of opportunity " is likely [33,457]. To achieve immunomodulatory effects, at least s25(OH)D levels between 30 and 60 ng /ml (up to a maximum of 130 ng / mL) are required as long-term therapy [200,493,494]. The effectiveness of a vit D supplement on the risk of MS and the influence on the course of MS results from the dose-effect relationship (biological gradient). A benefit can only be achieved if the dose of Vit D is in the range relevant to the disease (threshold value). A significantly lower MS risk was found with an s25(OH)D value above 99.1 nmol/L (39.5 ng / mL) [459,495].

Obesity requires a dose adjustment in the daily dosage and is based on the achieved s25(OH)D values [382].
Since PwMS is less responsive to Vit D suppl (Vit D-related genetic polymorphisms) influence the serological response to high-dose Vit suppl, especially in the presence of comorbidities, s25(OH)D values should be monitored initially every 3 months and later every 6 months in conjunction with serum Ca, phosphate levels (parathyroid hormone if necessary) [494,496].

14.4 The best preventive measure against multiple sclerosis is taking vitamin D

Obesity in childhood increases the susceptibility to early-onset MS by more than twofold [497] and should motivate parents who suffer from MS to supplement their offspring with vitamin D. The prevalence of calcifediol deficiency in overweight and obese children is reported to be 36-93% [498]. A positive correlation between obesity and MS severity is accepted [373]. The highest therapeutic goal is to prevent increasing disability by balancing the disturbed immune homeostasis as early as possible. There is only marginal discussion as to whether it is ethically justifiable to withhold the complex effect of 1,25(OH)D3 on immune dysregulation, the course of MS and the effects on comorbidities and pregnancy in PwMS.

While discussions between therapists and PwMS are very stressful as to whether DMTs should be continued or discontinued in order to reduce the risk of new disease activity, this does not need to be evaluated in the case of vit D supplementation. Because this question is particularly considered in older PwMS over 55 years of age [499], in the case of add -on therapy with Vit D, on the contrary, there is a demand to continue vit D supplementation as an endless form of therapy, because the increasing age-related comorbidities favor vitamin D therapy [490]. In the discourse on broad-based vitamin D supplementation, skeptics of long-term vitamin D therapy for existing vitamin D deficiency in MS regularly raise the possibility of reverse causality.

Although there is an accumulation of evidence to the contrary [15], the bottom line is that hypovitaminosis D is the cause of dysimmunity. Balancing this imbalance of anti-inflammatory and pro-inflammatory cytokines is the goal of vitamin D supplementation, so the etiology of the deficiency is not the decisive parameter. In analogy to the deficiency of the hormone insulin, whether due to autoimmunity (diabetes mellitus type 1) or after total pancreatectomy, there is no doubt that insulin supplementation is necessary. In MS, the hormone vitamin D must be supplemented to restore immune homeostasis - increasing anti-inflammatory cytokines and reducing pro-inflammatory cytokines [282].

In PwMS in the early stage of RRMS, T helper cells 17.1 (Th1) with high IFN-gamma content, high GM-CSF content and high IL-17 levels were measured, which have an increased ability to infiltrate the CNS. Methylprednisolone is administered during MS attacks, but glucocorticoid resistance can develop over the course of MS [500]. The simultaneous administration of Vit D and the glucocorticoid optimizes the suppression of pathogenic Th17.1 cells. Better therapeutic success and longer-term protection can also be expected here [501].

14.5 Prevention strategy of infections under DMTs

Pathophysiological mechanisms demonstrate the therapeutic potential of vitamin D supplementation for the prophylaxis and therapy of infectious diseases [

[398,502-504]. For this effect to be effective, Vit D supplementation must be administered continuously before infections begin, even in children or prenatally in late pregnancy [505-507].

A long-term analysis of PwMS and ocrelizumab therapy (B cells depleting therapy) up to 14 years showed infections as the most common side effect. Severe infections of the lower respiratory tract , urinary tract, abdominal and gastrointestinal tract, and skin were the most common serious adverse events. These depended on the phenotype of MS (RRMs with recent relapse activity), patients with primary progressive MS (PPMS) and severe walking disabilities (four-fold higher risk of severe infections [EDSS > 6]), comorbidities (more than 2), (diabetes mellitus, bladder problems). Because CD8+ T cells are also reduced by ocrelizumab, viral defenses may be weakened [508].

In particular, patients with PPMS require special monitoring, since low immunoglobulin IgG, IgM levels, obesity, heart and bladder problems determine the increased severity of the infection [239,257,509]. The three most common types of infections were nasopharyngitis, urinary tract infections and upper/lower respiratory tract infections [257].

In order to ensure that the increased risk of severe infections caused by anti-CD20 therapy is not overestimated in the risk-benefit assessment [510], concomitant VitD suppl provide infection protection/limitation and are part of preventive strategies to reduce the risk of infection when caring for PwMS [511-515]. The incidence rate of 6.67 serious infections per 100 patient-years was observed with anti-CD20 therapy (Rituximab/Ocrelizumab) [516]. Hypogamma globulinemia IgG occurred in 20% and IgM in 34% as an undesirable side effect and carries the risk of serious infections [517].

The risk of severe infections and urinary tract infections was highest in highly potent DMDs [239,518]. Infections may also occur before the detection of hypogammaglobulinemia [257,519], so proactive management by continuous Vit D supplementation is indicated.

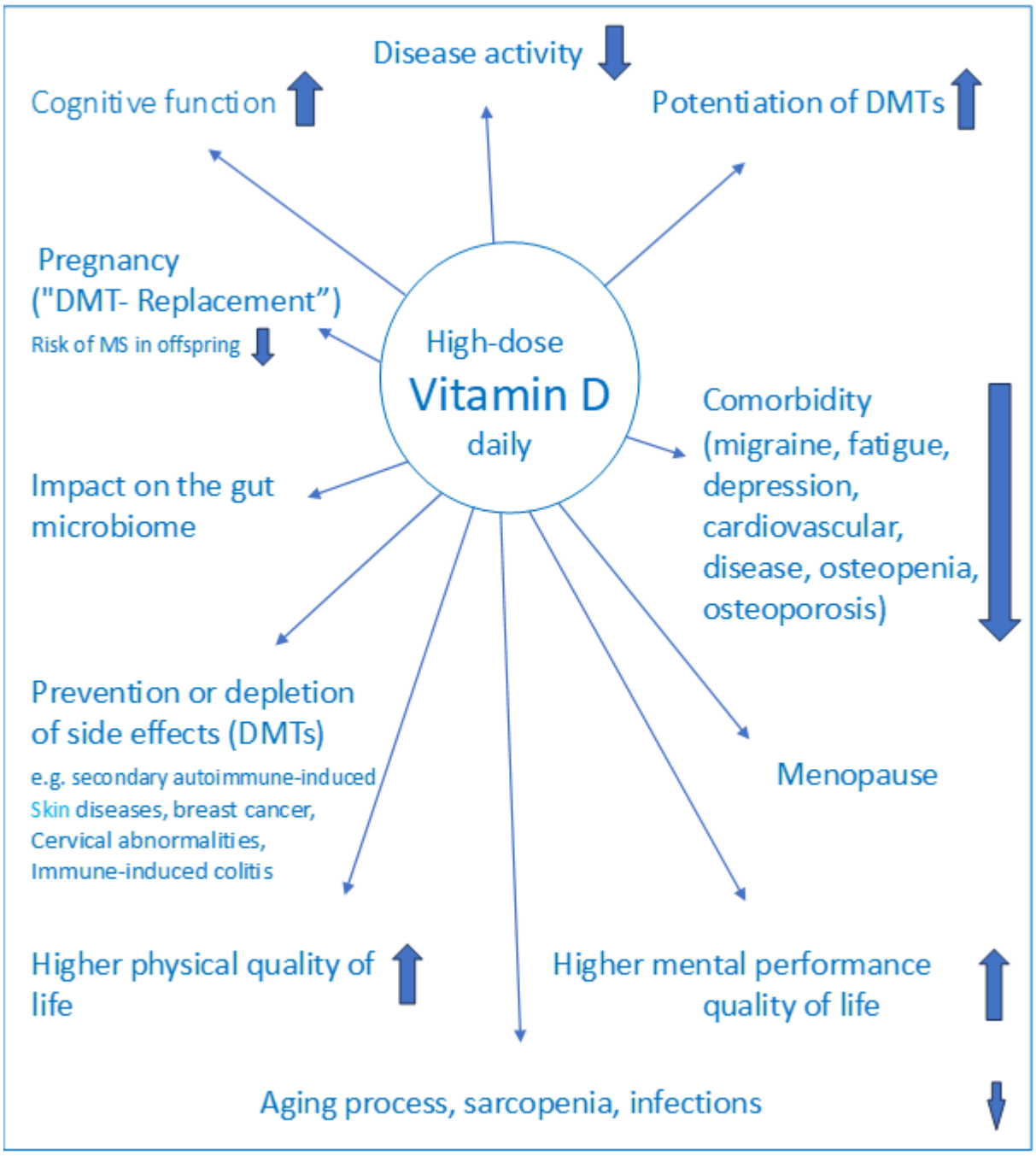
If individuals at general risk for influenza and/or COVID-19 are recommended to take 10,000 IU of vitamin D3 daily for several weeks to rapidly raise s25(OH)D concentrations, followed by 5,000 IU/ day to achieve 25(OH)D concentrations above 40–80 ng /ml (100–150 nmol /l) [520], this potential should be exploited even more to reduce risk in PwMS [203,239,515,521].

14.5 The best preventive measure for infections in MS is vitamin D supplementation

Previous vitamin D studies in critically ill patients with infections were practically always " underpowered " for the planned endpoint. In a recently published meta-analysis, a significant benefit of vitamin D administration for mortality (risk ratio 0.78) as well as a shorter intensive care unit stay (−3.1 days) and a shorter duration of ventilation (−5.1 days) was shown in the 16 available intervention studies with 2449 patients [522]. Various recommendations were made for critical patients, e.g. a single bolus administration of 540,000 IU to achieve sufficient 25(OH)D levels and further daily doses of 4000 IU over a period of 90 days (corresponding to a total vitamin D dose of 900,000 IU over a period of 90 days) [523].

In the camp of neurology community "with cautious recommendations of high-dose Vit D supplementation", however, those individuals should receive "best supportive preventive measures" in conjunction with first-degree relatedness, monozygotic/dizygotic twins, and childhood overweight/obesity [20,146,524,525]. An algorithm for identifying MS cases in large populations has already been presented [526].

This review aims to change the perception of adjuvant vitamin D among MS care providers and general practitioners and to highlight the synergistic effect of vitamin D.



Graphical abstract 2: Spectrum of effects of vitamin D supplementation in PwMS Increase (↑) decrease (↓)

The benefit of early daily high-dose vitamin D intake should be recognized and incorporated into the daily practice of all therapists.
The pathophysiological/pathoimmunological findings described in this overview should form the basis for this by the year 2025.

Conclusion

The results of research over the last two decades on the benefit of vitamin D supplementation in people with multiple sclerosis (PwMS) should be incorporated into a strategic therapy concept because of the full spectrum of vitamin D immunomodulation by 1,25(OH)2D3 in multiple sclerosis (MS). The influence of calcitriol on the risk of MS, in the prodromal stage, the course of the disease, and on comorbidities such as fatigue, mental illness, infection prophylaxis, chronic sinusitis, children with MS, pregnancy, long COVID and cancer prevention is highlighted. The risk-benefit assessment with a very good safety profile also indicates that treatment should begin as early as possible (window of opportunity). In the case of a chronic disease that is currently incurable, even if there is little benefit on the individual disease activities and comorbidities, the sum of all individual effects of calcitriol should be recommended as a therapeutic option, despite all discrepancies in the interpretation of studies on this issue. Science is based on debates, but these should not lead to the transformation of new findings into patient care practice being delayed for years or decades or not reaching the attending physicians/health care providers in the periphery at all. The almost unmanageable number of publications (studies) on Vit D suppl. in PwMS have not raised any suspicion of a harmful effect of calcitriol (except in the case of unintentional intoxication).

It would be of enormous importance and an as yet unmet need to develop an algorithmic approach to search for people with the earliest symptoms of MS, for example demyelination events, but who have not yet been diagnosed with MS.

By summarizing the findings on vitamin D supplementation up to the year 2025, the aim is to provide decision-making support to practicing physicians, general neurologists and non-MS specialists who have to take responsibility for the daily care of PwMS.

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