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REVIEW

Comorbidities in multiple sclerosis—a plea for interdisciplinary collaboration to improve the quality of life of MS patients

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Abstract: The negative influence of comorbidities on the quality of life of people with multiple sclerosis is evident and the problem is increasingly acknowledged by numerous international studies in long-term care. One therapeutic option would be an add-on therapy with vitamin D (VD), with the aim of achieving a therapeutically effective dose. The individually required VD dose must be tested, since the response to a certain dose is subject to variations between individuals. A possible toxicity with increased 1.25(OH)D3 (active VD metabolite) is largely prevented by increased activity of 24-hydroxylase (*CYP24A1*). Monitoring of serum VD levels as well as serum calcium and phosphate levels (optional Ca excretion in 24-hour urine, Ca creatinine ratio in urine) provides safety and is necessary because possible mutations on the (catabolic) *CYP24A1* gene can lead to a partial or total loss of 24-hydroxylase activity and provoke hypercalcemia/hyperphosphatemia. The main therapeutic objective is to maintain functional and social independence by using drugs with a high safety profile. The prevention and optimal management of comorbidities can influence the quality of life of patients with MS (PwMS) when included in patient care. Adequate measures can reduce the burden of MS only if the risk of comorbidity is reduced through targeted monitoring, early detection and diagnosis. Such a strategy will contribute to influencing the premature mortality of patients with MS. If VD is recognized as a "multi-purpose steroid hormone", it could also be used to maintain cognitive function and prevent premature possible dementia, especially as there is evidence that VD deficiency correlates with brain atrophy (hippocampus). At present, MS therapy is still a balancing act between therapeutically efficient action and the management of unexpected side effects, with VD add-on therapy being almost unproblematic and most likely to be accepted by PwMS.

Keywords: comorbidities in multiple sclerosis, improving quality of life, vitamin D therapy, pregnancy in MS

Introduction

The care of people with multiple sclerosis (PwMS) requires coordinated, multidisciplinary treatment, as it has been shown in practice that care is mainly provided by general practitioners and neurologists in private practice rather than by specialized multiple sclerosis (MS) centers. In Germany, more than 200,000 people suffer from MS.[1] Awareness of the high prevalence of comorbidities (Tables 1–3) and the evidence that these also influence the progression, cognition and quality of life of PwMS and increase premature mortality[2] indicates that these diseases must be appropriately prevented and managed.[3] This aspect is now included in the current

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Table 1 Lifetime prevalence rates of comorbidities in PwMS

Major depressive disorder	36–54%[16,127]
Anxiety disorders	35.7%[16,127]
Bipolar disorder	13%[127]
Adjustment disorders	22%[127]
Psychotic disorders	2–3%[128]

Abbreviaton: PwMS, people with multiple sclerosis.

2017 European Therapeutic Guidelines.[4] All therapists must be sensitized to the occurrence of comorbidities (CM) (including depression, anxiety, hyperlipidemia, migraine and anemia) before MS symptoms are registered.[5] In addition to "primary therapy" (course-modifying immunotherapeutics=disease-modifying treatment; DMTs) of relapsing-remitting multiple sclerosis (RRMS) with the aim of stopping progression, the best possible maintenance of quality of life is an essential target parameter. At present, however, there are no biomarkers in individual drug therapy planning which can predict the efficacy of the intended drug. The future determination of osteopontin (OPN) and serum neurofilament light chains (sNfL) in peripheral blood as valid biomarkers for diagnosis and prognosis would be a milestone in the treatment of PwMS with RRMS. When MS therapy has been effective, sNfL levels decrease approximately 3–6 months later.[6] Despite consideration of disease activity and the current European guidelines for drug therapy (14 drugs will be available for RRMS in the future), a period of "trial and error" is possible for PwMS. For example, six of the drugs used for the basic treatment of relapse reduction in RRMS achieve an absolute risk reduction of about 30–45%.

However, the almost daily increase in knowledge about the "influence of vitamin D (VD) on the course of multiple sclerosis and on comorbidities" allows practitioners to strive for an adequate VD level in all PwMS, despite controversial discussions about the dose level in VD supplementation. It is undisputed that PwMS want "complementary or alternative therapies" to prevent their disease from worsening.[7] The physician–patient relationship is positively influenced by the possibility of other therapies in addition to basic or escalation therapy.

In routine diagnostics, no genetic risk factors (eg HLA DRB1*1501) or variants of the genes of the vitamin D metabolizing enzymes 1-alpha-hydroxylase have been determined (rs12368653, rs10876994, rs118204009, rs10877013, rs703842 in *CYP27B1*), variations in *CYP2R1* (encodes the enzyme responsible for the 25 hydroxylation of VD) and rs2248359 in *CYP24A1*, *CYP2R1*, *DHCR7*, *GC* and *CYP27B1*). Because a selection of patients is not possible, a

Table 2 Variations in the prevalence of selected comorbidities in PwMS (eg depending on observation period, location and age of PwMS, gender, lifestyle factors, socioeconomic status, etc)

Depression	17.5–50%[3,20,33,134–138]
Anxiety	21.9–54.1%[3,33,90,134]
Mood and anxiety disorders	35.8%[18]
Bipolar disorders	2.6%[135]
Psychoses	4.3%[20]
Hypertension	10,5–29,7%[3,33,135,139]
Psoriasis	4–7.74%[20,124]
Thyroid diseases	2.08–18.5%[20,79,140]
Hashimoto's thyroiditis	(0–16.1%), Graves' disease (0–2.56%)[20]], 12.9–17.1%[139]
Diabetes mellitus (type 1)	10.5%[140]
Diabetes mellitus (type 2)	4.9%[124]
Reduced bone mineral density (observed over 17 years)	74.7–80%[43]
Women: 38% osteopenia, 44% osteoporosis, men 43% osteopenia, 37% osteoporosis.[40]	
Cardiovascular diseases	2.3–2.6%[134,135]
Anemia, other blood disorders	6.4–16%[1,27,77]
Hyperlipidemia	10.9–25.%[3,33,139,141]
Migraine	18.1%[33]
Chronic lung diseases	10–12,1%[3,28]
Asthma	5–12.9%[36,124]
Pain	20–90%[93]

Abbreviation: PwMS, people with multiple sclerosis.

Table 3 Frequency of selected comorbidities in routine clinic visits in 949 Canadian mutiple sclerosis patients in 2010–2011

1	Depression	(29%)
2	Hypertension	(17.8%)
3	Migraine	(17.3%)
4	Hyperlipidemia	(12,4%)
5	Anxiety	(11,5%)
6	Chronic obstructive lung disease	(9.8%)
7	Irritable bowel syndrome	(7.9%)
8	Thyroid diseases	(7.8%)
9	Osteoporosis	(6%)

Notes: Reprinted from Multiple Sclerosis and Related Disorders, 4, KM Fiest, JD Fisk, SB Patten, H Tremlett, C Wolfson, S Warren, KA McKay, L Berrigan, RA Marrie, Comorbidity is associated with pain-related activity limitations in multiple sclerosis, 470-476, Copyright (2015), with permission from Elsevier.[93]

broad supportive therapy would be discussed with VD. Since VD metabolism is influenced by some genetic polymorphisms that contribute to serum VD concentration, individuals probably need their own personal dose of supplementation.[8] The variability between individuals in terms of VD response can be influenced by single nucleotide polymorphisms (SNPs) involved in the synthesis, binding, transport and degradation of VD.

Children with MS and the allele HLA DRB1*1501 were significantly associated with VD serum levels and relapse rate.[9] Interactions between VD levels and Epstein–Barr virus (EBV) infection and HLADRB1*1501 exist, in particular relationships to antibodies to EBV antigen core 1 (anti-EBNA1). A high dose oral VD supplementation may affect the humoral immune response to the latent EBV antigen EBNA1 in RRMS, a decrease in anti-EBNA1 serum levels was observed;[10,11] two to three years prior to clinical manifestation of MS, low 25(OH)D levels were registered with elevated anti-EBNA-1 IgG titers in serum.

The problem of "vitamin D, multiple sclerosis, comorbidities/therapy" has been discussed as controversial for 10 years in about 1,026 publications (PubMed search), so the following document will focus on current, practical information and will not be a presentation of comparative studies, although it will refer extensively to current literature. In a recent Canadian study, it was estimated that VD supplementation (target: 25(OH)-D levels to/above 100 nmol/L) would eliminate 40% of MS cases and reduce MS health costs (in Canadian dollars) by $1.5 billion/year.[12,13] The estimated cost saving effect of improving vitamin D status in Germany could be up to €37.5 billion/year.[14]

Comorbidity anxiety and depression

Depression as CM occurs in about 20–40% (up to 50% depending on definition) of PwMS during the course of the disease, anxiety in 36%.[15,16] Anglin et al were able to find a correlation between a low VD level and an increased depression rate.[17] A follow-up period over 10 years on psychiatric CM was associated with progression of MS—Expanded Disability Status Scale (EDSS) three points higher than without psychiatric disorders). Almost half (49%) fulfilled the definition of "psychiatric disorder", with depression followed by anxiety and bipolar disorders being registered.[18] Due to different observation durations and evaluation criteria, the mean prevalence of depression was about 30% for other investigators, 26% for anxiety and 8% for bipolar disorders.[19–21] In PwMS with depression, sNfL were elevated as markers of neuroaxonal damage. This noninvasive biomarker may allow researchers to prove the efficacy of specific therapies.[6,22] Serum 25 (OH)-D levels above 100 nmol/L were associated with low NfL in cerebro spinal fluid.[23] Stress increases the risk of depression, relapses and new brain lesions. There are relationships between psychiatric diseases and elevated proinflammatory markers—tumor necrosis factor (TNF), interleukin-6 (IL-6).[24] Empirical studies indicate a relationship between insufficient VD levels and depression, so that deficits should be compensated for.[25] Quality of life is thus already impaired in the first year of the disease.[26] The mechanisms for how VD could reduce depression are not clarified in detail, but the phenotypic stability hypothesis might provide an indication that VD reduces the elevated neuronal levels of intracellular Ca^2+ within the inhibitory neurons that drive depression.[27] VD supplementation is a possible therapeutic attempt to influence the severity of the disease,[28] or to reduce the risk of recurrence. In children with MS, about one third of patients experience depression and fatigue.[29] An improvement in depression was achieved in adolescents by supplementation with VD at serum levels above 30 ng/mL 25(OH)D.[30]

If it is necessary to prescribe an antidepressant in the phase of progressive MS (PMS), clomipramine could have an additional influence on the pathological process of MS, especially on the pronounced neurodegenerative aspect of PMS. It has been shown to affect T and B cell proliferation, reduce iron (Fe)-mediated neurotoxicity and inflammation and microglia activation, and influence axonal integrity.[31]

Number of comorbidities related to disability and risk of relapse

Tettey et al found evidence of greater disability and risk of relapses with increased prevalence of CM, indicating that

increased attention and treatment can improve prognosis.[32] Persons with migraine, hyperlipidemia or a high comorbidity burden with three or more diseases showed an increased recurrence rate when observed over 2 years (14.9% in the first and 13.2% in the second year).[33] Simvastatin doses could be used for the treatment of hyperlipidemia, while allowing use of the immunomodulatory and neurotrophic effect of this drug. An already existing CM when MS was diagnosed led to a faster changes of therapy during the course of therapy due to intolerances in the first therapy.[34] CM were also associated with delayed diagnosis and increased mortality.[35]

Comorbidity asthma/respiratory infections

Asthma was detected in 12.9% of PwMS, which leads to an additional psychological burden.[36] VD supplementation lowered the rate of attacks requiring treatment, especially in people managing multiple sclerosis (PwMS) with a VD level of <25 nmol/L.[37]

Similarly, VD supplementation for the prevention of acute respiratory infections in PwMS with less than 25 nmol/L achieved the greatest benefit,[38] with a VD concentration of ≥38 ng/mL (≥95 nmol/L) reducing the incidence of upper respiratory tract infections. VD is a strong inductor for antimicrobial peptides (AMPs) on mucosal surfaces and immune cells. AMPs form the "first line of defense" for invading bacteria and viruses on the mucosal surfaces of the respiratory tract. The protective effect was only achieved with daily VD supplementation.[39]

Comorbidity osteopenia/osteoporosis

PwMS show reduced bone mineral density (BMD) demonstrated by dual-energy X-ray absorptiometry (DEXA) with a greater risk of osteopenia, osteoporosis (low bone mass, microarchitectural deterioration of bone tissue, reduction of bone function) and fragile fractures (osteopenia: −2.5 <T score<–1.0; osteoporosis T-score ≤−2.5). Fractures of the femoral neck were observed four times more frequently than in the normal population.[40] A number of studies have reported an association between VD receptor (VDR) gene polymorphisms and BMD.[41] Reduced BMD was measured in 80% of male patients after a mean disease duration of 17 years, of which 43% had osteopenia and 37% osteoporosis; 38% osteopenia was observed in women and 44% osteoporosis.[42] Simonsen et al found osteopenia or osteoporosis in 75% of MS patients.[43] The need for early attention to bone metabolism is supported by the observation of low bone mass in the early stages of MS and CIS (clinically isolated syndrome).[44] Among the causative mechanisms leading to the reduction of bone density, MS can be considered an inflammatory autoimmune disease per se with effects on the homeostasis of bone metabolism with destruction by osteoclasts and inhibition of bone regeneration by osteoblasts. Microarchitectural deterioration of bone tissue with increased risk of fracture has also been observed in previous therapies with antidepressants, hypnotics and anxiolytics.[45] In order to prevent fragile fractures, in PwMS it should be suggested to administer at least 4000 IU/VD, but high doses of 5000–10 000 IU/VD should also be considered in the absence of contraindications[46] where DEXA measurements indicate osteopenia or osteoporosis.

The target could be a VD-serum level of 75–125 nmol/L[47,48] and supplementation should take place at least from autumn to spring. Calcium absorption in the gut is insufficient at serum VD levels <20 ng/mL (<50 nmol/L) and leads to secondary hyperparathyroidism. A serum concentration of <50 nmol/L VD increases the risk of musculoskeletal complaints.[46]

Although there is no uniform national or international classification of VD serum levels (the accuracy of the measurement depends strongly on the method used), other cutoff values for 25(OH)D are proposed for patients where VD deficiency affects disease progression[49]

- Severe deficiency ≤50 nmol/L (≤20 ng/mL)
- Deficiency 52.5–72.5 nmol/L (21–29 ng/mL)
- Sufficient mirror ≥75 nmol/L (≥30 ng/mL)

Hypercalcemia as an expression of VD overdose can only be expected at 25(OH)D3 serum levels of >375–500 nmol/L (150–200 ng/mL).[50]

Comorbidity pain and migraines/headaches

Pain (headache) occurs in more than half of PwMS as a very distressing early symptom (prevalence estimated to be between 20 and 90%) and can contribute to increased disability (increased EDSS). Headache, especially migraine-type headache, may be a symptom of incipient MS (CIS or radiologically isolated syndrome, RIS) because it is frequently observed. There is increasing evidence of a relationship between low VD levels and various chronic pain conditions.[51–53] In a study with chronic pain patients, 71% showed a deficit (<20 ng/mL), in 21% showed an

insufficient (20–30 ng/mL) VD level and only 8% showed a VD level of >30 ng/mL. Low levels were associated with a higher intensity of pain.[54] Although there is no definitive knowledge on the effect of VD itself and supplementation despite numerous studies, at least one therapy attempt should be made and the serum 25(OH) levels should be titrated into the sufficient range.[55] VD-serum levels above 75 nmol/L should be targeted, values above 125 nmol/L are unlikely to result in further benefit and values above 250 nmol/L may be considered potentially harmful.[56,57] A decreased VD level also affects peripheral and parasympathetic nerve function.

The presence of VDR and vitamin-activating enzymes in the CNS as well as effects on neurotransmitters are being discussed. The main mechanism acting on the immune system, the anti-inflammatory effects, could play the largest role and patients with VD deficiency (<30 nmol/L) saw the greatest therapeutic benefit after supplementation.[39]

Meta-analyses have shown that there is a significant association between migraine and MS and a high prevalence (20–50%) especially in young women with RRMS. Migraine with aura could be an indication of early manifestation of MS. Migraine is more than twice as common than among controls.[58–61]

A randomized, double-blind, placebo-controlled migraine prophylaxis study combining simvastatin (20 mg, twice a day) and VD (1,000 IU, twice a day) has demonstrated efficacy in preventing headache with episodic migraine. The number of days with migraine was reduced (30% fewer migraine days).[62] Frequent comorbidities include hyperlipidemia in MS, so simvastatin treatment as part of personalized medicine could significantly improve quality of life in PwMS with both conditions in the long-term. Psychiatric CM (depression and anxiety) and physical CM as well as pain are closely related and increase the suffering of PwMS.[63]

Comorbidity and gravidity—closely related and a challenge for caregivers

Optimum VD mirror as a chance for positive pregnancy progression and childbearing outcomes

It is undisputed that treatment with DMTs achieves stability in MS, significantly improves quality of life and thus facilitates family formation. Approximately 20–30% of women with MS have children and the prevalence of pregnancy seems to have increased over the last 10 years.[64] When counselling PwMS with a desire to have children, CM urgently need to be addressed to provide optimal care during pregnancy. Timely interdisciplinary cooperation between neurologists, gynecologists and internists (endocrinologists) with knowledge of MS-specific immunological alterations due to VD deficiency is desirable.

In the "real world", family planning raises many questions, such as: concerns about the health of the child, about the course of the disease with the risk of relapses, about further therapy during and after pregnancy, mode of delivery, control of CM (eg hypertension, asthma, thyroid diseases), about breastfeeding behavior and reactions in the social environment to the "pregnancy of an MS woman", etc. Preventive counseling can reduce the incidence of depression/anxiety and is a prerequisite for individual patient management.

Gravidities should be planned and recommended in a "prepregnancy consultation" to take at least 1,000–4,000 IU VD/day before conception (influence on an optimal development of the placenta) and during pregnancy.[46] In case of unplanned pregnancy, VD supplementation should be started as early as possible, as starting therapy later minimizes the chance of a positive outcome.

At VD-serum values of >80 nmol/L (at least 100 nmol/L) fewer pregnancy-associated CMs were observed, which underscores the benefit, including the birth result.[3,65,66]

The VD metabolism of pregnant women differs drastically from that of nonpregnant women. The serum level of 1.25(OH)^2 D doubles, decoupled from calcium homeostasis, and there is no hypercalcemia or hypercalciuria.[46,66] At no other time of life is VD status as important as in pregnancy. Not only the mother and developing fetus are influenced; the child is also influenced later on as it grows.[66] A VD substitution with 4400 IU/which occurred during pregnancy in children during the first 3 years of life showed a clear reduction in bronchial asthma or recurrent wheeze attacks.[66] There is evidence that a VD deficit in pregnant women has negative effects on motor and social development in infants.

1.25-dihydroxy-VD has a direct and indirect effect on T cell lymphocytes and modulates the immune system in inflammatory reactions.[67–69] An optimal serum VD level stabilizes the balance between the T helper lymphocytes type 1 and type 2, a deficit is associated with more "disease-causing T cells" at the expense of regulatory T cells.[68,69] MS manifestation was most frequently observed in patients born in April/May.[68] As the vitamin D serum level is subject to seasonal fluctuations, the lowest relapse rate was observed in January/February, and the highest relapse rate was observed in March/April (late winter/early spring),[70,71] adequate VD substitution should be performed. Immunological alterations in VD deficiency may

occur earlier than clinical manifestations (relapses, about 2 months later).

25(OH)D has a biological half-life of about 2 months. Miclea et al were able to show, taking into account seasonally lowered VD levels, especially in winter and early spring, that VD supplementation (increase of serum levels 25(OH)D by 51 nmol/L) can reduce the relapse rate by about 50%.[71] VD supplementation is necessary to stabilize the course of the disease during pregnancy, the postpartum period and the lactation period where no DMTs are performed. In comparison to a control group, a 30% reduction of the NfL level could be achieved.[72]

Promoting depression and anxiety through caesarean section

In addition, there is sufficient evidence that severe VD deficiency (<37.5 nmol/L) represents a three-to-fourfold increased risk for a caesarean section.[73,74] The associated "negative stress" promotes depression, anxiety and fatigue.[75] In women without MS and elective caesarean section, a high prevalence of depressive symptoms and anxiety symptoms in late pregnancy could be verified, with depressive symptoms receding post partum faster than anxiety that persisted for longer periods after delivery. The pathophysiological explanation could be that the complex physiological and hormonal changes in vaginal delivery, with dramatic changes in the brain necessary to cope with their new situation, are not experienced by women who undergo caesarean section. Oxytocin plays a decisive role in reducing anxiety (further pathophysiology in).[76]

Comorbidity and anemia

CM anemia was observed twice as frequently in PwMS compared to controls and was also consistently associated with relapse frequency and greater disability.[32,77,78] Since anemia represents an increased risk for both mother and child, VD supplementation should be used. VD reduces pro-inflammatory cytokines and suppresses hepcidin mRNA transcription, meaning it may increase the availability of iron, and there is also evidence that VD may support erythropoiesis. Through these potential mechanisms of action, VD can prevent or improve anemia, in particular anemia of inflammation (pathophysiological mechanisms in).[79]

Thrombocytopenia

Thrombocytopenia in pregnant women without MS (platelet counts <150×10(9)/L) were observed to be 6.6–11.6% in the third trimester.[80,81] Moreover, epidemiological studies have shown a prevalence of ITP (immune thrombocytopenia) in MS patients 25 times higher than in the general population.[82,83] Gestational thrombocytopenia with 5–8% of all pregnant women (without MS) is the most frequent thrombocytopenia with 2/3 and is mild, asymptomatic without evidence of thrombocytopenia in the anamnesis and without increased risk for mother and child. The thrombocyte values are mostly between 130 and 150×10(9)/L, but almost always >70×10(9)/L[84,85] and return to normal within 2 weeks postpartum.

A primary ITP with platelet counts <100×10(9) is observed in 1–4% of gravidity, predominantly in the first and early second trimester. In ITP, which is caused by platelet antibodies (IgG class AK against glycoprotein complexes of the platelet membrane), AK can lead to thrombocytopenia in newborns due to diaplacental crossing. Therefore, such patients require special care during delivery and interdisciplinary monitoring of the newborn.[85]

Differential diagnosis of alemtuzumab-induced secondary thrombocytopenia in MS therapy is difficult because the determination of thrombocyte-AK in thrombocytopenia is technically complex, only available in specialized laboratories and interpretation is problematic due to different test systems. Alemtuzumab, a humanized monoclonal antibody against the glycoprotein CD52, causes depletion and repopulation of B lymphocytes and T lymphocytes, leading to prolonged changes in the adaptive immune system. It is used in patients with relapsing-remitting MS with (highly) active course. An extended differential diagnosis of thrombocytopenia in pregnancy can be found in the overview by Gernsheimer et al as well as Bergmann and Rath.[81,85] From a prophylactic point of view, an optimal 25(OH)D serum level should be achieved to avoid ITP. At very low VD values the ITP cases also showed a lower number of thrombocytes.[86–89]

Maximizing therapeutic opportunities to delay the transition from RRMS to secundary progressive multiple sclerosis (SPMS)

If anxiety is defined as "a feeling of worry, nervousness, or discomfort about something with an uncertain outcome," this applies unreservedly to PwMS. The anxiety of recurrences with the risk of being "wheelchair-bound" must also be reduced by using effective relapse therapy and all current therapeutic findings to stop further neurodegeneration. The permanent "negative stress" (fear of increasing disability) increases the

manifestation of depression, anxiety and fatigue.[75] If 36–54% of PwMS are confronted with anxiety and studies have clearly shown that anxiety (and depression) is also associated with cognitive impairment,[90] therapy counseling "in an open and honest partnership" with our PwMS is a conditio sine qua non.[91] The questionable association between "depression" and "DMT therapy" was investigated by Gasim et al (side effects of DMT with regard to psychiatric comorbidities in natalizumab, dimethylfumarate, teriflunomide and alemtuzumab).[92] DMTs have not been associated with an increased risk of adverse psychiatric effects and some may even reduce the incidence of depressive symptoms. This may reflect either a positive direct effect of immune modulation or an indirect effect resulting from a positive influence on disease activity or course.[92] PwMS with progressive course of MS also showed an increase in pain and disability.[93] To improve the well-being of PwMS, the latest research findings should quickly be put into practice as one way to reduce anxiety and depressive states. Giovannoni advocates for motivating PwMS as an effective disease-modifying therapy, albeit with side effects, in order to limit cognitive deficits.[91] Early cognitive impairment combined with progressive brain volume loss can only be stopped if the available therapeutic drugs are used. Since cognitive dysfunctions affect about 40–70% of PwMS over the course of their lives, can have a progressive course and since there is no established treatment, higher VD values should be sought, as Cortese et al at the 34th Congress of ECTRIMS 2018 demonstrated by a study that early VD supplementation could be neuroprotective.[94] High-dose VD supplementation (4,000 IU/day) improved non-verbal (visual) memory after 18 weeks, especially in those individuals where 25(OH)D levels were <75 nmol/L.[95]

It is essential to slow down the transition to SPMS if CMs such as anxiety, depression and personality changes, are to be reduced. In a survey, 80% of PwMS reported that neurologists and other caregivers never talked to them about "brain volume loss" or "brain atrophy". 77% of MS patients would be more open to further treatment if they were informed about this "creeping dementia".[91]

Although SPMS is associated with severe, irreversible disabilities, the medical literature focuses on the highly effective anti-inflammatory therapy of RRMS.[32] Fifty percent of RRMS patients experience the transition to SPMS without therapy in about 10 years and 90% in 20–25 years. DMTs can prolong these times. However, about half of patients with SPMS do not receive DMTs or the drug was not sufficiently efficient.[96] Anti-inflammatory treatment loses effectiveness in the late stage of RRMS and early progressive stage of SPMS and neurodegeneration predominates.

Such neurodegeneration affects the damaged brain and spinal cord, where the functional reserve capacity is exhausted, leading to a progression of disability with all its facets. Since the drugs available today can only prevent or curb progression to a limited extent, priority must be given to preventing the conversion of RRMS to SPMS. Whether the progression of neurodegeneration can be influenced by siponimod or simvastatin[97] is currently being investigated for siponimod in the EXPAND study (NCT01665144).[98] Siponimod is a second generation selective S1P1 and S1P5 receptor modulator and a further development of fingolimod. Evaluations to date have shown a positive oral effect at a daily dose of once 2 mg. Siponimod reduced the risk of disability.[98] The US Food and Drug Administration (FDA) has approved siponimod tablets 2019 to treat adults with relapsing forms of MS (RRMS), including CIS, and active secondary progressive disease. The manufacturer has also applied to the European Medicines Agency (EMA) for 2019 approval.

Siponimod reduces sNfL levels in the blood of SPMS. The sNfL blood levels are elevated in RRMS and SPMS and reflect neuronal damage.[6] Patients in a progressive stage who have a clinical manifestation with cognitive impairment and neuropsychiatric dysfunction may experience dramatic effects on their quality of life. Evidence that simvastatin (two times 40 mg/day), with its immunomodulatory and neurotrophic properties,[99] has a positive effect on frontal lobe function and improves physical quality of life and may expand the individual therapeutic repertoire in SPMS.[100–102] This high daily dose of simvastin reduced annual brain atrophy by 42%.[102]

Muris et al were able to demonstrate that low serum vitamin D levels (25(OH)D) lead to early conversion to SPMS.[103] In a national study in the Netherlands, a follow-up study with a minimum period of 3 years was conducted with 554 MS patients with a serum baseline of 25(OH)D and an EDSS. This national study was carried out in 2 centers of the Netherlands located at 51 degrees north latitude.

Vitamin D status is lower in SPMS patients than in RRMS. SPMS patient with a short RRMS duration also have low diagnostic 25(OH)D levels.

VD status is not only associated with the risk and onset of MS, but also influences the degree of disease activity

and progression. A 25 nmol/L higher VD level was associated with a 15% lower risk for later new T2 lesions in MRI and about 1/3 reduction for the risk of new gadolinium (Gd) enriching lesions.[104] The VD level is key for therapeutic success. A 50 nmol/L higher serum-25(OH)D level was associated with a 31% lower rate of new lesions.[105] VD values ≥100 nmol/L had a 47% lower rate of new T2 lesions and new Gd-enriching lesions compared to patients who had a VD level of 50–75 nmol/L.[105] VD values ≥100 nmol/L had a 47% lower rate of new T2 lesions and new Gd-enriching lesions compared to patients who had a VD level of 50–75 nmol/L. VD values ≥100 nmol/L had a 47% lower rate of new T2 lesions and new Gd-enriching lesions compared to patients who had a VD level of 50–75 nmol/L.[105] VD levels also showed an inverse correlation to grey matter volume loss, with 25 nmol/L higher 25(OH)D values associated with 7.8 mL higher grey matter volume (overview at).[106] There is evidence that insufficient 25(OH)D levels are associated with cognitive impairment and VD levels above 100 nmol/L improve executive function.[107] Since cognitive deficits have a high relevance in the everyday and professional lives of PwMS, even the slightest therapeutic effects should be taken advantage of.

Sun exposure, latitude gradient and vitamin D levels

The ultraviolet radiation (UVR) and the dietary intake of vitamin D (eg fatty fish, fortified foods) are decisive for the personal vitamin D level. A greater distance from the equator (higher latitudes) and the number of months with little sunshine increases the vitamin D deficiency. Other factors such as race, ethnicity (Blacks, Hispanics, Whites), genetic susceptibility, climatic variation, sun-seeking behaviors and clothing habits play a role.[108] There are differences between White patients, Blacks or Hispanics of a Mexican background. There is also evidence that UVR itself has immunological effects independent of the vitamin metabolic pathway[109] Sun exposure appears to be an important factor in reducing the risk of MS in all ethnic groups, especially in Blacks and Hispanics. A dark skin tone does not weaken the immunological effect.[110] Higher lifetime UVR exposure was associated with a lower risk of MS independent of serum 25(OH) D levels in Blacks and Whites with a similar magnitude of effect that did not reach statistical significance in Hispanics. Higher serum 25(OH)D levels were associated with a lower risk of MS only in Whites.[111]

Rito et al investigated vitamin D and disability in RRMS in PwMS with Hispanics and Mexican background. No correlation was found between vitamin D levels and EDSS score, annual relapse rate (ARR), progression index (PI) or duration of disease. The limitation of this study is that the VD levels in summer were determined and the mean vitamin D level for PwMS was insufficient (22.3 ng/mL).[112]

Influence of parental MS with comorbidities on the life path of children

The course of the disease also has a serious impact on the lives of children whose parents have MS, even late into adulthood. The social impact of MS is rarely discussed.[91] It is undisputed that CM additionally burden family life. The children are not only confronted with the problem of caring for the sick parent, they have to hide their feelings and desires. Fear and depression as well as shame are problems that have to be dealt with and can lead to a lack of openness. A greater disability of the MS parent (especially the mother) through mental and physical CM has an impact on children's health development.[113] At the age of 30, they were less often employed, and at the age of 30–40 they received a disability pension more often and their annual gross income at work was lower than that of their peers.[114]

Future aspects of vitamin D supplementation

Carlberg et al developed the concept of the "personal VD response index" and were able to classify persons receiving a VD supplementation as high, medium and low respondents. The "personal VD response index" describes the effectiveness of the molecular response to supplementation with VD. For example, persons with a low VD response index should aim for a high VD status in order to derive maximum benefit from VD's protective role. This suggests that the dose of daily VD supplementation should be adjusted to the VD response index of the individual and not only to VD status.[115] Measuring "vitamin D sensitive molecular parameters" would facilitate the controversial discussion about the recommended VD dose, although the determination in practice is still in the distant future.

Monitoring of the safety of (long-term) VD therapy

For all MS patients, including during pregnancy, multiple benefits can be expected from a VD supplementation of

Table 4 Positive effects of an optimal vitamin D status (target at least 25(OH)-D serum levels of 40–60 ng/mL [100–150 nmol/L]) on comorbidities, pregnancy and disease progression in MS

Depression/anxiety	25,28–30,142
Asthma	37–39
Osteoporosis	46–48
Pain, migraines/headache	51–61
Neurocognitive functions	49,94,95,132
Cardiovascular diseases (VD levels between 40 and 100 nmol/L)	129
Anemia (haemoglobin<12 g/dL for women, <13 g/dL for men)	78,79,86
Pregnancy (minimum intake of VD 4,000 IU before conception and throughout pregnancy, (minimization of preterm births, preeclampsia, gestational diabetes, positive influence on brain development, lung maturation and function of the fetus, postnatal asthma prevention).	65,127
Course of multiple sclerosis[143] reduction of risk of relapse, reduction of new T2 lesions and increase in size, reduction of gadolinium-enriching lesions, reduction of brain atrophy, reduction of transition from CIS to definitive MS.[30] sNfL levels as markers of axonal degeneration reduced by approximately 30% in PwMS [without DMTs]	72

Abbreviations: VD, vitamin D; CIS, clinically isolated syndrome; sNfL, serum neurofilament light chains; DMT; disease modifying treatment.

2000–5000 IU/for all forms of MS from a practical point of view, according to the current state of knowledge (Table 4). Before starting supplementation, it is useful to determine the baseline values of 25(OH)D and serum Ca in order to estimate the "saturation dose", including seasonal influences or obesity (requires about 2.5 times higher dose) in advance. An additional intake of calcium should be avoided at all costs. VD serum levels of at least 30 (40)–60 ng/mL (75[100]–150 nmol/L) are desirable. A control should be performed after about 3 months of treatment, with laboratory chemical monitoring dates varying depending on the individual baseline situation (initial VD serum level, VD dose level). There is little risk of hypercalcemia or other side effects with moderate add-on treatment[116] even with daily intake of VD up to 10,000 IU/day (46). Although it is known that VD increases the absorption of calcium from the gut, this effect is generally subject to physiological regulation.

At serum Ca levels above 80 nmol/L, further intestinal Ca absorption is not increased. There is a balance between net Ca absorption from the intestine and calcium excretion in the kidney. An excessive production of the active 1.25 (OH)D3 results in an adequate production of the catabolic enzyme 24-hydroxylase (*CYP24A1*), largely avoiding VD toxicity.[117] A possible (theoretical) mechanism of VD toxicity could be based on changes in the metabolic pathway by displacement of 1.25(OH)D from its binding protein (DBP). If the DBP binding capacity is exceeded, eg caused by 25(OH)D itself, hypercalcemia could occur.[46]

In long-term therapy with high VD doses, it is mainly the 25(OH)D serum level, but also the serum calcium and phosphate value, that must be determined in order to detect VD overdose/intoxication in good time. In very rare cases an imbalance of Ca/phospor homeostasis can occur without VD hypervitaminosis and in rare cases extremely high VD levels cannot cause hypercalcemia. Because VD intoxication without VD hypervitaminosis has been verified in anecdotal reports, a determination of Ca excretion in 24-hour collecting urine (hypercalciuria?) can optionally be performed to confirm this.[118] VD toxicity would be indicated by serum Ca above 2.75 mmol/L. The molar calcium/creatinine ratio in urine (>1) can also be used for identification.[119] The determination of parathyroid hormone (PTH) is more complex, whereby the 25(OH)D serum level is inversely associated with the PTH level. Elevated PTH serum levels were found at 40% (adults) with 25(OH)-values ≤50 nmol/L, while at ≤25 nmol/51% the PTH level was elevated "biochemical hyperparathyroidism".[120]

The period of monitoring should depend on the daily VD dose level, the season (summer/winter) and the interim control results (laboratory values), with a minimum of 6 or 12 months of controls required.

Based on the patient's medical history, it should be determined whether PwMS should carry out supplementation with high-dose VD up to 60,000 IU/the ("Coimbra protocol") as additional therapy with VD doses. This treatment protocol requires tight control of serum Ca and PTH levels and such extreme dosing should only be performed as part of a study. The PTH level should be close to the lower limit of the normal range, too low a PTH level would indicate a toxic effect of VD. In addition, a low-calcium diet without dairy products and a daily intake of 2.5 L of liquid is required to avoid kidney damage.[121]

Another possible cause of VD hypervitaminosis may be low activity of the catabolic enzyme 24-hydroxylase (*CYP24A1*). Mutations in the *CYP24A1* gene are associated with a partial or total loss of 24-hydroxylase activity, which may result in hypercalcemia.[117] In addition, nontoxic VD levels (<375 nmol/L) or nonhypervitaminotic levels (<250 nmol/L) have shown very rare cases of intoxication.

The threshold for toxic symptoms is generally a plasma level of about 750 nmol/L (300 ng/mL) 25(OH) D3. Considering this value and considering that the generally accepted upper limit of the normal range has been established as 250 nmol/L (100 ng/mL), there is still a wide margin of safety upwards, as values above this were not associated with toxicity (Tables 5 and 6).[122]

How do PwMS use vitamin D supplementation?

In an international survey (Internet platform) of over 2,000 PwMS more than 4 years ago, more than 81.8% took VD, with the calculated daily dose lying between 2000 and 5000 IU/day, while 18.2% did not supplement VD.[123] The "VD problem" will have to play a key role in improving the quality of life.

Neurorehabilitation and comorbidities

CM could become a central problem in rehabilitation. PwMS with CM showed more severe changes in MRI as an indication of increased neurodegeneration and demyelination. Anxiety, depression, hypertension, migraine and hyperlipidemia were the most common concomitant diseases in 885 participants observed over 2 years.[32] Therapeutic observation of CM could help to minimize the devastating effects of the disease. During a routine clinic visit within one year, CM was registered between 6 and 29% (Table 3) of patients. There may be a temporal discrepancy for when current clinical symptoms manifest (clinical-radiological paradox). This "time lag" could be explained by an existing functional reserve and possible plasticity mechanisms. When these compensating mechanisms are exhausted, however, a progressive clinical stage will very quickly set in.[124] The observation of (autoimmune) CM as an indication of a possible clinical and radiological progression of MS and the therapeutic attempt to stop this progression could impact patient quality of life. During rehabilitation, it is possible to discuss the possibilities of intervention with PwMS and to set the course for further therapies at home. These intentions will be pursued all the more frequently when it is realized that MS patients with migraine, hyperlipidemia and/or high stress with three or more CM have a higher rate of deterioration.[32] Since vascular CM are associated with faster disability progression and simvastatin affects vascular function and has immunomodulatory and neurotrophic effects, statin therapy may be a possible extension of the therapeutic arsenal. The potential for side-effects is known from years of use in lipid therapy.

As the prevalence of cognitive deficits is observed to be about 34–65%, the National MS Society, USA has asked experts (clinicians, rehabilitation physicians, researchers and PwMS) to develop recommendations for cognitive screening and cognitive impairment management in conjunction with existing CM to improve the quality of life of these groups of people in education, at work or at home. The Consortium of Multiple Sclerosis Centers and the International Multiple Sclerosis Cognition Society support the extensive concrete recommendations

Table 6 Conversions for laboratory values of different units

Conversions: 25-hydroxyvitamin D-level [25(OH)D]: ng/mL x 2.5=nmol/L
Equivalences: 1 ng/mL=2,5 nmol/L
Vitamin D conversions: 1 µg vitamin D=40 IU, 1IU=0.025 µg

Table 5 Orienting 25(OH)D levels for the practice

Interpretation of vitamin D status by measuring serum 25(OH)D level (calcidiol). No international consensus on definition of "VD deficiency" and no standard definition or agreement on "appropriate", "sufficient", "optimal" 25(OH) levels and VD targets[49] Comparisons from studies are made more difficult by the fact that inconsistencies exist in the "cutoff levels"[113]
≤20 ng/mL (≤50 nmol/L) VD-deficiency
21–29 ng/mL (51–74 nmol/L) VD insufficiency
≥30 ng/mL (75 nmol/L) VD-sufficiency
40–60 ng/mL (100–150 nmol/L "Ideal VD-level
≤100 ng/mL (≤250 nmol/L) "upper safety limit" of the VD level

Abbreviation: VD, vitamin D.

issued and call for increased awareness and education of physicians and patients about the prevalence, effects and appropriate management of cognitive symptoms (detailed recommendations in).[125]

Relationship of comorbidity to disease activation

The occurrence of mood swings, anxiety and depression can no longer be seen as a consequence of disease awareness and disability, but as something more complex.

Rossi et al found a correlation of mood changes with intrathecal inflammation and activities in cerebral MRI. The measurement of cytokines in cerebrospinal fluid revealed an association of IL-2 with anxiety and IL-1ß/TNF-α with depression. PwMS with active disease had higher anxiety and depression values in psychiatric examinations (Beck Depressions Inventory, BDI; State/Trait Anxiety Inventory, STAI). In a small group of 20 patients with active MS, 5-day methylprednisolone pulse therapy (1,000 mg/day) was performed and anxiety levels improved. This study suggests that inflammation itself may be responsible for mood swings and that this finding must be used to evaluate anxiety as an early indication of a subclinical relapse in RRMS before clinically abnormal symptoms occur.[126]

Conclusion for practice

According to the current state of knowledge, VD supplementation should be carried out with the aim of achieving the following goals:

- Correction of VD insufficiency detectable in the vast majority of MS patients (minimum target: VD serum levels 30–60 ng/mL (75–150 nmol/L). Safety in long-term VD supplementation by controlling serum VD, Ca and phosphate levels
- Prophylaxis against infections
- Prevention of osteopenia and osteoporosis as well as consecutive fragile fractures
- Reduction of comorbidity and slowing of disease progression

"The practice of medicine remains more an art than a science" (Gavin Giovannoni, 2017)[91]

"A gestational dose of vitamin D per day keeps the MS doctor away " (Ruth Ann Marrie, Martin Daumer, 2017)[130]

Disclosure

The author reports no conflict of interest in this work.

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