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Review

Assessment of evidence for a protective role of vitamin D in multiple sclerosis

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ABSTRACT

Evidence for a role of vitamin D insufficiency in determining risk in Multiple Sclerosis (MS) is supported by studies in both pediatric- and adult-onset patients. The potential role of vitamin D in modulating MS disease activity is an area of active clinical trials research, and the possibility of primary disease prevention with vitamin D supplementation in early life is an emerging concept. With Sir Austin Bradford Hill's criteria as a framework, the present review assesses the evidence for a causal relationship between vitamin D insufficiency and the pathobiology of MS, and discusses rationale for future clinical trials with vitamin D.

Contents

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1. Introduction

Although MS has been reported in most world regions, prevalence varies between different ethnic groups and across diverse geographical regions, supporting both genetic and environmental contributions to MS biology [1–4]. The prevalence of MS is greater in areas with temperate rather than tropical climates, it increases with distance from the equator and is inversely associated with average ambient UVB [5–10]. The striking difference in prevalence of MS and some other autoimmune diseases as a function of latitude has implicated vitamin D status as a determinant of risk. The potential role of vitamin D in several autoimmune diseases, particularly MS, has been the subject of several manuscripts and reviews [11–30]. While it is best known for its role in calcium homeostasis and bone mineralization, vitamin D is also involved in modulating immune function and cell proliferation, differentiation, and apoptosis [31]. In vitro and animal models of immune cell behaviour and central nervous system inflammation have demonstrated a pro-inflammatory impact of vitamin D insufficiency and an anti-inflammatory role for vitamin D supplementation.

At present, the totality of evidence for a protective role of vitamin D in MS has been deemed strong enough by some to warrant recommending vitamin D supplementation to people with MS and to individuals considered at high risk for MS [12]. Other investigators advocate large primary prevention population-based studies or randomized controlled Phase II and III studies in MS patients [19,26,32].

The present review will provide a brief outline of vitamin D metabolism, discuss the evidence for a causal relationship between impaired vitamin D status and MS and whether this evidence is sufficient to establish causality, and will propose concepts important in determining the therapeutic role for vitamin D in MS.

2. Vitamin D metabolism

In humans, cholecalciferol (vitamin D_3) is produced in the skin following exposure of 7-dehydrocholesteol to ultraviolet B (UVB) radiation. Vitamin D_3 can also be obtained from the diet; it is naturally present in oily fish and egg yolks and, in some countries, is added to foods such as milk, margarine, yoghurt, orange juice, and cereal. Estimating dietary intake of vitamin D is challenging for several reasons: Variation in mandatory fortification rules means that, between countries, different foods are fortified with varying amounts of vitamin D; discretionary fortification results in only certain brands or types of those foods containing vitamin D in some countries; and the amount of vitamin D naturally present in some foods may vary dramatically. For instance, natural vitamin D in animal-derived food products may vary with the season [33], the vitamin D content of the animals' diet [34], or other aspects of the animals' environment [33,35]. Vitamin supplements may contain either vitamin D_3 or ergocalciferol (vitamin D_2) and concentrations generally range from 50 IU in multivitamins to 1000 IU or more in products containing only vitamin D; vitamin D_2 is also present in some mushrooms, is added to some nut milks and is generally considered less bioactive than vitamin D_3 [36–38].

Following either cutaneous synthesis or ingestion, vitamin D is transported to the liver bound to the vitamin D binding protein (VDBP, also known as group-specific component of serum or Gc-globulin) [39]. Vitamin D is metabolized to 25-hydroxyvitamin D_3 [25(OH)D] by the hepatic cytochrome P450 mixed-function oxidases (CYP) CYP2R1 (microsomal) and CYP27A1 (mitochondrial) [40]. The concentration of the 25(OH)D metabolite in the serum represents vitamin D obtained from both UVB-catalyzed synthesis and diet, and is the accepted biomarker for vitamin D nutritional status [41,42]. The 25(OH)D metabolite is further hydroxylated by renal CYP27B1 to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D; calcitriol], the most bioactive of the naturally derived vitamin D metabolites. Vitamin D signaling is mediated by calcitriol binding to the vitamin D receptor (VDR), which forms a nuclear heterodimer with the retinoid X receptor. This complex is capable of binding to genomic vitamin D response elements (VDRE), modulating expression of a variety of genes. Renal-derived calcitriol circulates bound to VDBP and acts as a potent hormone targeting bone, kidneys and the intestines to modulate calcium homeostasis. Numerous extra-renal tissues also activate vitamin D to calcitriol for local regulation of multiple biological processes including immunological recognition of self [43,44]. Calcitriol is regulated, in part, through a biofeedback loop in which the calcitriol-induced gene, CYP24A1, encodes an enzyme that initiates the catabolism and clearance of vitamin D-related metabolites via hydroxylation of carbon 24.

3. Assessment of evidence for vitamin D in MS

In 1965, Sir Austin Bradford Hill proposed a set of viewpoints to aid in assessing the evidence for a causal relationship (**Panel 1**) [45]. Hill's criteria are arguably most appropriate for assessing evidence of causality under simplistic models of cause and effect whereby a specific outcome is attributed to a single causal agent. The criteria do not sufficiently capture the complexity of the relationship between causal complexes comprised of environmental and genetic risk factors that may be variably necessary or sufficient to induce a heterogeneous disease such as MS [46]. Nevertheless, the criteria do provide a generally well-rounded structure for a critical evaluation of evidence for causality.

4. Assessing the evidence for a relationship between vitamin D status and MS: The Bradford Hill criteria

4.1. Strength

The strength of an association can be defined as the magnitude of difference in the risk, odds, or severity of a disease outcome based on variations in exposure to the factor of interest. A strong association supports a causal relationship between two entities. However, a weak association does not necessarily negate a causal relationship, particularly if the association occurs only in certain contexts. How strong are the links between MS and vitamin D status—as defined by circulating 25(OH)D—or determinants of vitamin D status such as dietary intake of vitamin D, or sun exposure?

4.1.1. Vitamin D status in utero

Several studies have demonstrated a month of birth effect in MS cohorts. In Northern Sardinia—a region with very high MS incidence—an excess of spring births was observed in MS cases (29.4%) relative to their unaffected siblings (22.1%, $P=0.008$) and to the general population (24.6%, $P=0.036$) [47]. Pooled month of birth data from MS patients in Canada, Denmark, Great Britain and Sweden ($n=42{,}045$) demonstrated an excess of MS cases born in May (odds ratio (OR) 1.10, 95% confidence interval (CI) 1.07 to 1.13) and fewer than expected births in November (OR 0.91, 95% CI 0.87 to 0.95) [48]. Overall, the risk of MS in those born in May was 13% higher than

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for those born in November (95% CI 5% to 22%). Given the low ambient sunlight in winter months in the countries studied, these results could be interpreted to suggest that low serum 25(OH)D during pregnancy or low vitamin D in the breast milk during first few months post-birth influence subsequent MS risk [49,50].

4.1.2. Childhood sun exposure and MS risk

Four studies have demonstrated that high sun exposure in childhood is related to a decreased risk of MS. In a case–control study ($n=126$ MS and 272 controls) from Tasmania, high sun exposure between the ages of 6 and 15 years was associated with a decreased risk of MS (OR 0.31, 95% CI 0.16 to 0.59) even after adjustment for skin pigmentation and smoking status prior to MS diagnosis [3]. Furthermore, the study also found that moderate-to high grade (grades 4–6) actinic damage, a marker for lifetime sun exposure, was independently associated with a decreased risk of multiple sclerosis (OR 0.32, 95% CI 0.11 to 0.88, adjusted for the same variables and sun exposure post-MS diagnosis). Similar findings were reported in Norway where increases in outdoor activities in early life, particularly at 16–20 years of age, were associated with decreased MS risk (OR 0.55, 95% CI 0.39 to 0.78) [51]. A North American study of 79 pairs of identical twins discordant for MS found that the unaffected twin reported more sun exposure during childhood than did the twin with MS: Each one-unit rise in the sun exposure index score (range −9 to +9; 0 indicating no sun exposure difference, 9 indicating more relative sun exposure compared to twin in each variable) was associated with an OR 0.75 (95% CI 0.62 to 0.90) [52]. Finally, a case–control study consisting of participants from Cuba, Martinique and Sicily—regions of varying latitudes, ambient UVR, and MS prevalences—also observed a consistently reduced risk of MS related to measures of sun exposure before age 15, and increased risk of MS related to sun protection practices before age 15 years of age [53]. For instance, in multivariate analyses, weekday sun exposure of ≥ 1 h per day was associated with decreased MS risk (OR 0.90, 95% CI 0.85 to 0.98) while wearing pants when exposed to sunlight was associated with increased risk (OR 1.90, 95% CI 1.10 to 3.20). These four studies provide evidence supporting the hypothesis that sun exposure in childhood conveys protection against MS.

Further support for the importance of sun exposure in childhood in determining MS risk also comes from studies investigating place of childhood residence, migration patterns, and ethnicity of MS populations. Migration between areas of disparate MS prevalence before or during adolescence results in the individual adopting the risk of the new region. Migration in adulthood, however, does not influence MS risk [54–58]. In a study comparing the ancestry of pediatric and adult MS patients living in the same city, the pediatric MS patients were far more likely to be first generation Canadians, and to have parents born in world regions of low MS prevalence [59].

4.1.3. Vitamin D status prior to MS diagnosis

In a case–control study nested within a prospective cohort of over 7 million US military personnel, a decreased risk of MS (OR 0.38, 95% CI 0.19 to 0.75) was observed among white participants (148 cases, 296 controls) with serum 25(OH)D concentrations in the highest quintile (99.1–152.9 nmol/l) compared with the lowest quintile (<63.3 nmol/l) [60]. This paper will be discussed further below in the section on dose–response.

4.1.4. Vitamin D status at the clinical onset of MS

The first clinical manifestation of MS presents with acute neurological deficits in vision, strength, balance, or sensation, typically associated with evidence for CNS inflammation in cerebrospinal fluid (oligoclonal bands) and on brain imaging [61]. This first attack of demyelination can also represent a monophasic illness without subsequent relapses and without a future MS diagnosis. Determination of vitamin D status at the time of this first attack provides insight into whether vitamin D status predicts individuals destined for further relapse (and thus, confirmation of MS). Serum 25(OH)D levels in adults recently diagnosed with MS are low relative to controls. In a study from Finland, serum 25(OH)D concentrations (mean ± SD) were significantly lower in adults diagnosed with MS in the period of June through September (58 ± 3 nmol/l) compared to healthy controls samples in the same time period (85 ± 8 nmol/l, $P=0.022$) [62].

While the impaired vitamin D status at first attack or at the time of relapse (and MS diagnosis) provides support for vitamin D insufficiency in MS, it is also possible that low vitamin D concentrations occur as an epiphenomenon of acute illness. Serial evaluation of vitamin D status in individuals following a first attack are required to determine whether vitamin D concentrations remain low in individuals destined for further relapse.

4.1.5. Vitamin D status in individuals with established MS

Further to the above discussion, low serum 25(OH)D concentrations have been recorded at the time of clinical relapses in adults with established MS. Two Finnish studies [32,62] and one Argentinian study [63] reported that mean serum 25(OH)D concentrations were lower during relapses than remission. Similarly, researchers working in Tasmania reported a inverse relationship between relapses and both estimated serum 25(OH)D ($r=-0.31$, $p=0.057$) and erythemal UV (EUV; from EUV data 1.5 months prior to relapse; relapse rate ($r=-0.32$, $p=0.046$)) [64]. An inverse relationship was also observed between serum 25(OH)D levels in Tasmanian RRMS patients and risk of relapse, with each 10 nmol/l increase in 25(OH)D resulting in a 12% decrease in relapse risk [65] Also, amongst patients in the USA with pediatric-onset MS or clinically isolated syndromes (CIS), vitamin D status predicted subsequent rate of relapse: Each 25 nmol/l increase in seasonally adjusted 25(OH)D concentrations predicted a 34% decrease in subsequent relapse rate (incidence rate ratio 0.66, 95% CI 0.46 to 0.95) [66].

Vitamin D concentrations also correlate with some types of MRI evidence of MS disease activity. In one study, low serum 25(OH)D levels predicted an increased likelihood of gadolinium (Gd)-enhancing lesions in MRI scans performed in the subsequent two month period [67]. Although, as mentioned above, lower serum 25(OH)D was observed in relapses, serum 25(OHD did not correlate with MRI burden of disease (mm^2) [32] but, importantly, Gd-enhanced images were not included in this study. Taken together, these results provide support for relationship between vitamin D status and active MS disease as measured by relapses and Gd-enhancing lesions on MRI.

Important in the interpretation of vitamin D status in individuals with established MS is the confounding influence of disease-related limitations in physical and outdoor activity that may result in decreased sun exposure and thus, vitamin D status. Furthermore, Uhthoff's phenomenon, a transient heat-induced re-emergence of symptoms in previously demyelinated pathways, can also result in avoidance of sun or warm environments [68]. It is thus, important to characterize disability, physical activity and sun exposure in vitamin D-related studies of patients with MS. It is also important to obtain a careful dietary history that includes information on the use of vitamin supplements. The Internet provides numerous links to studies of vitamin D in MS and some neurologists already recommend vitamin D to those with MS [12]; thus, it is likely that many MS patients will take measures to raise their vitamin D status—such as increasing consumption of fortified dairy products or fish, taking vitamin D supplements or even increasing their sun exposure. Motivation to improve vitamin D status could be disproportionately higher in individuals with more active disease; therefore, unless supplemental vitamin D intake is well characterized, the ability to evaluate vitamin D status and MS disease activity is impaired. Serial serum 25(OH)D analyses of individuals with established MS will be important to determine whether vitamin D concentrations remain low independent of relapse, and whether such

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values differ between MS patients who report more or less active lifestyles or vitamin supplementation during the period of sampling.

4.2. Consistency

The underlying principles of consistency are that the cause of the disease should be constant across variable settings across different times and in different populations and that the relationship remains consistent even if other factors vary. While the relationship should remain constant, it is important to note that the relative risk conveyed may vary due to interactions with other factors. For example, even if vitamin D insufficiency is consistently associated with MS risk across diverse world regions, the relative contribution of vitamin D may differ due to interaction with variants in vitamin-D responsive genes such as HLA-DRB1*15 [69] (Fig. 1). Furthermore, consistency of association must be considered and evaluated to determine whether the association alone is sufficient for disease. In other words, vitamin D insufficiency is common in temperate climates, yet not all individuals with low serum 25(OH)D concentrations develop MS. The absence of MS in these individuals does not, however, negate the potential importance of vitamin D insufficiency as a risk factor for MS.

4.2.1. Low sun exposure and MS

Discussed further in other sections, low sun or UVR exposure—a measure that may be associated with lower circulating 25(OH)D—from varying regions is consistently associated with increased risk of MS [3,51–53], increased prevalence of MS [5,10,19,70], and increased risk of MS-related mortality [71].

4.2.2. Vitamin D status in MS

Consistency of data relating to impaired vitamin D status and MS is evidenced by studies of both adults and children with MS in Australia [72], the United States [60,66,73–75], and Europe [32,76–78]. While low vitamin D concentrations in MS patients have been documented across multiple studies, a few studies have failed to demonstrate this association [79–81] and one study found low 25(OH)D in the male MS patients but not in females [82]. Lacking to date are studies of vitamin D status in world regions where MS is exceptionally rare, such as peri-equatorial countries, Africa, and certain regions of Asia. Evidence of vitamin D insufficiency at the time of first attack in the rare individuals diagnosed with MS in such regions would strongly support the notion of consistency of association between vitamin D and MS.

4.2.3. Vitamin D dependent rickets and MS

Torkildsen et al. [83] reported a case series of three adult females with MS who, during childhood, were diagnosed with and treated for vitamin D dependent rickets type 1 (VDDRI), a rare genetic condition that ablates activity of the enzyme that converts 25(OH)D to $1,25(OH)_2D$. The chance co-existence of this extremely rare genetic form of rickets and MS is highly improbable. All patients received vitamin D_3 or calcitriol therapy following the diagnosis of VDDR1 and were reported to have "normalized" serum 25(OH)D following treatment; however, the most appropriate treatment for this condition is calcitriol, not vitamin D, and serum concentrations of 25(OH)D were not reported. This case series suggests that risk of MS may have been conferred pre-VDDR1 diagnosis when these individuals lacked normal vitamin D-related signaling. Further evidence for consistency comes from follow-up study discovered that all three of these patients carried at least one copy of the vitamin D-responsive HLA-DRB1*15; the significance of which will be discussed in another section [84].

4.3. Specificity

According to the Hill criteria, the likelihood of a causal relationship increases with the specificity of the relationship between a factor and an outcome. However, in describing the utility of this criterion, Hill himself noted that it was the least important of the criteria and did not always apply [45]. Furthermore, it is important to define "specificity". Specificity could be interpreted as a disease-specific association or more generally as specificity at the level of biological mechanisms. Given that calcitriol modulates expression of an as yet unknown number of genes in many tissues and organs, the manifestations of suboptimal vitamin D status could be relevant to many diseases and could operate either acutely or chronically, dependent upon stage of life, status of other nutrients [85], and genetic variants in vitamin D metabolism [86,87] or response [69]. Vitamin D insufficiency has been associated with systemic lupus erythematosus [88], inflammatory bowel disease [89], asthma and allergy [90], type 1 diabetes mellitus [91], rheumatoid arthritis, and other inflammatory disorders [92,93]. Thus, if one considers specificity as more broadly referring to

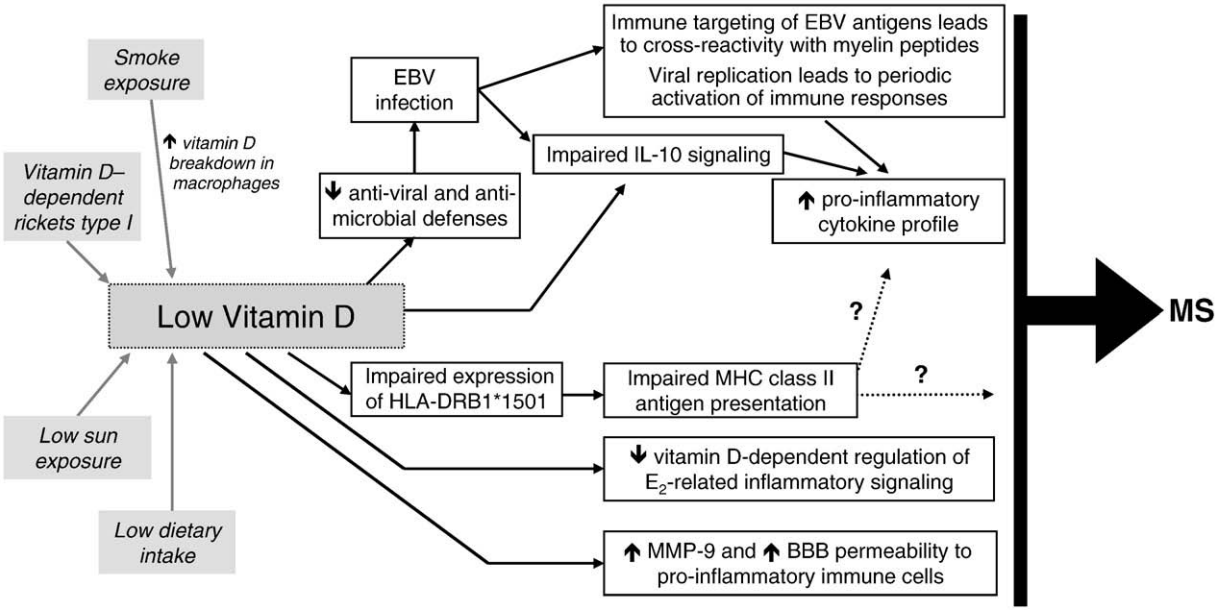

Fig. 1. Determinants of low or impaired vitamin D status and hypothesized intermediary mechanisms underlying increased risk and severity of multiple sclerosis.

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inflammation or misdirected immunological recognition of self tissues, then an argument for specificity between vitamin D status and MS (as a representative disease) can be made.

4.4. Temporality

An important determination of causality is evidence that the exposure precedes outcome. If impaired vitamin D status increases risk of MS, then it can reasonably be expected that vitamin D deficiency or suboptimal vitamin D status would precede MS onset.

Serum 25(OH)D levels are rarely evaluated in apparently healthy individuals prior to the onset of disease; however, one study did demonstrate that vitamin D status in early adulthood was inversely related to subsequent MS risk [60].

In the absence of serum 25(OH)D measures, other studies have used season, latitude, and questionnaire-based data regarding diet and sun exposure as proxies for estimated vitamin D status prior to disease onset. Studies examining the month of birth have revealed a deficit of MS births in November [48,94], and an excess of MS in spring births [47,48,95]. The vitamin D-sensitive HLA-DRB1*15 risk allele interacts with the season of birth such that the reported relationship with risk of MS appears to be predominately driven by those carrying at least one copy of the DRB1*15 risk allele [96]. Also, earlier disease onset has been reported among MS patients born during winter in low UVR locations vs. those born in other seasons in locations with higher ambient UVR [97]. Together, these findings suggest that low vitamin D in mid to late pregnancy—due to the low ambient UVB in winter and early spring—may contribute to increased MS risk. Also, as previously discussed, several retrospective studies demonstrated that greater sun exposure during childhood and adolescence was associated with a reduced risk of adult-onset MS [3,51–53] although these retrospective reports of childhood sunlight exposure in patients with adult-onset MS are challenged by the accuracy of recall. Migration from the tropics—with year round UVB sufficient to catalyze vitamin D synthesis—to temperate regions before or during adolescence, but not afterwards, confers increased risk of MS [58]. Sun exposure is arguably the most important predictor of vitamin D status; thus, the implication of these studies is that low sun exposure, hence a high likelihood of impaired vitamin D status, is associated with increased risk of MS later in life. Regarding vitamin D supplemental intake, women who reported consuming vitamin D supplements ≥ 400 IU/day prior to onset of MS were less likely to be diagnosed with MS compared to those who did not take vitamin D supplements [98]. These studies, conducted using differing methods in unique populations and regions strongly infer an important contribution of timing of vitamin D insufficiency and subsequent risk.

4.5. Biological gradient (dose–response)

Further evidence for vitamin D as an important determinant in MS can be considered in terms of (i) the degree of vitamin D insufficiency and relative risk of MS; and (ii) the extent of vitamin D supplementation and disease risk or clinical disease response.

Evidence to support a dose–response relationship between vitamin D insufficiency and MS risk comes from studies evaluating serum 25(OH)D concentrations prior to and at the time of clinical onset of MS. In one study, risk of MS in mid-adulthood in young white adults (mean age 23 years) decreased significantly with increasing serum 25(OH)D concentrations: the odds ratio of MS associated with a 50 nmol/l increase in 25(OH)D was 0.59 (95% CI 0.36–0.97) [60].

When evaluating dose–response aspects of causation, it is important to consider whether the doses being evaluated are in the range relevant to the disease. A threshold effect may well exist, in which biological impact is notable only once this threshold is exceeded. For instance, in the 2006 Munger et al. paper [60], the authors reported a significantly lower risk of MS in white patients with serum 25(OH)D over 99.1 nmol/l but did not find a significant association between vitamin D status and risk of MS in the black or Hispanic patients ($n = 109$ cases, 218 controls). More than 66% of the black and Hispanic participants had serum 25(OH)D concentrations below 50 nmol/l and the highest serum 25(OH)D concentration was only 97.9 nmol/l and a protective effect of vitamin D was not observed. However, if circulating 25(OH)D concentrations needed to exceed 99 nmol/l to confer benefit, then a benefit of vitamin D would not be expected in these groups since the maximum 25(OH)D concentration was below 99 nmol/l. The ability to detect a dose–response requires study of populations that have serum 25(OH)D concentrations spanning the biologically relevant threshold of effect (Fig. 2).

Dose–response or a biological gradient can also be considered in terms of the observed latitude gradient and varying amounts of UVR. The rate of first demyelinating events in Australia increased by 9.6% (95% CI 7.4 to 11.8) per higher degree of latitude [99], and in both North America and France, studies demonstrated that risk of MS increases with decreasing regional UVR [10,19,70,100]. A recent study compiled global MS prevalence data from 54 studies and calculated the degree of risk contributed by numerous factors. The authors report a highly statistically significant inverse correlation between regional annual available UVR and MS prevalence; the relationship between UV and MS prevalence was so strong that it surpassed the effects of all of the other risk factors by at least 20-fold [5].

In a pooled analysis of data from Canada, Denmark, Great Britain and Sweden, the OR for increased risk of MS outcome in May births compared to November births was calculated. When the countries were examined individually, the risk of MS outcome was proportional to MS prevalence in each country and, with the exception of Sweden, increased with the average latitude of residence for the counties' population—with risk being highest in Scotland (OR 1.89, 95% CI 1.09 to 3.28), intermediate in Denmark (OR 1.22, 95% CI 1.08 to 1.38) and lowest in Canada (OR 1.13, 95% CI 1.05 to 1.22) [48].

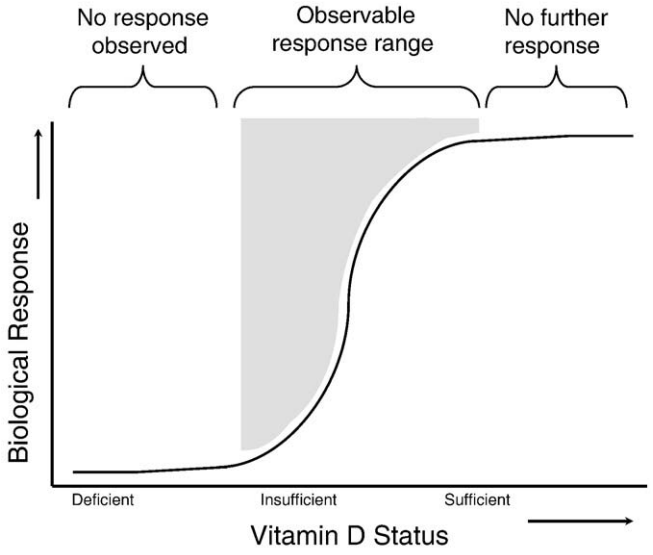

Fig. 2. Magnitude of biological response to increasing vitamin D nutritional status. Cross-sectional study of participants with ranges of serum 25(OH)D concentrations at either the low 25(OH)D or the very high levels of 25(OH)D is unlikely to yield significant dose–response related data because both groups are on plateaus of the Biological Response Curve. Likewise, if a vitamin D intervention does not succeed in elevating participants' serum 25(OH)D concentrations beyond the lower biological response plateau, it is unlikely to elicit a significant response. A significant biological response is most likely to be observed when participants' begin with insufficient vitamin D status and increase into the sufficient range. The circulating 25(OH)D concentrations defining sufficient vitamin D status remain unclear but expert consensus indicates that the minimum concentration is likely between 75 and 100 nmol/l [42].

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4.6. Plausibility

Clearly an important aspect of the Hill criterion is biological plausibility. What do we know about mechanisms that could be responsible for the relationship between vitamin D status and MS?

4.6.1. Animal studies

Biological plausibility is often easier to study in-depth in animal models of disease than in humans, and an inducible model of CNS inflammation, termed experimental autoimmune encephalomyelitis (EAE), in mice or rats provides such an opportunity for exploring the effect of vitamin D and calcitriol on EAE induction, severity and amelioration.

Administration of calcitriol prior to EAE induction prevented symptoms from developing [101–105]. Interestingly, an analog of calcitriol also demonstrated synergistic benefit when administered with interferon beta (IFN-β) [106] and additive effects with cyclosporine in the prevention of EAE [107] Calcitriol *per se* has attenuated symptoms when administered after induction of EAE [108] and has also reversed established EAE [109]. A variety of mechanisms underlying these effects have been proposed. Some of the calcitriol-related observations in EAE have been mediated via a reduction in monocyte activation [110], reduced macrophage accumulation within the CNS, reduced proliferation of self-reactive T lymphocytes in the CNS [109] and increased apoptosis of pro-inflammatory cells [111]. Also, one study of EAE, demonstrated that IL-10 signaling was essential for the calcitriol-mediated inhibition of EAE [104].

A recent set of experiments sought to evaluate the effect of relatively acute pre-induction and post-induction UVR exposure on EAE [112]. Although the authors concluded that UVR suppressed EAE independent of vitamin D_3 production, the circulating 25(OH)D levels at the time of EAE disease induction may have actually influenced EAE disease severity. In the first experiment performed, 25(OH)D concentrations were similar across groups at the time of EAE induction—despite differing pre-induction UVR protocols—and all groups experienced a similar EAE outcomes. In contrast, in the second study, 25(OH)D levels in the groups pre-treated with UVR were significantly higher than controls on the day of disease induction than in controls, and EAE was most severe in the control group. This difference in EAE outcome was observed despite the fact that circulating 25(OH)D concentrations did not remain higher in the UVR-treated groups post-induction. Thus, these UVR exposure studies suggest that UVR-stimulated vitamin D production prior to disease induction may affect subsequent EAE outcome.

Furthermore, some EAE studies have demonstrated that the effects of supplementation with vitamin D *per se* differ based on the sex of the animal. Vitamin D_3 supplementation prior to induction of EAE reduced signs of MBP-induced EAE in female mice but not in males or ovariectomized females [113]. In a follow-up study [114], administration of physiologically equivalent doses of 17β-estradiol (E_2) restored the vitamin D_3-mediated inhibition of MBP- and MOG_{35-55}-induced EAE in ovariectomized mice but did not reduced signs of EAE in the MOG_{35-55}-induced males. The authors reported synergistic interactions of vitamin D_3 and E_2 as the potential mechanism underlying the findings: Circulating E_2 was significantly elevated in the vitamin D_3 supplemented intact females mice, E_2 enhanced VDR expression within the central nervous system, and E_2 decreased expression of the vitamin D degradation enzyme, CYP24A1 [114]. In light of reported differences in cytokine profiles of MS between male and female patients [115], significant sex-based differences in the relationship between latitude and incidence of first demyelinating events observed in Australia [99], and the well-recognized—and increasing—female preponderance in MS [116,117], these sex-specific aspects of vitamin D in EAE are intriguing. They also support the need for future studies to evaluate whether vitamin D insufficiency is of particular concern in female MS patients, or whether vitamin D supplementation may be of greater benefit in females for both the prevention and treatment MS [118].

4.6.2. Biological plausibility based on vitamin D–genetic interactions in humans

One of the strongest mechanistic links between vitamin D and MS comes from a recent study demonstrating that calcitriol modulates the expression of the particular HLA-DRB1 allele most consistently associated with increased risk of MS, HLA-DRB1 *1501 [69]. Investigation of the major candidate genes, HLA-DRB1, HLA-DQA1 and HLA-DQB1 led to discovery of a conserved, functional vitamin D response element (VDRE) in the promoter region of the HLA-DRB1*1501 allele. Given that HLA-DRB1*15 was the only variant identified as having a functional VDRE in the promoter, expression of the other DRB1 variants would not be expected to be sensitive to vitamin D status. Among those carrying the vitamin D-responsive DRB1*15 allele, vitamin D deficiency or impaired vitamin D metabolism may lead to lower expression of the MHC Class II molecule [1]. Reduced expression of MHC Class II molecules could impair presentation of self-antigens during negative selection, resulting in a lack of tolerance being established against those self-antigens. If the immune system fails to establish and maintain immune tolerance to molecules derived from the blood brain barrier (BBB) or CNS myelin, this could result in the type of demyelinating immune attacks observed in MS. Alternatively, it could be that the high levels of MHC present in the context of vitamin D sufficiency may contribute to activation-induced cell death of overly activated CNS-reactive cells; a decrease in MHC due to vitamin D deficiency may weaken the strength of signal, and permit survival of cells that should be removed. On the other hand, this finding could even suggest a deleterious relationship whereby elevated vitamin D status increases expression of this risk gene, thus increasing antigen presentation and immune stimulation. However, this is not supported by the circumstantial evidence [1,96,119]. While the functional consequence of this finding is yet to be determined, it does form a conceptual basis for a nutrient–gene interaction; thus connecting the genetic and environmental evidence implicating sunlight and vitamin D in the determination of MS risk.

4.6.3. Biological plausibility based on vitamin D interactions with human cell cultures

Calcitriol down-regulates pro-inflammatory dendritic cell (DC) and T-helper lymphocyte 1 (Th1) activation and response, promotes an anti-inflammatory Th2 lymphocyte profile, suppresses the antigen presenting capacity of macrophages and DCs, and decreases proliferation of pro-inflammatory T lymphocytes [63,119–128]. In terms of cytokine profiles, calcitriol decreases production of pro-inflammatory cytokines such as IFN-γ [120,129], IL-2 [130–132], and TNF-α [120,124,133] while enhancing the secretion of the anti-inflammatory cytokine, IL-10 [63,121].

Various *in vitro* models have demonstrated that calcitriol also suppresses expression or reduces mRNA stability of matrix metalloproteinase 9 (MMP-9) [134–140] which increases the permeability of the blood–brain barrier to auto-reactive immune cells. MMP-9 is elevated in patients with MS, particularly RRMS and secondary progressive MS (SPMS) [141–143] and is also elevated during MS relapses [144]. This suggests that in addition to beneficial immune modulating effects, vitamin D could alter egress of immune cells into the CNS.

4.7. Coherence

Any causal relationship should be relatively compatible with observations of the natural history and biology of the disease. Common mechanisms may even be identified that explain similar effects of different risk factors on MS. Regarding common mechanisms of risk

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factors in MS, Fig. 1 illustrates plausible interactions between putative factors involved in the pathobiology of MS outlined in this section.

It is important to consider the vitamin D-related evidence in the context of other identified risk factors for MS, including as sex, smoking, infections such as Epstein Barr virus (EBV) and genetics (discussed in relation to HLA, above).

Female sex is clearly over-represented in adolescent and adult-onset MS [117,145], and the animal studies performed to date support a differential response to vitamin D supplementation *per se* in females with intact ovaries [113] and in ovariectomized females given physiologic levels of estrogen, compared to males or estrogen-deficient ovariectomized females [114]. Gender differences in cytokine profiles and vitamin D status in MS have been the subject of recent review [118], further highlighting the possibility of sex-based differences in the relationship between vitamin D status and MS disease activity.

Cigarette smoking and exposure to cigarette smoke has been linked to increased MS risk ([146] and reviewed in [147]) and worse outcomes in those with established MS [148]. Smoking induces a pro-inflammatory milieu that may be exacerbated by concurrent vitamin D insufficiency. A combustion product from cigarette smoke, benzo[*a*]pyrene (B[*a*]P), enhanced in vitro breakdown of vitamin D in human macrophages [149], suggesting that smoking may exacerbate vitamin D insufficiency in immune cells (Fig. 1). That B[*a*]P is only produced when tobacco is smoked, may be one explanation for why tobacco smoking—not Swedish snuff use—was associated with increased risk of MS [150].

Immune reactivity to viral infection serves not only as a critical aspect of human survival, but may also contribute to stimulation of aberrant immune activity. Prior infection with EBV has been strongly associated with MS risk [151–153]; an interaction between vitamin D status and viral infection is plausible. In both children and adults, impaired vitamin D status has been associated with increased risk of viral infection [154,155], and in a recent wintertime randomized, double-blind, placebo-controlled trial, vitamin D_3 reduced risk of influenza A virus in children [156]. Thus, it is possible that low vitamin D status may increase susceptibility to infection with EBV [20,157]. Furthermore, a possible interaction between microbial infection and vitamin D status in MS has been proposed based on the interaction of both infection and vitamin D on the production of the anti-inflammatory cytokine, IL-10 [158]. For instance, production of viral IL-10 by Epstein Barr virus (EBV) could conceptually down regulate human IL-10 production, which would be further suppressed in the presence of vitamin D insufficiency. This overall could lead to an enhanced pro-inflammatory state [25] (Fig. 1). While these interactions remain largely speculative at this point, they all provide avenues for further research that might serve to enhance the biological plausibility of vitamin D in MS.

Beyond environmental determinants, serum 25(OH)D concentrations are also under some genetic control [79,87,159,160]. Studies of genes involved in vitamin D metabolism have revealed mixed findings regarding the relationship between certain variants and MS risk [161–166]. Further investigation of such genes in highly informative individuals—either those with markedly impaired vitamin D status or individuals diagnosed with MS despite residence in world regions with high ambient UVR—might provide novel information that may link specific aspects of vitamin D metabolism to MS.

4.8. Experiment

A causal association is considered to be one in which a change in the exposure results in a corresponding change in the outcome of interest. While double-blind, placebo-controlled experimental or intervention studies have the potential to produce the strongest evidence for a role of vitamin D in MS, they are limited in that it is obviously unethical to withhold an essential nutrient from patients in the placebo arm to determine whether low vitamin D increases MS risk or disease activity. Thus, in humans, experimental evidence for a causal role of vitamin D in reducing MS disease severity comes from vitamin D or calcitriol supplementation studies.

To date, primary prevention trials have not yet been attempted in humans to determine whether optimizing vitamin D status will reduce risk of MS. There are, however, a limited number of small studies that have explored vitamin D—and even calcitriol—supplementation in adults with established MS; such studies primarily demonstrate the safety profile of vitamin D supplementation, and provide a preliminary view into efficacy.

In a double-blind, placebo-controlled trial, 17 adults with MS received 800 mg calcium plus 1000 IU/day vitamin D over 6 months while 20 adults received calcium alone [73]; only biochemical outcomes were reported. Vitamin D supplementation increased serum 25(OH)D levels from a mean of 42.5 to 72 nmol/l while serum 25(OH)D did not change in the placebo group. Vitamin D supplementation increased TGF-β1 but did not change concentrations of the pro-inflammatory cytokines, TNF-α or IFN-γ, nor the anti-inflammatory IL-13. The mean resultant serum 25(OH)D concentration in the vitamin D group did not reach the estimated minimum concentration for sufficiency (75 nmol/l) [42], which may have limited the ability to detect a significant effect (Fig. 2). On the other end of the vitamin D status spectrum, a phase I (safety or dose-finding) study administered 1200 mg elemental calcium plus doses of vitamin D_3 that increased from 4000 to 40,000 IU/day to 12 patients with active MS over 28 weeks. Mean serum 25(OH)D concentrations at baseline were already just within the estimated range of sufficiency at 78 nmol/l and they increased significantly to 386 nmol/l with no adverse events, changes in liver enzymes, electrolytes, or serum calcium, creatinine, or protein observed [80]. The number of Gd-enhancing lesions decreased from a mean 1.75 to 0.83 per patient ($P = 0.03$) while relapse rate, EDSS scores and ambulation indices remained stable. A follow-up study, an open label phase I/II study of 49 adults with relapsing–remitting MS receiving 1000 mg calcium plus vitamin D_3 in doses escalating from 4000 to 40,000 IU/day [167]. In the vitamin D treatment arm, mean serum 25(OH)D increased from 78 to 413 nmol/l without adverse clinical or biochemical outcomes. A statistically significant decrease in neuronal antigen-induced T-cell proliferation was observed after 1 year compared to baseline values and to age-, sex- and treatment-matched controls at one year. The vitamin D_3 intervention also resulted in a statistically significant decrease in annualized relapse rates (ARR) compared with the previous year. Goldberg et al. [168] supplemented 10 adult MS patients with a lower dose of vitamin D_3 (5000 IU/day in cod liver oil) and body-weight defined doses of calcium, magnesium and demonstrated a statistically significant reduction in relapses by 12 to 24 months; unfortunately, serum 25(OH)D concentrations were not reported at baseline or end of study. Importantly, none of these studies, particularly the Kimball and Burton studies administering up to 40,000 IU/day, reported adverse outcomes or biochemical indication of vitamin D toxicity—hypercalcemia or hypercalciuria—even though they provided calcium in addition to vitamin D at doses above the current North American Dietary Reference Intake's (DRI's) adult "adequate intake" (AI) of 400 IU/day [73] and in excess of the current 2000 IU/day "Tolerable Upper Intake Level" (UL) [169]. These studies were relatively short-term and it is unclear whether the observed benefits could be replicated by providing vitamin D alone or whether it must be in combination with a calcium supplement.

In a single trial that administered calcitriol, rather than vitamin D_3, a reduction in relapse rate of 27% was noted [170]. However, in contrast to the vitamin D supplementation trials, this 48-week trial of calcitriol therapy led to mild hypercalcemia, even among patients compliant with the calcium-restricted diet protocol, highlighting the challenge and potential for toxicity in administering the non-nutrient, hormonal form of vitamin D [171].

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4.9. Analogy

According to this criterion, a potential risk factor may be more readily accepted as a cause of a disease if a similar factor has already been shown to cause the same or related disease. As mentioned above under the criterion of specificity, vitamin D insufficiency is a presently a candidate risk factor for some other diseases that share the similarity of being immune-mediated inflammatory disorders. Thus, this co-existing interest in vitamin D as a common putative risk factor in numerous immune-mediated inflammatory diseases provides preliminary analogous evidence for a role of vitamin D in MS.

5. Discussion

The most obvious question remaining is whether optimizing vitamin D status will reduce the risk MS or be of therapeutic benefit following onset of disease. Embedded in that question are three others: Is there a window of susceptibility in which vitamin D status is most critical; what dose or doses are safe and effective; and will oral supplementation with vitamin D provide the same apparent benefits as cutaneously derived vitamin D due to UVR exposure?

Regarding the stage of life, studies demonstrating that birth season [47,48,97], childhood sun exposure [3,51,52], and migration before adulthood [54,56–59,172–174] can affect subsequent MS risk, suggest that interventions may need to begin as early as the prenatal time period. Further study must not only define whether intervention with vitamin D reduces risk of MS but must also define the time of life within which vitamin D-related risk reduction is operative, the doses needed to optimize vitamin D status in different populations and at different life stages, and whether or not optimal calcium intake is essential for benefit. A primary prevention trial would require an ambitious, relatively long-term international collaborative effort that could be aided by focusing interventions on women of childbearing age, infants, children and adolescents at increased genetic risk of MS [175] in countries reporting the highest prevalence and incidence of MS such as Hungary, the United Kingdom, Norway and Canada [176].

Consideration of vitamin D as a therapeutic agent for established MS will require further information on dose and efficacy. However, apart from the potential disease-modifying effects of vitamin D, there is already good rationale to encourage vitamin D supplementation for MS patients: As previously discussed, low 25(OH)D levels are frequently observed in patients with established MS [32,62,67,72–78], and many MS patients have low bone mineral density, increased risk of fracture, and possess multiple risk factors for osteoporosis [30,74,75,77,177,178]. Compromised vitamin D status exacerbates bone loss and increases risk of fractures [179]. Vitamin D_3 supplementation is relatively simple, inexpensive and, in contrast to calcitriol, is safe even in doses that exceed of the current UL (2000 IU/day) by several fold in adults [80,167,180]. The safety profile of vitamin D in pediatrics is less well defined. A recent review of the available literature indicates that intakes in excess of the current vitamin D AI of 200 IU/day from infancy through adolescence are safe and even necessary for optimizing growth and bone health [181].

Given the risks associated with both acute and chronic UVR exposure [182] and the challenge in establishing a UVR dose to produce and maintain a certain level of circulating 25(OH)D [35], MS clinical trials have, thus far, tested the effects of oral vitamin D supplements rather than UVR exposure. However, ingested vitamin D does not completely reproduce the effects of UVR exposure: UVR stimulates neuroendocrine [183] and immune-modulating [184] pathways that may function independently of vitamin D production or that may act in concert with vitamin D produced in the skin. It is, thus, plausible that achievement a particular range of circulating 25 (OH)D via controlled UVR exposure could result in significantly different immune-related and clinical outcomes as compared to the same 25(OH)D levels achieved via oral vitamin D supplementation. Whether or not the non-vitamin D, UV-stimulated mechanisms do, in fact, also contribute to the apparent benefit conferred by UVR on MS risk remains unclear.

In summary, the available evidence for vitamin D in MS reasonably fulfills all but one of Hill's criteria; it is that remaining criterion—of disease prevention by intervention—that is most critical. The logistics and demands of this type of primary prevention study are daunting, given the relatively low incidence of MS (generally <10 per 100,000 per year), the variable age of MS onset, and the uncertainty about the optimal dose or the optimal period of life to target.

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