Multiple Sclerosis and Vitamin D: A Review and Recommendations

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Abstract A relationship between vitamin D and several diseases, including multiple sclerosis (MS), has recently received interest in the scientific community. Vitamin D appears to have important actions beyond endocrine function, particularly for the immune system. Risk of development of MS, as well as disease severity, has been associated with vitamin D in a variety of studies. There remains a need for prospective studies to further establish this relationship. Given the current evidence of the potential benefits of vitamin D, it appears to be reasonable and safe to consider vitamin D supplementation at dosing adequate to achieve normal levels in patients with MS and clinically isolated syndrome.

Keywords Multiple sclerosis · Vitamin D · Demyelinating · 25-hydroxyvitamin D · 1,25-dihydroxyvitamin D · Deficiency · Review · Prevention

Introduction

Within the past decade there has been an increasing interest in an association between multiple sclerosis (MS) and vitamin D [1••, 2–6]. Data derived from research focused on epidemiologic findings, genetic polymorphisms, MRI, animal models, and clinical studies have strengthened this association. The aim of this article is to provide an up-to-date review of the literature concerning the actions of vitamin D, the relationship of vitamin D to disease and immune function, evidence for a possible relationship with MS, and guidelines for testing and supplementation that will be useful for the clinical neurologist.

Vitamin D

Physiology

In humans, vitamin D is obtained primarily through synthesis in the skin. Dietary intake provides additional vitamin D. Fatty fish, mushrooms, and egg yolk contain small quantities of vitamin D [7, 8••]. Milk and other products, such as juice and breads, are often fortified with vitamin D in the United States [8••]. Dietary supplements are also available, including vitamin D_2 derived from fungal and plant sources and vitamin D_3 from animal sources.

Exposure to ultraviolet B (UVB) irradiation through sunlight catalyzes the formation of cholecalciferol (vitamin D_3) from 7-dehydrocholesterol (pre-vitamin D_3). Vitamin D_3 derived from UVB or dietary intake and vitamin D_2 from the diet are hydroxylated in the liver to form metabolically inactive 25-hydroxyvitamin D, or calcidiol (Fig. 1). 25-Hydroxyvitamin D subsequently is hydroxylated to its active form, 1,25-dihydroxyvitamin D, or calcitriol, within epithelial cells in the proximal renal tubule of the kidney [7, 8••, 9, 10].

Calcitriol has a circulating half-life of approximately 4 h and binds to the vitamin D receptor (VDR) to exert its effect. The VDR functions as a ligand-activated transcription factor that binds to vitamin D-responsive genes and

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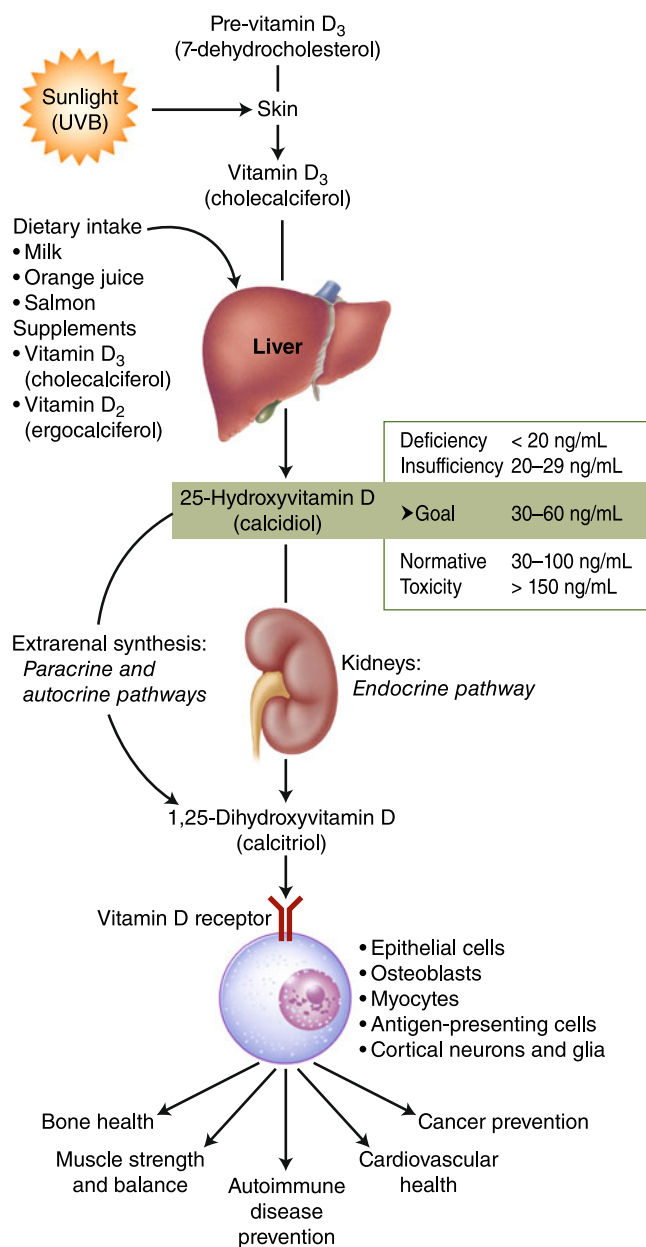
Fig. 1 Vitamin D metabolism and biologic effects. *UVB* ultraviolet B

influences the rate of their transcription. Thus, vitamin D functions more like a hormone than a vitamin [7, 10]. Calcitriol is tightly regulated by plasma parathyroid hormone, serum calcium, and serum phosphorus levels [7, 8••]. When in excess, vitamin D metabolites are excreted through the liver [7]. Autoregulation of calcitriol through negative feedback mechanisms also has been demonstrated.

In addition to the kidney, several other cell types in the body contain 1-alphahydroxylase and convert 25-hydroxyvitamin D to calcitriol, which then acts through autocrine or paracrine pathways [7, 10]. Such extrarenal synthesis of calcitriol has been found in epithelial cells,

antigen-presenting cells, parasympathetic ganglia, basal keratinocytes, hair follicles, pancreatic islet cells, the cerebellum, and the cerebral cortex [7]. VDRs have been found in most organs of the body, including the small intestine, colon, pituitary, pancreas, bone, muscle, prostate, ovary, breast, and brain, and within the immune system [7, 8••]. Through the influence of more than 200 genes, vitamin D affects cellular proliferation, differentiation, apoptosis, and angiogenesis [8••]. The widespread distribution and function of the VDR likely is directly related to the increasingly recognized association between vitamin D deficiency and a large variety of diseases.

Deficiency

Although several acquired and inherited disorders may lead to vitamin D deficiency, the most common cause remains reduced skin production. Vitamin D status is determined by measuring 25-hydroxyvitamin D, as it most accurately represents the endogenous and exogenous sources of vitamin D and has a longer half-life than active calcitriol (1,25-dihydroxyvitamin D). In this article, we use the term *vitamin D levels* to refer to serum measurements of 25-hydroxyvitamin D in nanograms per milliliter. It is important to note that in some studies, 25-hydroxyvitamin D levels may be reported in nanomoles per liter. Although there still is no consensus regarding an optimal vitamin D level, most experts define vitamin D deficiency as 25-hydroxyvitamin D below 20 ng/mL and insufficiency at levels of 21 to 29 ng/mL [7, 8••, 9]. Accordingly, an estimated 1 billion individuals worldwide suffer from either deficiency or insufficiency [7, 8••].

In the United States, a large proportion of elderly people, children and young adults, postmenopausal women, individuals with dark skin pigment, and other populations are at significant risk for deficiency, with a prevalence well above 50% [8••, 10]. Many of these populations do not receive adequate vitamin D from UVB exposure or diet. Skin pigmentation, use of sunscreens, time of day, season, and latitude all affect one's ability to produce cutaneous vitamin D. Strict vegetarian and vegan diets also may lead to vitamin D deficiency.

Deficiency and Systemic Disease

It is well known that inadequate vitamin D results in absorption of only a small fraction of dietary calcium and phosphorus. Deficiency in vitamin D therefore may result in rickets or osteoporosis and is associated with increased risk of fractures [8••, 10]. Chronic vitamin D deficiency also results in muscle weakness, appears to influence balance, and may increase the risk of falls [7, 8••, 10]. Epidemiologic research suggests an increased risk of

several malignancies in association with vitamin D [7, 8••, 10]. Recent studies also suggest an increased risk of hypertension, cardiovascular disease, and asthma with vitamin D deficiency [8••].

Immune Function

The immune function of vitamin D likely is related to its association with systemic and autoimmune disease [1••, 2–6, 8••, 10–13]. Recent literature has characterized the important actions of vitamin D within the immune system [11–13]. Through the VDR, vitamin D appears to enhance innate immunity, regulate adaptive immune responses, and act as an immunomodulator [11–13].

The major cellular components of the immune system—T cells, B cells, macrophages, and dendritic cells—express the VDR and produce as well as respond to 1,25-dihydroxyvitamin D_3 [11]. Binding to the VDR modulates and even inhibits dendritic cell differentiation and function, which in turn influences T-cell development and activation [11–13]. Through inhibition of maturation of dendritic cells, vitamin D modulates the T-cell response and may inhibit T-cell activation [13]. The resulting interaction between immature dendritic cells and T cells also leads to cell tolerance through induction of regulatory T cells [13]. Vitamin D also appears to prevent upregulation of monocytes and to inhibit the ability of macrophages to produce proinflammatory cytokines such as interferon-γ [13]. Vitamin D may also suppress Th1 and induce Th2 T-cell responses [13]. Through interactions with toll-like receptors and T cells, vitamin D also appears to be an important component of the antimicrobial response following injury [11]. In addition to important modulation of T-cell function, vitamin D has been found to affect B-cell apoptosis, B-cell proliferation, generation of memory B cells, plasma cell differentiation, and immunoglobulin production [11].

Autoimmune Disease

Recent literature suggests vitamin D status as an environmental factor affecting prevalence and severity of autoimmune disease [1••, 2–6, 8••, 10–13]. Vitamin D supplementation may reduce the risk of developing type 1 diabetes and improve symptoms in psoriasis and inflammatory bowel disease [8••, 11, 13]. Vitamin D deficiency has also been associated with disease prevalence and severity in rheumatoid arthritis and systemic lupus erythematosus [11–13]. Although the literature exploring an association between vitamin D and many types of immune-mediated disease is limited, a significant number of studies have suggested a relationship between vitamin D and MS.

Multiple Sclerosis and Vitamin D

Latitude

Latitude, ultraviolet (UV) radiation from the sun, and season have an interrelated effect on the ability to synthesize vitamin D and have been found to be associated with MS. Epidemiologic studies have suggested there is an increase in incidence and prevalence of MS with increasing latitude north and south of the equator [1••, 4, 14•]. Recent studies have confirmed a latitude gradient risk for MS, whereas other studies have suggested this phenomenon is diminishing [15•, 16]. Migrant studies indicate that this environmental influence on individual risk of disease may be established during the first two decades of life [17, 18].

Sunlight

Latitude influences the duration and intensity of sunlight. Decreased availability of UV radiation to produce cutaneous vitamin D may explain the association between MS prevalence and latitude. A recent study using geospatial analysis found a significant increase in risk for MS in areas with a low level of UV radiation [14•]. Additional studies suggest that daily sunlight may reduce the risk of MS in high-latitude regions [19–21] and that UVB radiation appears to correlate more closely than latitude alone with MS risk [20]. Further supporting the hypothesis that solar radiation may have a protective influence on the development of MS, skin cancer has been found to be less common in individuals with MS [22]. Preliminary results from a recent case-control study examining lifetime sun exposure indicate that cases with a first demyelinating event had lower skin sun damage scores compared with controls. The magnitude of this effect increased with latitude [23].

Season

Available sunlight fluctuates with season. The ability to synthesize vitamin D often is limited during the winter. Several population studies have suggested a "timing of birth effect" such that a lower risk of developing MS was found for births occurring after summer whereas those occurring after winter conferred a higher risk [24]. In utero or maternal vitamin D deficiency may influence subsequent risk of MS. Additional research also found an association with disease progression and timing of birth, an effect a recent study was not able to identify [25]. Similarly, season and low available sunlight have been associated with clinical relapses of MS and new enhancing lesions on MRI, whereas additional studies have not been able to confirm this correlation [5]. Twin studies suggest that early sun avoidance precedes the diagnosis of MS, independent

of genetic susceptibility [26], and a recent study found that timing of birth may be a more important risk factor than genetic factors for developing MS [24].

Genetic Polymorphisms to the VDR

MS risk likely is related to an interplay between genes and the environment. The gene encoding the VDR is located on chromosome 12q13.1 and contains just over 100 kilobases divided into eight introns and nine exons. More than 30 polymorphisms within the VDR gene have been identified, and only a few have been studied in regard to risk of autoimmune disease [27].

Through a limited number of studies, specific single nucleotide polymorphisms (SNPs) of the VDR have been linked to lower vitamin D metabolism in individuals with MS, as well as greater susceptibility to disease and disability [2, 27, 28]. In a study of 512 individuals with MS of greater than 10 years' duration, the frequency of a particular SNP of the VDR was significantly associated with a lower Expanded Disability Status Scale (EDSS) score (a measure indicating less disability) compared with other known SNPs of the VDR [2, 27]. In one recent study, the association between risk of MS with a VDR SNP appeared to depend on past sun exposure [2]. Several studies of VDR SNPs also found no association with MS prevalence or disability [2, 28]. In studies finding a significant association, there was a potential for high exposure to vitamin D through sunlight or diet in the population studied [27]. Several authors have hypothesized that it therefore is possible that the association of a VDR gene polymorphism with MS might be penetrant only in a population with sufficient vitamin D, and the lack of association found in other studies may be the result of relative vitamin D insufficiency [27].

Risk of Disease

In addition to a relationship indirectly implicated by research focused on latitude, sunlight, seasons, and genetic polymorphisms, research focused on vitamin D exposure has revealed significant evidence for a direct association between vitamin D and prevalence of MS. In 2004, a large prospective cohort study supported a protective effect of vitamin D intake on the risk of developing MS [29]. The study included two cohorts—the Nurses' Health Study (92,253 women followed up for 20 years) and the Nurses' Health Study II (95,310 women followed up for 10 years)—in which 173 new cases of MS were found. Vitamin D intake from diet and supplements was quantified by questionnaires. After adjusting for other known MS risk factors, the study investigators found that the use of supplemental dietary vitamin D, primarily through multivitamins—estimated at a

dose ≥400 IU/d—was associated with a 40% lower risk of MS compared with no use of supplements. A prospective nested case-control study among 7 million US military personnel, published in 2006, suggested a similar association [30]. Serum samples were stored with the Department of Defense, and cases of MS were identified through disability databases over a span of 12 years. Diagnosis of MS was confirmed, and 257 cases were each matched to two controls. This study found that the risk of MS decreased with increasing serum levels of vitamin D, but only in Caucasian individuals. There was a 41% decrease in MS risk for every 20-ng/mL increase in measured vitamin D level. MS risk was highest among individuals with levels of 6 to 25 ng/mL and lowest in a group with levels of 40 to 61 ng/mL.

A recent prospective study of 125 children presenting with an initial episode of central nervous system (CNS) demyelination found that at 1-year follow-up, children diagnosed with MS had significantly lower vitamin D levels at the initial demyelinating episode than those who did not have progression to MS [31]. The authors suggested that vitamin D insufficiency is a risk factor for recurrent CNS inflammation and therefore a diagnosis of MS. A very recent study focused on the effect of maternal vitamin D exposure during pregnancy on the risk of MS in offspring [32•]. In utero vitamin D exposure and risk of adult-onset MS were examined among a cohort of 35,794 nurses whose mothers participated in the Nurses' Mothers' Study. MS was diagnosed in 199 women, and risk of MS was reduced by approximately half among women born to mothers with high milk or vitamin D intake during pregnancy compared with those whose mothers had low intake. This suggested a protective effect of milk and vitamin D intake on MS prevalence.

Risk of Relapses and Disability

There is emerging evidence that vitamin D not only may influence the initial development of disease and conversion to clinically definite MS, but also may affect disease severity. It is important to acknowledge that relapses and severe disability may prevent adequate exposure to UVB and thereby increase the risk of vitamin D deficiency. Several studies have attempted to control for this possibility. In a population-based case-control study of 136 individuals with MS, half had vitamin D insufficiency, and increasing disability was strongly associated with lower levels of sun exposure and lower levels of vitamin D compared with matched controls [33]. Over a mean of 2.3 years, a prospective population-based cohort study of 199 individuals with MS in Tasmania—an estimated 78% of the eligible MS population—demonstrated that relapse rates were inversely associated with UV radiation exposure

and vitamin D levels [34]. Several smaller prospective studies of individuals with MS also found lower vitamin D levels during relapses compared with periods of remission [35, 36].

A recent large study collected serum samples from 267 individuals with MS and measured current and previously collected MS parameters [37•]. Of the individuals with relapsing–remitting MS (RRMS), 49% had levels considered insufficient at less than 28 ng/mL, whereas 81% of individuals with secondary progressive MS and 69% of those with primary progressive MS had suboptimal levels. Thus, vitamin D levels were significantly lower in progressive forms of MS compared with the RRMS phenotype. In addition, high vitamin D levels were associated with a high chance of remaining relapse-free in individuals with RRMS. When all individuals with and without relapses were compared in this group, the relative risk of remaining relapse-free in the previous 2 years increased by 51% for each 4-ng/mL increase in serum vitamin D. In this study, low levels of vitamin D also were associated with a high score on a common disability scale used in MS (EDSS), indicating more severe disability.

A very recent retrospective study of 110 patients with pediatric-onset MS or clinically isolated syndrome (CIS) recruited into a prospective cohort resulted in similar findings [38•]. After adjusting for confounding factors, in this group with a mean adjusted vitamin D level of 22± 9 ng/mL, every 10-ng/mL increase in serum vitamin D was associated with a 34% decrease in the rate of subsequent relapses.

Human Immunologic Studies

Immunologic laboratory data from MS patients obtained during the course of their disease also support the influence of vitamin D on disease activity. The percentage of regulatory T (Treg) cells, demonstrated to suppress disease activity in animal models of MS, recently was found to be correlated with vitamin D levels in a small study of individuals with MS, most of whom were not on disease-modifying therapy [39]. A study of 132 individuals with MS and controls indicated not only that individuals with RRMS had decreased levels of serum vitamin D compared with controls, but that these levels were lower during relapses than during remissions [40]. This study also found an association between the active vitamin D metabolite calcitriol and a significant increase in Treg cells in the individuals with MS. Lastly, a small controlled study that examined cerebrospinal fluid (CSF) proteins in individuals with MS found significantly decreased levels of vitamin D–binding protein in the CSF of individuals with MS compared with controls, identifying a new biomarker that may be evaluated for use in diagnosis or treatment [41].

Animal Models: Autoimmune Encephalomyelitis

Further direct evidence confirming a relationship between vitamin D and MS comes from animal trials with vitamin D. Murine experimental autoimmune encephalomyelitis (EAE) is a long-established animal model for MS. An important study in 1991 found that vitamin D inhibited disease induction, antibody production, and development of histologic lesions in EAE [42]. A significant number of subsequent studies exploring an association between vitamin D and EAE have been reported over the past two decades. Vitamin D repeatedly has been found to prevent disease before induction, halt disease once it has begun, reduce disease severity, and reduce disability in EAE with a corresponding reduction in histopathologic inflammation of the CNS [1••, 5]. These effects of vitamin D were dose dependent and disappeared once therapy was discontinued [5]. Thus vitamin D therapy in EAE appears to have a significant protective and curative effect [1••, 5].

Gender

Gender- and sex-related immunologic differences may have an influence on the association between vitamin D and MS. In one animal study, vitamin D resulted in fewer clinical, histopathologic, and immunologic signs of EAE in female mice compared with ovariectomized females and intact or castrated males [43]. A recent 1-year prospective controlled cohort study found that for every 4-ng/mL increase in serum vitamin D level, the odds of developing MS were reduced by 19% in women only [43]. A negative correlation also was found between EDSS and vitamin D levels only in women in the study. Many studies investigating an association between vitamin D and MS have not been stratified by gender for analysis.

Vitamin D Therapy and MS

Only a few clinical trials of vitamin D therapy in individuals with MS have been completed, and most report data from unblinded, uncontrolled study designs. In a recent open-label safety study, 12 individuals with MS and active gadolinium-enhancing lesions received dose escalation therapy with vitamin D_3 (cholecalciferol) over 28 weeks [44•]. Serum concentrations of vitamin D averaging 155 ng/mL and a dosage of 40,000 IU/d of vitamin D_3 for 5 weeks were found to be safe and associated with no toxicity. Relapse rate and EDSS remained stable, and gadolinium-enhancing lesions were significantly decreased at the end of the study. An extension of this study included 25 treated individuals and 25 controls. After receiving doses up to 40,000 IU/d of vitamin D_3 over 4 months, the study participants received 10,000 IU/d for 3 months, then

8,000 IU/d for the next 2 months, followed by a 1-month washout, for a mean dosage of 14,000 IU/d for 52 weeks [45]. The maximum mean serum vitamin D level approached 156 ng/mL without adverse effects, and fewer relapses were observed in the treatment group compared with the controls [45].

In addition, two unblinded and uncontrolled prospective studies, each enrolling 16 patients, found that disease activity stabilized over 2 years after supplementation with vitamin D in combination with other supplements [46, 47]. Two additional small open-label safety studies, one investigating 1α-hydroxy-D$_3$ (alfacalcidol) supplementation in five individuals with MS for 6 months and the other studying 1,25-dihydroxyvitamin D (calcitriol) in 15 individuals with MS for 12 months, reported good tolerability and mild hypercalcemia [48, 49]. A recent retrospective study of vitamin D levels in 199 individuals with MS and transverse myelitis found a large percentage of vitamin D insufficiency (85%), defined as levels of 20 to 40 ng/mL, and deficiency (31%), defined as less than 20 ng/mL [50]. In this study, low-dose vitamin D supplementation with ≤ 800 IU/d of vitamin D$_3$ was not adequate to raise levels to a goal of 40 ng/mL. In the same study, a supplementation regimen of 50,000 IU of vitamin D$_2$ was more effective at reaching this level, but it was achieved only in fewer than 40% of individuals within 7 to 12 months. It is important to note that no double-blinded randomized placebo-controlled trials of vitamin D for the treatment of MS have been completed.

Vitamin D Supplementation

For more than 25 years, there has been much debate in the literature regarding the optimal intake and serum level of vitamin D for bone health or prevention of other systemic diseases associated with vitamin D deficiency. A vitamin D level ≥ 30 ng/mL is commonly recommended [8••], although the literature suggests there may be additional benefits at higher levels [10]. In the aforementioned study among military personnel, MS risk was lowest among individuals with a vitamin D level greater than 40 ng/mL [30].

Excess vitamin D causes increased intestinal calcium absorption and induction of bone resorption [9]. As a result, toxic levels of vitamin D are associated with hypercalcemia, renal calcinosis, and renal injury. Clinically, toxicity may present with drowsiness, polyuria, polydipsia, anorexia, nausea, vomiting, constipation, hypertension, and ultimately coma [7]. These symptoms have been mistaken for gastroenteritis, and hypercalciuria may be a more sensitive marker for toxicity than hypercalcemia [9]. Excessive sunlight and adipose stores do not cause toxicity.

Although a recent small study of individuals with MS reported no toxicity with high doses of vitamin D$_3$ [44•], vitamin D intoxication in the form of hypercalcemia and hyperphosphatemia has been observed at levels of 150 ng/mL and oral vitamin D$_3$ supplementation of 50,000 IU/d [8••, 9]. Most literature on vitamin D emphasizes the evidence that supplementation of up to 10,000 IU/d of vitamin D$_3$ for up to 5 months has not been associated with toxicity [8••, 9]. Reference ranges for laboratory testing commonly reflect levels less than 100 ng/mL as safe based on existing data.

Oral supplementation is widely recommended for deficiency and insufficiency, and cholecalciferol (vitamin D$_3$) has been found to be superior to ergocalciferol (vitamin D$_2$) in terms of potency and duration of action [7]. However, prescription-strength vitamin D$_2$ is also commonly recommended, particularly in severe deficiency [8••, 10]. A variety of supplementation approaches have been recommended to raise serum vitamin D levels. As detailed by Holick [8••], in clinical situations other than inadequate sunlight or dietary intake, dosing may vary by etiology for deficiency or insufficiency [10]. Authors in the field of MS acknowledge that no optimal dose or level is yet known for benefits in MS.

Conclusions

Emerging literature has strengthened the association between vitamin D and MS. This relationship may have important consequences for the risk of developing MS, as well as subsequent disease activity and severity. Further research is needed, particularly in the form of prospective, randomized, placebo-controlled, double-blinded clinical trials. While awaiting this data, given the strength of published studies thus far, it appears reasonable and safe for the practicing neurologist to consider screening for and treating vitamin D deficiency or insufficiency in patients with MS.

A 25-hydroxyvitamin D level of 30 to 60 ng/mL appears safe and may have benefits for MS as well as a variety of other chronic diseases. An optimal level remains unknown. It is important to consider alternative etiologies for vitamin D deficiency or insufficiency, including renal disease, hepatic disease, and malabsorption syndromes, and to take care to avoid hypercalcemia in granulomatous disease such as sarcoidosis. We follow the guidelines published by Holick [8••] for supplementation in adults with inadequate sun exposure or dietary intake.

For individuals with CIS or MS and vitamin D deficiency (<20 ng/mL), we recommend supplementation with 50,000 IU/wk of vitamin D$_2$ (ergocalciferol) for 8 weeks and subsequent evaluation of serum level.

Continuation of vitamin D_2 therapy for 8-week periods until the 25-hydroxyvitamin D level is greater than 30 ng/mL may be necessary. Maintenance supplementation with vitamin D_3 at 1,000 to 2,000 IU/d may be initiated once deficiency is corrected and in individuals found to have insufficiency (20–29 ng/mL).

It is also reasonable and likely safe to consider maintenance supplementation for individuals with MS or CIS at risk for deficiency or insufficiency of vitamin D due to inadequate dietary intake or sun exposure. Because current research also suggests pediatric and obstetric benefit from vitamin D with regard to the risk of developing MS, pediatricians and obstetricians may be consulted when considering vitamin D supplementation in children and during pregnancy.

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