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Review Article

Vitamin D Deficiency as a Risk Factor for Multiple Sclerosis: Evidence from Epidemiology, Animal Model, Genetics, and Immunology

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Abstract

Vitamin D deficiency has now been recognized as a global health concern. Classically associated with calcium metabolism, a newer role of vitamin D as an immune modulator has been increasingly gaining prominence due to accumulating data for its role in pathogenesis of various diseases. Of particular interest are the reports linking vitamin D deficiency with autoimmunity. Along with Epstein - Barr virus (EBV) infection and smoking, vitamin D deficiency is known to be an important factor risk factor associated with multiple sclerosis (MS). This review aims to summarize the current understanding about the role of vitamin D deficiency during disease onset and progression. Evidence from geographical pattern of disease distribution, birth month effect, animal model of disease, immunological findings as well as genetic links between vitamin D and MS genes have been scrutinized to understand the underlying mechanisms by which vitamin D may regulate disease progression. The review also summarizes the findings of various clinical trials conducted thus far. We summarize that although there is strong evidence linking vitamin D and MS, the beneficial effect of vitamin D therapy may depend on various factors such as type of diseases, timing, dose and form of supplement used, gender of patient, etc. Based on this evidence, we conclude that the preventive effects of vitamin D supplements may be more beneficial than its therapeutic effects during disease progression. Thus, supplement therapy should not only be considered in patients with active diseases, but also in population at risk of MS.

Keywords: Vitamin D; Multiple Sclerosis; VDR; VDRE; EBV

Abbreviations

EBV: Epstein- Barr Virus; MS: Multiple Sclerosis; FDA: Food and Drug Administration; VDR: Vitamin D Receptor, CYP2R1: Cytochrome P450 2R1; CYP27B1: Cytochrome p450 27B1; RXR: Retinoid X Receptor; VDRE: Vitamin D Response Element; EBNA-3: Epstein Barr Nuclear Antigen-3; EAE: Experimental Autoimmune Encephalomyelitis; UVB: Ultra Violet B; Th: T Helper; CNS: Central Nervous System; 25(OH)D: 25- hydroxyvitamin D; 1,25-D3: 1,25-dihydroxyvitamin D3; TLR: Toll like Receptor; TNF: Tumor Necrosis Factor ; IL: Interleukin; CCL: Chemokine (C-C) motif Ligand; GPR30: G Protein-coupled Receptor 30; CYP24A1: Cytochrome P450 24A1; ILT: Immunoglobulin-like Transcript; MHC: Major Histocompatibility Complex; HLA: Human Leukocyte Antigen; IU: International Units; nM: Nano Moles

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurological disorder and a common cause of disability, especially in young adults. The disease has autoimmune pathology, where auto-reactive T cells against myelin proteins enter the central nervous system, and bring about the neuronal tissue damage. What dose triggers these auto-reactive T cells in periphery is still not clearly understood, however, genetics and environmental factors are known to play an important role. Clinically, disease manifests with symptoms such as central paralysis, sensory impairment, impaired cognitive functions, difficulty in coordination and balance, fatigue, etc. The course of MS varies from patient to patient and is highly unpredictable and variable. Based on course of progression, the disease has been categorized into four classes: *Relapsing–remitting MS (RRMS)*: the most common form marked by relapses of symptoms followed by periods of remission, when symptoms improve or disappear. Some patients of RRMS may develop *Secondary progressive MS (SPMS)* where the disease symptoms continue to worsen with or without periods of remission. A more rare form of the disease is the *Primary Progressive MS (PPMS)* where the symptoms continue to worsen gradually from the beginning itself, without any relapses or remissions. However, there may be periods of plateau in between. The rarest course of disease is the *Progressive-relapsing MS (PRMS)* affecting only about 5% of MS patients. Here, the disease is progressive from the start. However, there are periods of flare-ups of worsening symptoms, without any periods of remission [1]. Currently, no effective FDA approved cures are available for MS. Thus, the main aim of available therapy in MS is to decrease the duration as well as frequency of flare ups, reduce disease activity, and provide symptomatic relief [2]. Since MS is known to impact quality of life in terms of both physical and mental health components, there is a constant need for exploring different therapies to address the onset as well as progression of MS.

The most important factors linked with MS so far are smoking,

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EBV, and vitamin D deficiency [3,4]. Since EBV is ubiquitous in its presence and no successful vaccine is as yet present [5], therefore, cessation of smoking and vitamin D supplementation become the more practical options for MS management. Of these, vitamin D supplementation is particularly lucrative because of its ease of execution as well as relatively low cost, as compared to economic burden of the disease.

The first documented association of vitamin D deficiency as a risk factor for MS was proposed way back in 1960s by Sir Donald Acheson, in his paper where he examines the relationship of the distribution of multiple sclerosis to latitude [6]. Since then, there have been numerous reports that link vitamin D deficiency with MS. The interest in this aspect of MS pathogenesis was further fuelled by the recent unraveling of a wide variety of biological functions of vitamin D besides its classical role in mineral metabolism. Of particular interest was the discovery that vitamin D receptor (VDR) is expressed on wide variety of cells and has role in immune modulation [7]. This article reviews the current understanding of association of vitamin D with MS, as suggested by various epidemiological, genetic, and immunological studies. We have also summarized the key findings of various clinical trials of vitamin D therapy in an attempt to understand its potential as a supplement therapy for MS patients. Thus, the main aim of this review is to provide the latest information on role of vitamin D in MS in a concise manner. For detailed information, the readers are suggested to refer to the latest articles cited in each section.

Vitamin D metabolism: enzymes, intermediates and interacting partners

Vitamin D is present in our body in two forms: Vitamin D3 (colecalciferol), which is the major form, or vitamin D2 (ergocalciferol), the minor form. The major sources of colecalciferol are skin exposure to ultra violet B sunlight and/or vitamin supplements, whereas diet such as fortified foods and fatty fish provide both vitamin D2 and vitamin D3. Exposure of skin to the ultra violet B (UVB) fraction of sunlight in the range of 290–315 nm range converts the vitamin D precursor 7-dehydrocholesterol to pre-vitamin D3, which then isomerizes to colecalciferol. Both colecalciferol and ergocalciferol are biologically inactive. For conversion into biologically active form 1, 25-dihydroxyvitamin D, the precursors are first converted to 25-hydroxy vitamin D in liver by enzyme Vitamin D 25 hydroxylase also called CYP2R1. Measuring the vitamin d levels in serum is based on the amount of 25-hydroxyvitamin D present, since it is a more stable metabolite with a relatively longer half-life of around 1-2 months days, as compared to 1, 25-dihydroxy vitamin D, with a half- life of only 4-6 hours in circulation. 25-hydroxyvitamin D undergoes the final hydroxylation to give the active form, 1,25-dihydroxyvitamin D or calcitriol, by the action of enzyme 25-Hydroxyvitamin D3 1-alpha-hydroxylase, also known as cytochrome p450 27B1 (CYP27B1) [8]. The enzyme is present in proximal tubules of kidney, keratinocytes in skin, osteoclasts in bones and various immune cells, which are the site of vitamin D production [9].

The biological activity of vitamin D is associated with a nuclear receptor called the Vitamin D Receptor (VDR). VDR acts as transcription factor, and is also present in cell membrane. As transcription factor, it can undergo heterodimerisation with various receptors such as Retinoid X Receptor (RXR), and then binds to vitamin D response element (VDRE) and brings about the transcription of vitamin D responsive genes [10]. These vitamin D responsive genes vary widely in their biological activities ranging from mineral homeostasis, skeletal integrity, anti-proliferative effects, etc. In a double blind pilot clinical trial of 2013, vitamin D supplementation was shown to affect the expression of 66 genes which were important for transcriptional regulation, immune function, response to stress and DNA repair, in white blood cells from subjects with baseline vitamin D deficiency, as compared to subjects with baseline level of 25(OH)D>20 ng/ml [11]. The discovery of VDR in cells of the immune system and the presence of the 1α-25(OH) vitamin D3 hydroxylase in dendritic cells and macrophages suggest that locally produced 1,25(OH)2D3 has regulatory autocrine and paracrine properties at the site of inflammation. The VDR is also important for adaptive immunity, where it modulates the T and B lymphocyte function [12,13].

Another important interaction partner for VDR with reference to its role in MS is the Epstein Barr Nuclear antigen-3 (EBNA-3) produced by Epstein-Barr virus. Upon its interaction with VDR, this protein has been shown to block the transcription of VDRE genes in lymphoblast B cell [14]. This finding is interesting for determining MS research, since together with smoking; EVB and vitamin D deficiency are known to be the most important risk factors for MS.

Vitamin D has also been shown to interact with estrogen signaling pathway by regulating the expression estrogen synthesizing aromatase [15]. Furthermore, estrogen downregulates the expression of the vitamin D binding protein, in turn up regulating VDR [16]. This interaction of vitamin D and estrogen may be helpful in explaining the higher prevalence of MS in females. This theory is further corroborated in the animal model of the disease, where it was observed that vitamin D3 inhibited experimental autoimmune encephalomyelitis (EAE) in intact female mice, but not in ovariectomized females or in males [17]. It was further shown that estrogen implants alone did not rescue the mice from disease, but did so in presence of vitamin D3. Gold and Voskuhl reported that the protective mechanisms of estrogen treatment in EAE involves anti-inflammatory mechanisms, affecting cytokines, chemokines, matrix metalloproteinase-9 (MMP-9), antigen presentation and dendritic cell function as well as induction of Tregs [18,19]. All of these biological activities are also known to be associated with vitamin D. These observations, along with the fact that MS patient show clinical improvement during pregnancy (when estrogen levels are high) have led to exploring the potential of estrogen therapy in clinical trial for MS.

Evidence for association between vitamin D and multiple sclerosis

Geographical distribution and birth month effect: The first evidence linking vitamin D deficiency with risk of MS came from studies on latitudinal gradient of MS prevalence, whereby the risk of MS increased with increasing latitude in both northern and southern hemisphere [20]. This is because vitamin D synthesis in skin is known to be proportional to sunlight intensity, as well as duration, both of which are inversely proportional to the latitude. This hypothesis was further strengthened by the fact that in the high latitude areas of rural Norway where consumption of fatty fish rich in vitamin D was high,

the prevalence of MS was lower than expected [21]. In US, the risk of MS also decreased in people of northern states, who migrated to southern states for work [22].

In recent times, however, this latitudinal gradient of MS appears to be diminishing. This could be due to better diagnosis or increased reporting of MS from previously low prevalence area such as Middle East and Mexico. Traditionally, MS was considered to be predominantly a disease of white population. However, this trend is changing, with the disease becoming more common in dark-skinned, probably due to their migration to areas of high latitude. The melanin in the skin of dark colored people absorbs UVB radiations, thus, hindering the production of vitamin D. Thus, change in life style such as spending more time indoors, use of sun block creams, etc. are expected to have a much greater effect on vitamin D levels of dark colored populations. We observed a similar finding in our study of North Indian population, which receives abundant sunshine throughout the year, where most of the healthy controls (hospital staff) recruited in the study were deficient in vitamin D [23]. Thus, the diminishing gradient seems to be more of an effect of increase in incidence in lower latitude areas rather than a decrease in prevalence of high altitude areas. This is further supported by the meta-analysis of current studies by Koch-Henriksen and Sorenson [24], which shows that latitude gradient of MS prevalence still remains, however, it is the latitudinal gradient of MS incidence that seems to be decreasing.

Another phenomenon with associates MS to vitamin D due to sunlight exposure is the birth month effect. It was based on the observation that children born in spring months of either hemispheres were at a slightly elevated risk of developing MS than general population. This was explained on the basis that mothers received inadequate amounts of UVB sunlight during pregnancy, and hence were deficient in vitamin D. The review by Dobson *et al.* even shows a reduced risk in those born in October and November [25]. Distano *et al.* have gone a step ahead to show that vitamin D exerts its effect due to its effect on thymic development, since thymic output and T cell development also showed a month of birth effect [26]. This association of birth month with MS has, however, been recently questioned. In their review, Fiddens *et al.* have used the national birth statistics form two continents to assess if there is any seasonal variation and latitudinal variation in birth in general population [27]. Surprisingly, they report a significant correlation both between birth rates and latitude as well as season. Thus, the apparent seasonal patterns for month of birth, initially suggested to be specific for multiple sclerosis is indeed observable even in the general population. Hence, the association of MS with season may be by chance alone. Thus, proving such a hypothesis may require more objective data collection, where the actual sun exposure or vitamin D levels during pregnancy, is done and the results are normalized for confounding factors such as birth rates in a particular season in general population. This becomes even more important with the increased awareness about vitamin D deficiency and easy availability of supplements, thus questioning a direct association of sunlight availability or exposure to vitamin D deficiency in modern scenario.

Lessons learnt from animal model of diseases: For the past three decades, experimental autoimmune (or allergic) encephalomyelitis has (EAE) has been the most successful disease model for MS. The experimental disease can be generated in all mammals including nonhuman primates, thus, making it an indispensable tool for advanced preclinical studies [28]. A PubMed search done in March 2014, with "vitamin D" and "EAE" as search term yielded 69 results. These studies provide an in-depth insight of the various immune as well as non-immune mechanisms by which vitamin D affects the disease outcome of EAE. Some of the main highlights are discussed here.

At the level of innate immunity, vitamin D3 was shown to induce tolerogenic dendritic cells (DCs), leading to increased number of Tregs in lymph nodes and a concomitant increase of autoreactive T cells in CNS in rat model of EAE [29]. Another molecule of innate immune response, TLR8, was shown to be a target of vitamin D3. By inhibiting the TLR8 signaling cascade in monocytes, vitamin D conferred protection from diseases by decreasing the production of inflammatory cytokines TNF-a and IL-1b, the expression of which depends on IL-8 signaling [30]. Recently, vitamin D was has also been shown to effect the NKT cell function, and it has also been shown that IL-4 derived from NKT cells conferred the vitamin d mediated protection from EAE in mice [31]. Vitamin D also has an effect on the adaptive arm of immune response in EAE. Most observations point to the fact that vitamin D inhibits the number or function of inflammatory T effector cells (Th1 as well as Th17, and their cytokines) while increasing the regulatory (Tregs) or immunosuppressive (IL-10, Th2 cells) T effector cells functions.

Another interesting report suggesting that protective effects of vitamin D is immune mediated, is the study of Spanier *et al.* which showed that Ifn-g gene was needed for VDR gene expression in CNS. This may explain why certain populations such as Sardinians have a high risk of MS despite high ambient UV availability from sunlight, since Sardinian MS patients frequently carry a low Ifn-g expresser allele [32]. It is also interesting to note here that UV radiations have been found to suppress EAE independent of vitamin D. This seems to be mediated through local suppression of CCL5 production in CNS (due to UV exposure), in turn preventing migration of inflammatory cells to CNS. A systemic increase in immunosuppressive cytokine IL-10 was also reported in the same study [33].

A major lesson learnt from animal model of disease is that not only vitamin D levels, but the form in which it is present in the body is critical in determining its protective role in MS. It was reported almost two decades ago that in contrast to calcitriol, neither UVB nor 25-hydroxyvitamin D administered after the onset of EAE could inhibit disease progression. It was shown that 1,25-D3-treated rats showed an almost complete inhibition of CD4 antigen expression and significant decrease in the number of OX42-positive cells in various brain tissues, thus establishing 1,25 dihydroxyvitamin D3 (calcitriol) as a promising therapy for multiple sclerosis [34]. Later, it was also reported that while calcitriol prevents EAE in both male and female mice, colecalciferol was found to be effective only in female [17]. This was found to be dependent on the 17β-estradiol levels [35]. In their study in mice model, Subramanian *et al.* have shown that GPR30 membrane estrogen receptor (MER) is the key mediator in estradiol dependent regulatory effects of vitamin D3 in EAE [36].

Besides exerting its protective through immune mediators, vitamin D may also be effective in MS therapy due to its more direct

effect on CNS. It was shown that vitamin D enhances the neural stem cell proliferation and oligodendrocyte differentiation, thus promoting CNS recovery [37].

Genetics evidence: It is now well understood that genes are important predisposing factors in all autoimmune disorders. The most important amongst them are the polymorphisms in the major histocompatibility complex (MHC). With reference to MS, MHC haplotypes especially those containing HLA-DRB1*1501 has been shown to have a strong association with increased MS risk, being strongest in North European population, but have been reported for other populations as well . In 2006, a vitamin D response element (VDRE) was identified in the HLA-DRB promoter region [38], thus suggesting a direct gene-environment interaction in MS.

Since vitamin D deficiency is thought to be associated with a greater MS risk, it can be expected that variants of vitamin D metabolizing genes should be associated with MS risk too. Single Nucleotide polymorphisms in CYP27B1, the enzyme that converts 25- hydroxyvitamin D to 1,25-dihydroxyvitamin D, namely, rs12368653, rs10876994, rs118204009 and rs703842; and rs2248359 polymorphism in CYP24A1, the enzyme that initiates the degradation of 1,25-dihydroxyvitamin D, were shown to be associated with MS in Caucasian populations [39]. In a cross-sectional study published in 2014, the authors report a significant association of SNPs in GC, i.e., the group-specific component (vitamin D binding) protein and CYP2R1 (enzyme found in liver that concerts vitamin D to 25-hydroxyvitamin D) on 25(OH)D in MS patients [40].

In 2013, International Multiple Sclerosis Genetic consortium reported the presence of 110-MS associated risk variants outside of the MHC locus [41]. Interestingly, VDR binding sites were found to be significantly enriched near these genes. All these findings highlight the importance of gene-environment interaction in complex autoimmune diseases such as MS, where the exact disease pathogenesis is not clearly understood.

Vitamin D in immunopathogenesis of MS: With the discovery of Vitamin D receptor on a variety of immune cells, a lot of interest has developed in recent times in exploring the various immune functions mediated by vitamin D. This makes it an important molecule to study in reference to an autoimmune disease such as MS, where the major pathological changes are conferred by component of host's own immune system. In the previous section on "lessons learnt from animal models of disease", we have already seen how various vitamin D metabolites can affect various components of immune system. In this section, we briefly review the various human studies that link vitamin D deficiency to immunopathogenesis of MS.

Immunoglobulin-like transcript (ILT) 3 molecules are inhibitory receptors which when highly expressed on surface of antigen-presenting cells can renders them tolerogenic, thus, in turn inhibiting T cell proliferation and increasing suppressor T cell activity [42]. The work of Waschbisch *et al.* shows that ILT 3 expression on APCs by IFN beta can be further enhanced by vitamin D [43]. Another study linking vitamin D with ILT 3 was published in 2010, which showed that vitamin D intake during pregnancy increased the mRNA levels of ILT 3 and ILT4 in umbilical cord blood, thus explaining the protective effect of vitamin d during pregnancy in reducing the risk of MS in the offspring [44].

In the randomized controlled trial study of 49 MS patients, PBMC proliferative responses to neuron antigens myelin basic protein and exon-2 were suppressed in patients treated with colecalciferol. This further suggests an immune suppressive action of vitamin D in autoimmunity [45].

Vitamin D supplementation

To utilize vitamin D supplementation as therapy in MS, serum vitamin D levels have to be closely monitored. Also, there is a need to define vitamin D deficiency in measurable quantities. Clinical testing for vitamin D requires the measurement of 25-hydroxyvitamin D in serum. According to the Vitamin D council, serum levels less than 50 nM/L are considered deficient, 51 -74 nM/L as insufficient, and more than 75 nM/L as sufficient. Vitamin D levels greater than 375 nM/L are considered toxic and may cause increased levels of calcium in blood, or hypercalcemia.

As discussed previously, the biochemical form of vitamin D may also have an important role, especially with regard to its protective role in MS. Currently; vitamin D supplements are available in various forms such as alfacalcidiol, calcifediol, calcitriol, colecalciferol, or ergocalciferol. It is to be noted here that colecalciferol (the same form that the body produces upon sunlight exposure) is converted 5 times more than vitamin D2 or ergocalciferol in body. It has been shown that colecalciferol is significantly more effective than ergocalciferol in increasing serum 25-hydroxyvitamin D levels [46]. In their 2006 review, Houghton and Vieth present a case against using ergocalciferol as vitamin D supplement, primarily, because the metabolites derived from it had decreased ability to increase serum 25-hydroxyvitamin D levels, showed decreased binding to VDR, and shorter shelf life [47]. Now, as it is clear from existing literature that VDR binding is crucial for exerting the protective role of vitamin D in MS, especially for the immunomodulation, hence, it may be concluded that colecalciferol should be the supplement of choice for Vitamin D therapy in MS. It is to be noted here that most of the ongoing clinical trials in MS are, indeed, using colecalciferol supplements [48]. However, as previously discussed, studies on EAE suggests that while calcitriol can inhibit disease progression, colecalciferol could not, and hence, the metabolite being used as supplement may also determine the efficacy of vitamin D therapy in MS.

The recommended treatment of vitamin D deficiency is either 6,000 IU/day or 50,000 IU/week of vitamin D3 or vitamin D2 for 8 weeks. A dose of 2,000 IU/day (or more) is likely to be needed to maintain blood levels at 75 nM/L, which is considered as adequate in most adults. Higher dosing may be required and treatment at two or more times this dose may be required especially in obesity. Although considered quite safe at recommended dose, sustained high levels of vitamin D of 10,000 IU/day or more may cause renal damage or calcium deposits with other tissue injury, therefore, doses higher than 4,000 IU daily should be given under medical supervision.

Findings of clinical trials

An important consideration while inferring vitamin D as a risk factor of MS is whether it is truly an association or not. It has been argued that since MS is a disability disorder, the patients may have restricted outdoor activities, and hence lower vitamin D levels. Thus, the observation that MS patients have lower serum vitamin D levels can indeed be an effect of disease itself, rather than a cause. The only

argument against this theory comes from observation where adequate vitamin D levels in early life decreased the risk of MS. Clinical trials can provide an important insight into resolving this query.

In their systematic review of randomized, double-blind, placebo-controlled trials, the authors extracted and examined data from the 5 clinical trials on clinical efficacy of vitamin D in multiple sclerosis published till 2012 [49]. The authors concluded that there is insufficient data on this aspect, and the existing studied also have a handicap due to their small study sizes and heterogeneity of dosing, form of vitamin D tested (vitamin D3 in four trials, and vitamin D2 in one), and outcome clinical measures.

In their 2013 review, Dörr *et al.* provides the list of various ongoing clinical trials on vitamin D in multiple sclerosis [48]. It is to be noted that all these trials are using colecalciferol as the vitamin D supplement at a relatively high dose of 5000IU/ day, either as daily doses, weekly or monthly dose. The primary clinical outcomes in these trials are either relapse rate or development of new lesions. All of these trials are randomized double blind controlled phase II trials, with the exception of trial number NCT01667796, which is a non-randomized phase I trial. Also, this is the only study that cytokine levels and percentages of T and B cells, and gene expression as secondary clinical outcomes. Once concluded, these trials may shed some light on improving our current understanding on role of vitamin D supplement therapy in MS.

Thus, to truly understand whether vitamin D therapy can alleviate MS symptoms and disease progression, well defined prospective studies that normalizes the data for other variables such as dose of therapy, form of vitamin D supplements used, gender, early life exposure to sun, place of origin, place of work, are required. Moreover, it will also be beneficial to assess the study subjects for their genetic profile (alleles and polymorphisms of susceptibility genes) as well as immunological markers such as different T effector populations, pro and anti-inflammatory cytokines, chemokines, etc. This will also help in unraveling the possible cascade of events through which vitamin D may be influencing the course of MS.

Conclusion

The epidemiological, genetic and immunological evidence for association of vitamin D deficiency with increased risk of developing MS is quite compelling. Thus vitamin D supplementation is emerging as a promising therapy supplement in MS. This becomes even more significance in the light that vitamin D deficiency is becoming a more common global problem with change in lifestyle. However, because of ease of administration, low cost, and almost no toxicity even at relatively high dose, as well as numerous and diverse biological health benefits of vitamin D, it may be beneficial to evaluate this supplement therapy not only in MS, but also in general population. This in turn may further help in reducing MS risk, as it is now clear that the protective effect of vitamin D during disease onset may be far more important than its therapeutic role in modifying the course of disease. Thus, maintaining sufficient levels of vitamin D as early as in-utero (maternal vitamin D levels), and from early childhood till late adolescence may prove to be the most effective in reducing the risk of disease onset. However, since various environmental and genetic factors interact with vitamin D in exerting its protective role, hence, such factors must especially be considered in planning future trials to draw meaningful inference on the efficacy of vitamin D therapy in MS. Moreover, appropriate dose, as well as form of supplementation (such as calcitriol) will also be critical to achieving the protective effect of the therapy. As of now, it can be concluded that although the exact mechanism of protective role of vitamin D in MS may still not be very clear, vitamin D supplement therapy can still be safely administered to MS patients and may even prove beneficial.

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