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Vitamin D Deficiency and Multiple Sclerosis: Investigating a Potential Association

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ABSTRACT

Multiple sclerosis, an autoimmune demyelinating illness, is a common disease in young adults. Low vitamin D levels are a risk factor associated with multiple sclerosis. Numerous regulatory functions, particularly those related to the immune system, depend on vitamin D. Following the discovery of seasonal and geographic variations in the incidence of multiple sclerosis worldwide, it was suggested 50 years ago that vitamin D may play a role in the risk of developing and relapsing multiple sclerosis. This literature review aims to investigate how vitamin D may influence the development or recurrence of multiple sclerosis. The following mesh terms were used to select 21 articles: Cholecalciferol, vitamin D, multiple sclerosis, and relapses of multiple sclerosis. In addition to the indirect beneficial effects of sunlight exposure, vitamin D appears to be crucial for the immunological mechanisms underlying multiple sclerosis. To the best of our knowledge, there is no clear consensus regarding the precise role that vitamin D plays in helping people with MS. It is recommended that more multi-center randomized clinical trials be conducted to determine whether vitamin D can prevent or treat MS.

Keywords: Hypovitaminosis D, Vitamin D, Multiple sclerosis, Relapsing-remitting multiple

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Introduction

Debilitating and devastating neurological results are the result of multiple sclerosis, a chronic autoimmune demyelinating disease of the central nervous system that typically affects young adults worldwide [1, 2]. The precise aetiology is still unknown, and the most often affected age range is 20-40 years old [1, 2]. However, contributing variables associated with MS pathophysiology include hereditary and environmental factors, including low vitamin D, smoking, Ebstein-Barr virus (EBV) infection, lack of physical activity, and childhood obesity [1-4]. MS is a neurodegenerative illness in addition to an autoimmune inflammatory disease [1]. Based on the history of the disease, MS has been divided into four classes: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) [1]. A phase without relapses (PPMS), which is defined by a continuous progression of worsening symptoms from the beginning of the disease, might precede an MS course that starts with RRMS and progresses to SPMS [5, 6].

Focused inflammation and demyelination zones are present in MS lesions, which trigger a glial response and ultimately axonal damage [5].

Ataxia, tremors, weakness, and spasticity are among the clinical consequences that MS can cause. Furthermore, in MS patients, fatigue—defined as a loss of force-generating capacity during sustained motor activity—further advances to impairment. Relapses, attacks, and flare-ups are neurological impairments that last for a few hours to several days [7]. The systemic T and B cells that activate immune cells and penetrate the blood-brain barrier (BBB) are the fundamental immunopathologic mechanism of multiple sclerosis [8]. Furthermore, it is estimated that more than 2.5 million individuals worldwide suffer from multiple sclerosis (MS), an incidence that has significantly increased since 1990. Additionally, between 250,000 and 300,000 persons in the US suffer from MS [2].

One of the lipid-soluble vitamins produced after 7-dehydrocholesterol is converted to vitamin D by the skin is vitamin D (cholecalciferol). For this conversion, ultraviolet (UV) B radiation is required. Furthermore, compared to women in the southern states, 3.5 times as many women in northern states lived with MS, according to a major cohort trial conducted in the United States. In places with less than 2000 hours of sunshine each year, MS is reported to be more common. Additionally, MS is known to exhibit seasonal variability, with the highest disease activity occurring in the spring and the lowest in the autumn. This can be linked to the winter months' reduced exposure to sunlight [9]. Therefore, it was proposed that the correlation between low vitamin D and multiple sclerosis is not coincidental.

Results and Discussion

Physiology of vitamin D and its function in immunological and central nervous system development

The skin (via sunlight or UV rays), liver (hepatic hydroxylation by CYp27A1 and CYP2R1), and kidney (1α-hydroxylation) all produce vitamin D, a steroid lipid-soluble hormone, into the hormonally active form 1,25 dihydroxy vitamin D (1,25D) (calcitriol) [10, 11]. The calcium-regulating parathyroid hormone (PTH) stimulates the kidney to carry out this conversion. It is well-known that vitamin D plays a major role in calcium homeostasis due to the stimulation of intestinal calcium absorption. Additionally, vitamin D is essential for adequate development and function of the brain, immune cells, and immune response modulation. In vitro, vitamin D metabolites influence the phenotype and function of several immune cells, mainly through interaction with the vitamin D receptors (VDR) [12].

Cells called VDR, which belong to the nuclear receptor superfamily and are found in the skin, bone, muscle, gut, gonads, B and T lymphocytes, microglia, activated monocytes, and central nervous system, are responsible for identifying the active form of vitamin D [10, 11]. Additionally, the CNS expresses 24-hydroxylase and 1α-hydroxylase, which means that the CNS may be where vitamin D metabolism and catabolism take place. Additionally, mice who received intrauterine vitamin D depletion developed brain disorders and had lower amounts of nerve growth factor at birth, highlighting the critical function of vitamin D in the brain [13].

Chylomicrons carry dietary vitamin D into the bloodstream after it has been absorbed in the small intestine. Several conditions, including high levels of calcium, phosphorus, and plasma calcitriol, as well as the lack of parathyroid hormone and renal illness, can impede the synthesis of 1,25D. The typical range of 1,25D is 8 ng/mL (20 nmol/L) to 15 ng/mL (37.5 nmol/L), according to the dietary reference intakes [14]. According to the dietary reference intakes, assuming insufficient exposure to sunlight, the recommended daily intake of vitamin D is 5–15 μg, depending on age, sex, pregnancy, and breastfeeding. Since 1 μg of vitamin D is equivalent to 40 IU, adults should consume 5 μg (200 IU), adults aged 51–70 years should consume 10 μg (400 IU), and those under 70 years should get 15 μg (600 IU) of vitamin D [14]. Cereal, fortified dairy products, and fatty fish are dietary sources of vitamin D [9]. The reduced incidence of MS in Norway's Atlantic coastline region compared to other Scandinavian regions is believed to be caused by a diet high in vitamin D [9].

Immune cell differentiation, transcription, and proliferation are all known to be regulated by VDR activity [10]. Additionally, 1,25D modulates the adaptive and innate immune responses for a variety of immune cells that express VDR, including T lymphocytes, antigen-presenting cells, and neutrophils like dendritic and macrophage cells [11]. T regulatory cells (Treg), important mediators of the immune system's maturity, are produced and act as a result of 1,25D's stimulation of dendritic cell tolerogenicity. Additionally, 1,25D directly suppresses the growth of T cells [11]. Furthermore, low vitamin D can affect cytokines, which are mediators of communication

between immune cells and other organ cells; to be clear, when vitamin D levels are raised in MS patients, there may be an impact on cytokine gene expression, which may alleviate symptoms [14].
Notably, MS patients have lower levels of numerous anti-inflammatory cytokines and higher amounts of inflammatory cytokines (such as interleukin-2, interferon-γ, and tumor necrosis factor-α) than healthy persons [14]. Numerous studies have shown that vitamin D administration raises interleukin-10 and 17 levels. High-dose vitamin D increases central memory CD4 T-cells and naive CD4 T-cells while decreasing the percentage of IL-17-producing CD4 T-cells [12]. In addition, more than 1000 genes in the human genome are regulated by 1,25D signaling. The extra-skeletal functions of 1,25D signaling, such as their function in controlling the innate and adaptive immune systems, are facilitated by the widespread expression of VDR and CYP27B1 in a variety of tissues. Additionally, VDR is thought to be crucial for innate defense against viruses and bacteria [15].

Sunlight exposure and MS activity
With a lower prevalence in equatorial regions and a higher incidence in high-latitude regions (both hemispheres), multiple sclerosis exhibits a classical geographical distribution. For example, compared to the southern regions, the MS prevalence is higher in the northern European and American regions. On the other hand, the southern coast of Australia indicates a lower MS prevalence compared with the sub-tropical northern coast. Furthermore, compared to low altitudes, a lower prevalence of MS has been seen in Switzerland at higher elevations, which is consistent with the higher elevations receiving more optimum sunlight. Hence, the geographical differences are considered a contributing factor to the MS typical distribution [11].
The early questionnaire studies assessed the average amount of time spent outdoors on weekends and vacations throughout the first two decades of life in MS persons compared to the control. As a result, participants who spent most of their adolescent years outside had a noticeably lower risk of developing multiple sclerosis. Skin actinic activity investigations, which assessed the dorsal side of the hand and indicated total sun exposure, also supported the latter research; in a similar vein, those with the highest actinic activity level were at the lowest chance of developing multiple sclerosis. Furthermore, a meta-analysis examined 52 studies from various countries worldwide. According to the preliminary findings, there is a highly substantial correlation between the yearly UV amount in various nations and the prevalence of MS. Pierrot-Deseilligny and Souberbielle [16] found a link between the frequency of MS and sunshine maps that depict a wide climate.
Furthermore, an Australian case-control study assessed whether the first demyelinating episode was related to the latitude difference and the relationship between solar exposure and 25(OH)D status. Similarly, higher levels of 25(OH)D were substantially linked to decreased odds of demyelinating events, as were higher levels of actinic skin damage. Additionally, a 32% rise in the frequency of initial demyelinating events was noted from Australia's low to high-latitude regions. This independent relationship between MS risk and sun exposure suggests that UV radiation may have an impact on MS risk. A study on experimental autoimmune encephalitis (EAE), which showed that whole-body UV light irradiation could prevent the illness in rats, may lend credence to the latter theory [17].
UV light may have an immunomodulatory effect on the development of multiple sclerosis, according to another animal study. Rats that received US radiation every other day or every third day showed significantly slower EAE progression than the group that received only pretreatment. Female rats with EAE (the animal model of MS) were randomly assigned to receive UV radiation every third day or only pretreatment with UV radiation. The group exposed to UV light every other day experienced a notable postponement of the start of symptoms and a reduction in the peak intensity of symptoms. Particularly, the cumulative illness index of EAE showed a substantial decline in both the every-other-day and every-third-day UV radiation groups [18]. Remarkably, a recent Australian study revealed that the chance of developing multiple sclerosis is negatively correlated with the amount of UV light received during the first trimester of pregnancy [19].

Vitamin D and MS activity
A link between MS and solar radiation was first suggested over the past fifty years, and then it was suggested that enough vitamin D and calcium supplementation during CNS development could reduce the risk of MS. However, it is still unclear exactly how vitamin D and sun-induced hormonal changes affect the progression of MS [19]. A high risk of MS, a worsening of the disease's course, and a higher chance of relapses have all been connected to low vitamin D levels. Depletion of vitamin D has also been found in 70% of MS recurrence patients. Furthermore,

a high serum vitamin D level was linked to a lower Expanded Disability Status Scale (EDSS) score, weariness, and relapse risk [20].

People who eat a diet strong in vitamin D, such as fish oil, have been found to have a lower chance of developing multiple sclerosis. Additionally, elevated levels of vitamin D in the blood were linked to: a lower chance of getting multiple sclerosis Patients with MS who had better T-cell regulatory function had better clinical results and a higher chance of not relapsing as children. In animal models of MS, 1.25D had also shown a preventative effect for EAE, reversibly preventing the course of MS when vitamin D was administered after symptoms began [19].

Numerous studies have demonstrated that decreased bone mass, fracture risk, and dental caries were highly prevalent in individuals with multiple sclerosis and vitamin D deficiency. Due to high maternal turnover and higher vitamin D requirements during late lactation and pregnancy, MS symptoms in postpartum women deteriorated throughout the first three months of their lives. In the mid-1980s, a group of young MS participants showed a decrease in relapse after taking vitamin D, calcium, and magnesium supplements for one to two years. Additionally, MS is uncommon among Greenland Eskimos, perhaps as a result of a diet high in vitamin D, including fish oil. Vitamin D supplementation reduced the lifetime risk of MS by 40% for women, according to a prospective longitudinal study that assessed the relationship between vitamin D intake and the incidence of MS. It was the first big prospective trial to confirm the positive impact of vitamin D supplementation in preventing multiple sclerosis [21].

257 MS patients were included in a different study along with 514 control subjects and young American soldiers (77 black and 148 white) who had at least one serum sample taken before the beginning of any neurological symptoms while serving in the military. The MS risk was considerably lower in the group with high vitamin D levels (99–152 nmol/l) than in the group with low levels (15–63 nmol/l). This study concluded that participants, especially white people, who had normal or high vitamin D levels were less likely to develop multiple sclerosis. Based on the latter study, Ascherio and Munger concluded that maintaining the circulation vitamin D level over 100 nmol/l during adolescence and childhood could prevent about three-quarters of MS cases. Furthermore, the positive impact of vitamin D was demonstrated in France following a verified association between the average level of vitamin D in the general population and the incidence of multiple sclerosis in the same area [12].

According to a meta-analysis by Zheng *et al*. [22] assessing vitamin D's impact on MS patients, vitamin D as an adjuvant therapy did not significantly improve MS based on the EDSS score. In addition, there was no difference in the MS group's Annualised Relapse Rate (ARR) as compared to the placebo group. Nevertheless, this finding is predicated on preclinical research and a small sample size.

Conclusion

Vitamin D is important for many bodily organs, including the development of the central nervous system, and it also plays a part in immunological processes. Vitamin D may help treat or prevent multiple sclerosis, according to several observational studies. To our knowledge, however, no conclusive randomized clinical trial has validated the positive effects of vitamin D in MS patients. Vitamin D can be given to MS patients because it has no negative effects and has been shown in multiple trials to have a possible positive benefit. To determine the preventative and therapeutic effect of vitamin D in MS, more multi-center randomized clinical trials would be necessary.

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