Review Article

Vitamin D and multiple sclerosis: Potential pathophysiological role and clinical implications

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Abstract

Multiple sclerosis (MS) is thought to arise due to an interplay of genetic and environmental risk factors. Vitamin D, besides maintaining bone health and calcium metabolism, is thought to play an immunomodulatory role in the central nervous system. Studies have shown that patients with the highest level of Vitamin D (99–152 nmol/l) had a significantly lower risk of MS than the subgroup with the lowest levels (15–63 nmol/l). Furthermore, populations having a high oral intake of vitamin D had a decreased risk of MS. Hypovitaminosis D is one of the environmental risk factors for MS based on numerous physiological, experimental and epidemiologic data, which can be corrected to provide an effective therapeutic option for this debilitating disease.

Key words: Immunomodulatory, multiple sclerosis, vitamin D

Introduction

Vitamin D, besides maintaining bone health and calcium metabolism, is involved in a number of functions through its action on Vitamin D receptors (VDR), which are present in most cells and tissues of the body. Vitamin D could play an immunomodulatory role in the central nervous system (CNS). Hypovitaminosis D is currently one of the most studied environmental risk factors for multiple sclerosis (MS) and is potentially the most promising in terms of new clinical therapeutic implications.

MS is thought to arise due to an interplay of genetic[1,2] and environmental risk factors.[3,4] Hypovitaminosis D has long been suspected to be a risk factor for MS.[5-8] The hypothesis that vitamin D plays a substantial protective role in MS comes from diverse experimental and epidemiological studies.

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Physiological and metabolic basis

Vitamin D is a steroidal hormone metabolized successively in the skin (by sunlight or UV rays), the liver and the kidney to the active metabolite 1, 25 dihydroxyvitamin D (calcitriol). This metabolite is recognized by tissues containing specific VDR, which are present in many parts of the body like skin, muscle, bone, gonads, intestine, CNS, microglia, activated monocytes and B and T lymphocytes. Activation of VDR is known to alter transcription, proliferation and differentiation of immune cells.[9-11]

Vitamin D, ingested orally or formed in the skin, is transformed to the major circulating form, 25-hydroxyvitamin D (25-OH-vitamin D) in the liver, and its levels are sensitive to vitamin D intake and sun exposure and are markers of Vitamin D availability to tissues, best reflecting the vitamin D status of the patient. Maintaining blood concentrations of 25-OH vitamin D above 80 nmol/l (approx 30 ng/ml) not only is important for maximizing intestinal calcium absorption but is also important for providing the extra-renal 1 alpha-hydroxylase that is present in most tissues to produce 1, 25 dihydroxyvitamin D.[12]

This is the biologically active metabolite, with most biological effects mediated through binding to the VDR. In addition to its well-known action on calcium and phosphorus metabolism, vitamin D seems to have other important general effects, in particular anti-inflammatory, anti-proliferative and also modulatory effects, on

neurotrophins, growth factors and neurotransmitters in the CNS of mammals.

Experimental and immunologic basis

There have been extensive studies in favor of vitamin D having a major role in experimental autoimmune encephalitis (EAE). Recent studies suggest that this role could be both anti-inflammatory and immunomodulatory. Vitamin D has a protective and curative role in preventing the induction of EAE in mice if given before the triggering of the disease and improves clinical signs and symptoms, if given later.[11,13-17]

In EAE, vitamin D is thought to have an anti-inflammatory effect[18] by reducing macrophages[16] and by regulating certain cytokines,[19,20] a protective effect on myelin by activating oligodendrocytes[21] and an immunomodulatory effect on T lymphocytes by inhibiting the T-helper 1 subset (TH1) development and increasing T-helper 2 subset (TH2) and regulatory T lymphocyte (Tr) restoration.[11,22,23]

A study by Smolders *et al.*[24] has reported a correlation between serum 25-OH vitamin D levels (indicative of vitamin D stores) and regulatory T cell function. In contrast, levels of calcitriol, intact parathyroid hormone and total calcium were not involved in the correlation between vitamin D status and T cell regulation. Therefore, vitamin D is thought to have a mode of action that may be similar to interferon β. The above study lends credence to a marked immunomodulatory effect of vitamin D.

Epidemiological studies

Latitude affects the prevalence of MS, which increases with distance from the equator, both in northern and southern hemispheres. Geographical areas with low supplies of Vitamin D (Scandanavian countries) correlate with regions having a high incidence of MS.[25,26] A recent study has found a correlation between latitude and serum vitamin D level in Caucasian adult subjects in a metaanalysis covering 394 studies.[27] Vitamin D deficiency is an unrecognized epidemic in both children and adults in the United States.[12] In a study conducted in an outpatient setting in Boston, 41% of the 169 otherwise healthy adults between 49 and 83 years of age were found to be vitamin D deficient throughout the year.[28] The prevalence of vitamin D insufficiency is 40–45% in the German population, and an additional 15–30% people are vitamin D deficient.[29]

While vitamin D deficiency is a recognized problem in some northern latitude countries, recent studies have shown that even in sunny countries like India[30] and Australia,[31] vitamin D deficiency may be more prevalent than that thought initially.

A study undertaken in Tasmani,a which included 136 MS patients and 272 controls, showed that the risk of MS was found to be lower in those who, in their childhood, had been exposed to sunlight during their holidays and weekends than in those who had not benefited from such an exposure ($P < 0.01$), a finding that also correlated with the degree of actinic damage to the skin (an indicator of cumulative skin exposure) ($P < 0.01$)[32] Modern day lifestyles that cause children and young adults to stay indoors and never see daylight or wear sun protection always are also at risk.

A landmark study analyzed the risk of MS based on the serum level of 25-OH vitamin D in normal subjects before MS occurred in some of them. It found a direct link between level of 25-OH vitamin D and the risk of MS without having to rely on latitude or sun exposure.[33] It was observed that the subgroup that had the highest vitamin D level between 99 and 152 nmol/l had a significantly lower risk of MS than the subgroup with the lowest levels (between 15 and 63 nmol/l) ($P < 0.01$). This led the authors to conclude that almost three quarters of MS might be avoided if serum levels of 25-OH vitamin D were maintained above 100 nmol/l during childhood and adolescence in the general population. Studies have shown that populations that had a high oral intake of vitamin D in the form of oily fish[34] or vitamin supplements[35] had a decreased risk of MS.

Clinical studies

Clinical studies on vitamin D levels in patients with MS are accumulating, thereby suggesting a possible role for vitamin D in MS. In three different studies, patients had significantly lower levels of vitamin D during relapses than at other times.[36-38]

In several studies, serum levels of 25-OH vitamin D levels in MS patients were significantly reduced when compared with control subjects.[36,39] In a study of 167 consecutive outpatients with relapsing-remitting form of MS referred to a hospital in Paris, 83% of the patients were found to have vitamin D insufficiency, with levels of 25-OH vitamin D below 75 nmol/l, with 17% in a state of deficiency (<25 nmol/l). Nearly 95% of the patients did not reach the currently recommended level of 100 nmol/l, with an overall mean of 52 nmol/l.[40] All these studies strongly suggest that most patients with MS have serum vitamin D levels that are significantly low when compared with the current recommended norms.

Studies on the use of vitamin D in MS are rare and limited in scope. In a study published by Goldberg in 1986, 10 patients of MS had a 60% reduction in the predicted number of relapses when given a 2-year course of treatment with vitamin D (5000 IU/day in the form of cod liver oil). This study however did not include any control group.[41] In another uncontrolled study, 15 patients who received 100 IU/day

of vitamin D for 48 weeks experienced a 50% reduction in relapses.[42]

In a study conducted by Mahon *et al.* on 39 patients with MS (17 treated with 1000 IU/day of vitamin D3 for 6 months and 22 control subjects), the serum levels of transforming growth factor- β1 (TGF-β1) increased significantly from a baseline value of 230 ± 21 pg/ml to 295 ± 40 pg/ml over a period of 6 months in treated patients. Placebo treatment did not have any effect on serum TGF-β1 levels. No change was seen in the levels of tumor necrosis factor alpha (TNF-α) interferon-gamma (IFN-γ) or interleukin-13 (IL-13) following vitamin D supplementation. Vitamin D supplementation was also associated with increased vitamin D status.[43] Possibly, serum TGF-β1 levels along with increased vitamin D levels could signify recovery or improvement in the status of MS.

Researchers from Canada have recently demonstrated that the use of high doses of vitamin D3 (14,000 IU/day) for a long period of 6 months to 1 year did not induce hypercalcemia or notable side-effects, despite serum vitamin D levels of nearly 400 nmol/l.[44]

Based on physiologic evidence, experimental and epidemiologic data, limited but encouraging clinical studies, the hypothesis that hypovitaminosis D is one of the environmental risk factors for MS has rapidly gained support and needs to be confirmed by extensive therapeutic trials. Since all the previous studies used different dosages of vitamin D3, ranging from 100 IU/day to 14,000 IU/day, appropriate vitamin D3 dosages would need to be determined for different populations and age groups.

Conclusions

The existence of a widespread deficiency of vitamin D in the general population and the consequent hypovitaminosis D, due to its possible role in MS, can be easily corrected to provide a simple, yet effective, therapeutic option for this debilitating disease.

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