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Review articles

Why vitamin D deficiency is thought to be a risk factor for multiple sclerosis?

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Geographic variation in the incidence of cause unknown multiple sclerosis (MS) supports the probability that environmental factors are involved in the etiology. Vitamin D inhibits the development of autoimmune diseases such as diabetes, rheumatoid arthritis, lupus and multiple sclerosis. Vitamin D for humans is obtained from sun exposure, food and supplements. Preliminary evidence suggests that persons with high circulating levels of vitamin D are at lower risk of MS, thus, vitamin D supplementation may reduce the risk of developing MS, also may reduce the relapse rate among patients with relapsing-remitting MS. The results of previous studies suggested that MS risk is related to vitamin D status at different ages, possibly starting in utero and extending through early childhood, adolescence and adult life. Independent data may argue for potential additional mechanisms associated with a 25-OH-D decrease immediately prior to disease manifestation. Here are referred evidence for the relationship between sun exposure, vitamin D, and the data of MRI in patients with multiple sclerosis.

Key words: vitamin D, vitamin D deficiency, multiple sclerosis

Vitamin D was named in 1922 by American biochemist Elmer McCollum (1879-1967), who performed experiments to understand the contents of fish liver oil. It was named "D" because it was the fourth substance he identified.

Vitamin D is a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium and phosphorus in our bones and aid in cell to cell communication throughout the body. Five forms of vitamin D have been discovered, vitamin $D_1 - D_5$. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol). Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements [14]. The body can also synthesize vitamin D (specifically cholecalciferol) in the skin, from cholesterol, when

sun exposure is adequate (hence its nickname the "sunshine vitamin") [3]. Vitamin D_3 is made in the skin when 7-dehydrocholesterol reacts with ultraviolet light at 270-300 nm wavelengths - peak vitamin D_3 production occurs between 295-297 nm. It is only when the UV index is greater than 3 that these UVB wavelengths are present. Frequent exposure of the skin to sunlight promotes sufficient vitamin D synthesis without the need for supplements, however, adults who have darker skin pigmentation or frequently wear sun protection during outdoor activities are often vitamin D deficient.

Vitamin D deficiency is prevalent in infants who are solely breastfed and who do not receive vitamin D supplementation and in adults of all ages who have increased skin pigmentation or who always wear sun protection or limit their outdoor activities. Vitamin D deficiency is often misdiagnosed as fibromyalgia. A new dietary source of vitamin D is orange juice fortified with vitamin D. The recommended adequate intakes vitamin D in the absence of exposure to sunlight is a minimum of 1000 IU vitamin D/d to maintain a healthy concentration of 25(OH) D in the blood [9].

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees [6,13,17]. MS is considered to be multifactorial with an autoimmune component. There is growing evidence suggesting that hormones can affect and be affected by the immune system [5]. The hypothesis that there was insufficient vitamin D in the body, as a risk factor for developing MS, formed and developed for over 50 years [1]. Further experimental, epidemiological and genetic studies showed that the mediator between sunlight and immune system is likely to be vitamin D [2,8].

Low levels of vitamin D are associated with multiple sclerosis. Supplementation with vitamin D may have a protective effect, but there are uncertainties and unanswered questions. "The reasons why vitamin D deficiency is thought to be a risk factor for MS are as follows: I - MS frequency increases with increasing latitude, which is strongly inversely correlated with duration and intensity of UVB from sunlight and vitamin D concentrations; II - prevalence of MS is lower than expected at high latitudes in populations with high consumption of vitamin-D-rich fatty fish; III - MS risk seems to decrease with migration from high to low latitudes." A clinical trial sponsored by Charite University in Berlin, Germany, was begun in 2011, with the goal of examining the efficacy, safety, and tolerability of vitamin D_3 in the treatment of multiple sclerosis [2, 15, 16].

According to modern concepts, hormones such as prolactin and vitamin D, and more recently identified ones, such as leptin and gherlin, may be used to modulate the immune response and may also influence the course of MS [5]. The influence the course of MS has been a matter of controversy for a long time.

Results from epidemiological and clinical studies clearly suggest that changes in vitamin D serum concentrations are correlated with the magnitude of the risk of developing MS, the phases of relapsing-remitting MS and with gender differences in vitamin D metabolism. Experimental and clinical studies also have established that 25-hydroxy vitamin D (25(OH)D) and 1,25-dihydroxy vitamin D (1,25(OH)2D) exert an immunomodulatory effect in the CNS and peripheral organs of the immune system [18].

Issues that are discussed include the vitamin D serum concentration needed to suppress the aberrant immune response in MS patients; a subgroup of MS patients suitable for vitamin D treatment, the vitamin D being applied in optimally effective and safe dosage.

The majority of MS patients are deficient in vitamin D in the blood serum or failure of its consumption. It is also noted that during exacerbations of MS, vitamin D concentration in the blood is lower than during remission and exacerbation severity is inversely proportional to it. Furthermore, studies have shown that during the months of low irradiation, the number of multiple sclerosis exacerbation increases.

In animal experiments it was shown that calciferol is able to prevent the development of acute autoimmune encephalomyelitis (AAE - MS model), and reduces the severity of the clinical manifestations of the introduction to the advanced stage of the disease. UV irradiation and also the introduction of cholecalciferol is largely prevented the development of the AAE. In vitro studies have also shown that the protective effects of vitamin D appears to relate to the stimulation of cells that produce IL-10 (anti-inflammatory agent), reduction in the number of cells secreting interleukins 6 and 17 (a substance activating inflammation) and with increasing amounts of regulatory T cells (regulate the inflammation process) [2].

A study, participants were more than 7 million Americans, was conducted in the United States. It showed that the level of vitamin D in the blood at least 99.2 nmol/L reduces the risk of developing MS by 62 %, compared to individuals, having concentration of serum vitamin D less than 63.2 nmol/L. At the same time, this study showed that the concentration of vitamin D in the blood serum of healthy young people of the white race is an important risk factor for the development of their MS, regardless of place of birth and latitude of residence [2]. Professor G. Ebers said, "There is absolutely no problem with taking vitamin D up to 4000 IU/day." [10].

Although no significant association between high-dose vitamin D treatment and risk of MS relapses was found, the studies were limited by several methodological limitations [12]. Further larger, more prolonged studies are merited. Any randomized controlled trial assessing the effect on the relative risk of relapse of any formulation or dose of vitamin D, in participants with MS, was eligible [12].

Disease occurrence and progression are considered by some to be associated with low serum levels of vitamin D. Studies investigating vitamin D supplementation in MS patients have illustrated a noticeable improvement in the course of the disease [11].

Until recently, there has been a paucity of data from randomized controlled trials to establish clear cut beneficial effects of vitamin D supplementation during pregnancy. An overview of vitamin metabolism, states of deficiency, and the results of recent clinical trials conducted in the U.S. are presented with an emphasis on what is known and what questions remain to be answered [19].

Prior research evaluated the role of vitamin D deficiency as a risk factor for development of MS and as a modifier of its clinical course as well as of common symptoms of patients with MS, such as pain and depression. The interaction between IFN-β and vitamin D in terms of their combined efficacy was also previously studied both clinically and in an animal model, with yet conflicting results [7].

The present randomized, double-blind, placebo-controlled trial, though modest in its sample size, did not detect beneficial effects of vitamin D supplementation on IFN-β -related Flu-like symptoms in patients with MS, but did provide support to its immunomodulatory properties. Vitamin D appears to influence IL-17 secretion in IFN-β -treated patients in a dose dependent manner. While serum IL-17 was significantly increased after low dose vitamin D treatment, heterogeneous responses were noted after high dose vitamin D [7].

The findings are in-line with a series of clinical trials of vitamin D supplementation for patients with MS, which generally did not show added benefit in terms of clinical efficacy, but did show clues for improvement in markers of inflammation and related MRI findings, beyond the reported effects on disease prevention. Further large scale trials and meta-analyses of available data are needed to elucidate the role of vitamin D for immunocompetence and as part of the treatment armature of immune-mediated diseases as MS [7].

In a study involving 200,000 women, who for 30 years were under observation, it was shown that increased levels of vitamin D in serum are associated with a reduced

risk of multiple sclerosis. In women who took a daily dose of 10 mg vitamin D or more, the risk of MS decreased by 42%. Norwegian scientists have demonstrated that regular (more than three times per week) use of marine fish reduces the risk of MS in young people living in the Arctic Circle (high-risk zone MS).

As Zivadinov said "Sun exposure may have direct effects on MRI measures of neurodegeneration in MS, independently of vitamin D." [20].

For healthy individuals, serum vitamin D concentrations of 50-125 nmol/L (20-50 ng/mL) are generally considered adequate for bone and overall health, according to the Institute of Medicine. Serum vitamin D concentrations of 75-100 nmol/L (30-40 ng/mL) have been proposed as optimal for patients with MS. Achieving these levels may require the use of supplemental vitamin D in doses up to 3000 IU daily; maintaining these levels appears to require doses of 500 to 800 IU daily. The safety and effectiveness of vitamin D supplementation among patients with MS remains unclear [13].

The primary objective of the Golan's study was to test whether vitamin D supplementation may ameliorate IFN-β-induced Flu-like symptoms. Secondary objectives were to evaluate the safety and tolerability of vitamin D in two different regimens, to determine the extent it influences serum 25-OH-D and to assess the effect of vitamin D supplementation on IFN-β- treatment efficacy, determined by relapse rate and EDSS, as well as on the serum levels of cytokines associated with immune-mediated diseases such: IL17, IFN γ and IL-10, proposed to be associated with MS disease fluctuating activity [4,7].

Higher 25-OH-D serum levels were reported with lower risk to develop MS later in life. Likewise, prior to first clinical disease manifestation was associated with an increased risk for MS. The aim was to investigate both 25-OH-D serum levels and Immunoglobulin G (IgG) response against Epstein-Barr virus (EBV) before the first clinical MS manifestation in individuals who had donated blood prior to disease onset [4].

In some studies when considering vitamin D as a key environmental factors were not taken into account or excluded the effect of other proven risk factors (infection with the EBV, smoking) [2]. In the study of insolation is important to remember that the relationship between the amount of vitamin D formed and the level of insolation is not direct, it contribute to the presence of clothing, use of sunscreens, skin type and color, as well as the time of day. In addition, there are indications that the insolation has independent immunomodulatory effect of vitamin D. Thus further studies on possible interactions between different environmental factors and these factors' role in the disease pathogenesis are justified and necessary.

In conclusion, low vitamin D may be associated with clinical MS breakthrough within 2–3 years [4].

Therefore, until further high quality evidence is available, clinicians may wish to consider relevant MS guidelines on vitamin D supplementation when making decisions about the care of people with multiple sclerosis [11]. Adequately powered, multicentre trial with a focus on clinical as well as immunological and MRI outcomes that are meaningful to people with MS, and are able to provide insight into the benefits of vitamin D in people with MS, are still required.

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