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Review Article

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Vitamin D and Multiple Sclerosis; Is There a Real Association?

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ABSTRACT

Multiple sclerosis is a demyelinating autoimmune disease that commonly affects young people. Several risk factors are associated with multiple sclerosis, including low vitamin D levels. Vitamin D is essential in various regulatory processes, particularly in the immune system. Fifty years ago, vitamin D was suggested to have a role in the risk of multiple sclerosis development and relapses, which was proposed after reporting seasonal and geographic variation of multiple sclerosis incidence around the world. This literature review is intended to review the potential role of vitamin D in the risk of multiple sclerosis development or relapses. 21 articles have been selected according to the following Mesh words: Multiple sclerosis, multiple sclerosis relapse, vitamin D, cholecalciferol. Vitamin D seems to play an essential role in the immunological processes involved in multiple sclerosis, along with the indirect beneficial impact of sunlight exposure. However, up to our knowledge, there is no established consensus about the exact vitamin D's beneficial role of among MS patients. Further multi-center randomized clinical trials are recommended to establish the preventable or therapeutic role of vitamin D in MS.

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

INTRODUCTION

Multiple sclerosis is a chronic autoimmune demyelinating disease of the CNS, affecting commonly young adults worldwide and resulting in debilitating and disabling neurological outcomes [1, 2]. The most common affected age is between 20 to 40 years, and the exact etiology remains unclear [1, 2]. However, genetic predisposition and environmental factors, such as low vitamin D, smoking, Ebstein-Barr virus (EBV) infection, lack of physical activities, and childhood obesity are predisposing factors involved in MS pathophysiology [1-4]. MS is not only an autoimmune inflammatory disease but also a neurodegenerative condition [1]. MS has been classified into four classes based on the disease course; secondary progressive MS (SPMS), primary progressive MS (PPMS), relapsing-remitting MS (RRMS), and clinically isolated syndrome (CIS) [1]. MS course can be initiated with

RRMS followed by SPMS and can begin directly with a phase without relapses (PPMS), characterized by a constant course of worsening symptoms from the onset of the disease [5, 6]. MS lesions demonstrate focal demyelination areas and inflammation, leading to a glial reaction and ultimately axonal damage [5].

MS can result in various clinical outcomes, including weakness, spasticity, tremor, and ataxia. In addition, fatigue, which is described as a loss of force-generating capacity during maintained motor activity, further progresses to disability in MS patients. Neurological deficits for a period of hours to days are named relapses, attacks, exacerbations flares [7]. The primary immunopathologic mechanism of MS is mainly through systemic T and B cells, which activate immune cells and across the blood-brain barrier (BBB) [8]. Moreover, the prevalence of MS has markedly increased since 1990, estimating that more than 2.5 million people have this condition worldwide. Additionally, in the United States, MS affects almost 250,000-300,000 people [2].

Vitamin D (Cholecalciferol) is one of the lipid-soluble vitamins synthesized following the skin conversion of 7-dehydrocholesterol to vitamin D. Ultraviolet (UV) B radiation is needed for this conversion. Moreover, An US large cohort trial revealed 3.5 times more residing women in northern states were affected by MS in comparison to women in the southern states. MS is reported more prevalently in areas where sunshine exposure is less than 2000 hours annually. Besides, MS is well-known to represent a seasonal variability, with the most eminent disease activity in the spring and lowest in the fall, which can be corresponded to the decreased sunlight exposure in the winter [9]. Hence, it was suggested that an association between MS and low vitamin D is not a coincidence.

RESULTS AND DISCUSSION

Vitamin D; Physiology and its role in the development of the immune and central nervous system

Vitamin D is a steroid lipid-soluble hormone synthesized by the skin (through sunlight or UV rays), the liver (hepatic hydroxylation by CYp27A1 and CYP2R1), and the kidney (1α-hydroxylation) to the hormonally active form 1,25 dihydroxy vitamin D (1,25D) (calcitriol) [10, 11]. The kidney performs this conversion after being stimulated by the calcium regulatory parathyroid hormone (PTH). 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].

The active vitamin D form is identified by cells VDR, a member of nuclear receptors superfamily that are present in various body organs, such as skin, bone, muscle, intestine, gonads, B and T lymphocytes, microglia, activated monocytes, and CNS [10, 11]. Also, 24-hydroxylase and 1α-hydroxylase are expressed in the CNS; hence, vitamin D metabolism and catabolism may occur in the CNS. Further, intra-uterine vitamin D depletion resulted in the diseases of brain development and decreased levels of nerve growth factor at birth in mice, which underline the essential role of vitamin D in the brain [13].

The absorption of Dietary vitamin D occurs in the small intestine and transferred into the bloodstream by chylomicrons. 1,25D formation can be prevented by several situations, such as high levels of plasma calcitriol, calcium, and phosphorus, in addition to the parathyroid hormone absence and renal disease. Based on the Dietary Reference Intakes, the normal range of 1,25D is 8ng/mL (20nmol/L) to 15 ng/mL (37.5 nmol/L) [14]. Based on the Dietary Reference Intakes, assuming lack of sufficient sunlight exposure, the adequate daily intake of vitamin D is between 5-15 μg/day, based on several factors, including sex, age, pregnancy, and lactation. 1 μg of vitamin D is equal to 40 IU; hence, the adequate intake is 5 μg (200 IU) in adults, 10 μg (400 IU) in adults 51-70, and 15 μg (600 IU) for <70 years of age [14]. The dietary source of vitamin D includes fatty fish, fortified dairy products, and cereal [9]. In the Atlantic coastal area of Norway, the incidence of MS is lower than in other Scandinavia areas, which is thought to be related to a vitamin D-rich diet [9].

VDR activation is a known regulator for proliferation, transcription, and immune cell differentiation [10]. Furthermore, VDR is expressed in various immune cells, such as T lymphocytes, antigen-presenting cells, and neutrophils such as dendritic and macrophages cells, for which the adaptive and innate immune responses are modulated by 1,25D [11]. 1,25D stimulates dendritic cell tolerogenicity, leading to the production and function of T regulatory cells (Treg), significant mediators of the immune system maturity. Also, 1,25D directly inhibits T lymphocytes proliferation [11]. Moreover, cytokines, which is the communication mediators between immune cells and other organ cells, is influenced in the sitting of low vitamin D; to clarify, when vitamin D is augmented in MS patients, there is a potential influence of cytokines gene expression, which can result in symptoms improvement [14].

Notably, in comparison to a healthy individual, MS patients have higher levels inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-2, and interferon-γ), in addition to decreased levels of several anti-inflammatory cytokines [14]. Vitamin D supplementation leads to increased levels of interleukin-10 and 17, which had observed in various studies. High-dose vitamin D reduces the proportion of IL-17-producing CD4 T-cells and elevates central memory CD4 T-cells along with naive CD4 T-cells [12]. Besides, 1,25D signaling is involved in over 1000 genes regulation in the human genome. VDR and CYP27B1 are widely expressed among several tissues contributing to extra-skeletal actions of 1,25D signaling, for instance, their role in regulating innate and adaptive immune systems. VDR is also proposed to play an essential role in antibacterial and antiviral innate immunity [15].

Sunlight exposure and MS activity

MS displays a classical geographical distribution with a low prevalence in equatorial regions compared to the high latitude regions (both hemispheres), where the incidence of MS is higher. For instance, the north Europ and US regions have a higher MS prevalence compared with the southern regions. On the other hand, the southern coast of Australia displays a decreased MS prevalence compared with the sub-tropical northern coast. Moreover, in Switzerland, a decreased MS prevalence has been noticed at higher altitudes in comparison with low altitudes, which corresponded with the more optimal solar radiation at greater heights. Hence, the geographical differences are considered a contributing factor to the MS typical distribution [11].

The average outdoor time spent during weekends and holidays in the first 2 decades of life in MS individuals in comparison with control was evaluated by the initial questionnaire studies. As a result, a significantly lower MS risk was noticed in subjects who spent most of their time outdoors during the adolescent period. Also, the latter studies were supported by skin actinic activity studies, which measured on the dorsal of the hand and represented total sun exposure; similarly, subjects with the highest actinic activity level had the lowest risk of MS. Additionally, a meta-analysis analyzing 52 studies from several nations around the globe. The initial results reported a highly significant association between the prevalence of MS and the annual UV amount in different countries. Vukusic *et al*. had observed a correlation between sunshine maps showing large climate with the prevalence of MS [16].

In addition, an Australian case-control study evaluated the correlation between sunlight exposure combined with 25(OH)D status and the first demyelinating event and if this was linked to the latitude difference. Likewise, the higher the sunlight exposure levels, greater actinic skin damage, and high 25(OH)D levels were significantly associated with lower risks of demyelinating incidents. A 32% increase in the incidence of first demyelinating incidents was also observed from the low to high latitude regions in Australia. This independent correlation between sunlight exposure and MS risk indicates that UV light may affect MS's risk. The latter suggestion might be supported in a study on experimental autoimmune encephalitis (EAE), which showed that this condition could be prevented by whole-body UV light irradiation in rats [17].

Another animal study has confirmed that UV radiation has a possible immunomodulator impact on the development of MS. Female rats with EAE (the animal model of MS) had randomized to receive UV radiation every third day or only pretreatment with UV radiation; as a result, rats who received US radiation every other day or every third day were significantly slower in EAE progression in comparison to the only pretreatment group. Every other day UV radiation group had a significant delay in onset of symptoms and decreased peak severity of symptoms. Notably, both every other day and every third day UV radiation groups demonstrated a significant decrease in the cumulative disease index of EAE [18]. Impressively, during the first trimester of pregnancy, a recent Australian study showed that the risk of MS development is inversely related to the amount of UV radiation [19].

Vitamin D and MS activity

Over the last five decades, a correlation between MS and solar radiation was initially proposed, followed by a theory that decreased MS risk can be achieved by proper supplementation of vitamin D and calcium during CNS development. Nonetheless, the exact role of vitamin D and sun-induced hormonal changes on MS courses remains elusive [19]. Low vitamin D level has been linked to a high risk of developing MS, worsening of the disease course, and increased risk of relapses. Vitamin D is also observed to be depleted in 70% of patients who experienced MS relapses. In addition, high serum vitamin D level was found to be associated with a decreased risk of relapses, fatigue, and Expanded Disability Status Scale (EDSS) score [20].

It was noticed that the population who consume high vitamin D-rich diet (such as fish oil) has a lower risk of MS. Moreover, high circulating levels of vitamin D were associated with: risk reduction of developing MS improved T-cell regulatory function in patients with MS improved clinical outcomes and a high probability of being free of relapse during childhood. 1.25D had also demonstrated a preventive effect for EAE in animal models of MS, reversibly blocking the progressions of MS when vitamin D was given after symptoms started [19].

Several studies have shown that subjects with MS and vitamin D depletion had a high prevalence of reduced bone mass, fracture risk, and dental caries. In postpartum women, symptoms of MS worsened in the first three months in correspondence to high maternal turnover and increased vitamin D demands during late lactation and pregnancy. Vitamin D, calcium, and magnesium supplementation for 1-2 years have revealed relapse reduction in a group of young MS subjects in mid-1980. Further, in Greenland Eskimos, the incidence of MS is low, possibly due to a diet rich in vitamin D, such as fish oil. A prospective longitudinal study evaluated the correlation between vitamin D consumption and the incidence of MS if women found that vitamin D supplementation decreased the lifetime incidence of MS by 40%. The latter study was the first large prospective designed study that confirmed the beneficial effect of vitamin D supplementation in MS prevention [21].

Another study involved 257 MS patients among 514 control subjects and young American soldiers (77 black and 148 white), who had received at least one serum sample before the onset of any neurological manifestations during their military duty. The high vitamin D level group (99-152 nmol/l) had a significantly lower MS risk than the low vitamin D levels (15-63 nmol/l). It had concluded in this study that subjects with normal or high vitamin D levels had a lower risk of MS, particularly in white individuals. Ascherio and Munger, based on the latter study, concluded that around three-quarters of MS cases could be avoided if the circulating vitamin D level was maintained above 100nmol/l during adolescence and childhood. Moreover, the beneficial effect of vitamin D had been established in France after a confirmed correlation between mean vitamin D level in the general population and the MS prevalence in the same region [22].

A meta-analysis conducted by Zheng *et al*. evaluating the effect of vitamin D among MS patients resulted in: vitamin D as add-on therapy showing no significant beneficial effect on MS based on the EDSS score. Besides, the Annualized Relapse Rate (ARR) was not affected in the MS group in comparison with the placebo group [23]. However, this result is based on a limited sample size and preclinical studies.

CONCLUSION

Vitamin D plays a significant role in several body organs, including the CNS development, and is involved in various immune processes. Multiple observational studies have demonstrated that vitamin D might have a beneficial therapeutic or preventive role in multiple sclerosis. However, there is no definite randomized clinical trial that approved the beneficial impact of vitamin D among MS patients, up to our knowledge. As a potential beneficial effect of vitamin D has been confirmed in several studies, vitamin D can be provided to MS patients as it has no harmful effect. Further multi-center randomized clinical trials would be warranted to establish the preventive and therapeutic role of vitamin D in MS.

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REFERENCES

1. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527-46. doi:10.1093/brain/aww258
2. Nishanth K, Tariq E, Nzvere FP, Miqdad M, Cancarevic I. Role of Smoking in the Pathogenesis of Multiple Sclerosis: A Review Article. Cureus. 2020;12(8).
3. Moosavy SH, Nejatizadeh AA, Davoodian P, Eftekhar E, Zare S, Nazarnezhad M, et al. Evaluation of Vitamin D Levels in Patients with Hepatitis B Virus. Int J Pharm Phytopharmacol Res. 2019;9(3):98-106.

4. Raoof NK. Influence of Pulsed Magnetic field on RBCs and therapeutic action of vitamins C and E. J Adv Pharm Edu Res. 2019;9(2):122-30.
5. Bigaut K, De Seze J, Collongues N. Ocrelizumab for the treatment of multiple sclerosis. Expert Rev Neurother. 2019;19(2):97-108. doi:10.1080/14737175.2019.1561284.
6. Syed YY. Ocrelizumab: A Review in Multiple Sclerosis. CNS Drugs. CNS Drugs. 2018;32(9):883-90.
7. Howard J, Trevick S, Younger DS. Epidemiology of Multiple Sclerosis. Neurol Clin. 2016;34(4):919-39. doi:10.1016/j.ncl.2016.06.016.
8. Ancau M, Berthele A, Hemmer B. CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date. Expert Opin Biol Ther. 2019;19(8):829-43. doi:10.1080/14712598.2019.1611778.
9. Brown SJ. The role of vitamin D in multiple sclerosis. Ann Pharmacother. 2006;40(6):1158-61. doi:10.1345/aph.1G513.
10. Dudani SJ, Kalhan S, Sharma SP. Vitamin D and multiple sclerosis: Potential pathophysiological role and clinical implications. Int J Appl Basic Med Res. 2011;1(2):71-4. doi:10.4103/2229-516X.91146
11. White JH. Vitamin D metabolism and signaling in the immune system. Rev Endocr Metab Disord. 2012;13(1):21-9.
12. Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. J Neurol. 2009;256(9):1468-79. doi:10.1007/s00415-009-5139-x
13. Smolders J, Damoiseaux J, Menheere P, Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. J Neuroimmunol. 2008;194(1-2):7-17. doi:10.1016/j.jneuroim.2007.11.014.
14. Mark BL, Carson JA. Vitamin D and autoimmune disease--implications for practice from the multiple sclerosis literature. J Am Diet Assoc. 2006;106(3):418-24. doi:10.1016/j.jada.2005.12.009.
15. Ismailova A, White JH. Vitamin D, infections, and immunity. Reviews in Endocrine and Metabolic Disorders. Rev Endocr Metab Disord. 2021:1-3.
16. Pierrot-Deseilligny C, Souberbielle JC. Is hypovitaminosis D one of the environmental risk factors for multiple sclerosis?. Brain. 2010;133(7):1869-88. doi:10.1093/brain/awq147
17. Sintzel MB, Rametta M, Reder AT. Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol Ther. 2018;7(1):59-85. doi:10.1007/s40120-017-0086-4
18. Summerday NM, Brown SJ, Allington DR, Rivey MP. Vitamin D and multiple sclerosis: review of a possible association. J Pharm Pract. 2012;25(1):75-84. doi:10.1177/0897190011421839.
19. Fernandes de Abreu DA, Landel V, Féron F. Seasonal, gestational and postnatal influences on multiple sclerosis: the beneficial role of a vitamin D supplementation during early life. J Neurol Sci. 2011;311(1-2):64-8. doi:10.1016/j.jns.2011.08.044.
20. Bagur MJ, Murcia MA, Jiménez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, et al. Influence of Diet in Multiple Sclerosis: A Systematic Review. Adv Nutr: An Int Rev J. 2017;8(3):463-72. doi:10.3945/an.116.014191
21. Chaudhuri A. Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis. Med Hypotheses. 2005;64(3):608-18. doi:10.1016/j.mehy.2004.06.022.
22. Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. J Neurol. 2009;256(9):1468-79. doi:10.1007/s00415-009-5139-x
23. Zheng C, He L, Liu L, Zhu J, Jin T. The efficacy of vitamin D in multiple sclerosis: A meta-analysis. Mult Scler Relat Disord. 2018;23:56-61. doi:10.1016/j.msard.2018.05.008.