Libyan International Medical University

Faculty of Basic Medical Science

Vitamin D and Multiple Sclerosis

Submitted by: Hashim H. Almatri, Student, Faculty of Basic Medical Science, Libyan International Medical University.

Supervisor: Dr. Sarah Almagerhi, Tutor, Faculty of Basic Medical Science, Libyan International Medical University.

Date of submission: 14/4/2018

Abstract

The purpose of this report is to provide a brief description of research findings on the role of vitamin D in multiple sclerosis (MS). Observational studies document a positive relationship between vitamin D from the environment (sunlight or diet), circulating vitamin D status, and improved symptoms or prevention of multiple sclerosis (MS), as the geographic incidence of MS indicates an increase in MS with a decrease in sunlight exposure. The effects of vitamin D on the immune system and in the CNS have begun to be described and there is some information on the mechanisms underlying the effects of vitamin D in MS, It plays an important role in T cell homeostasis during the course of multiple sclerosis. While It's been found that higher serum 25(OH)D levels robustly predicted a lower degree of MS activity, MRI lesion load, brain atrophy, and clinical progression during the 5 years of follow-up. As evidence continues to accumulate supporting a protective role for vitamin D in MS etiology and progression, additional research on the timing and dose-response relationship will be crucial for designing future prevention and treatment trials.

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space. It is the most common of the demyelinating disorders, having a prevalence of approximately 1 per 1000 persons in most of the United States and Europe. The disease may become clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare. Women are affected twice as often as are men. In most individuals with MS, the clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual, partial recovery of neurologic function. The frequency of relapses tends to decrease during the course of time, but there is a steady neurologic deterioration in most affected individuals.[1]The lesions of MS are caused by an immune response that is directed against the components of the myelin sheath. As in other autoimmune disorders, the pathogenesis of this disease involves both genetic and environmental factors. The incidence of MS is 15-fold higher when the disease is present in a first-degree relative and roughly 150-fold higher with an affected monozygotic twin.[1]

Vitamin D3, a lipid-soluble vitamin, is produced by sunlight in the skin, and can also be provided by the diet. It is a precursor of the metabolic active hormone 1,25-(OH)2D. Sunlight has long been recognized as a major provider of vitamin D3 for humans. Radiation in the UV-B (290–315 nm) portion of the solar spectrum photolyzes 7-dehydrocholesterol (provitamin D3) in the skin to previtamin D3 which in turn, is converted by a thermal process to vitamin D3. The synthesis of vitamin D3 in the skin is self-regulating. Excessive exposure to sunlight causes a photodegradation of previtamin D3 and vitamin D3 to prevent vitamin D3 intoxication.[2]

In addition to the production in the skin, vitamin D is supplied by food in two forms; vitamin D2 (ergocalciferol, activated ergosterol), found in irradiated yeast, and vitamin D3 (cholecalciferol), found in fish liver oils and fatty fish, including herring, mackerel, and sardines. The natural human diet can only be considered as a secondary source of the vitamin, when there is enough exposure to sunlight.[2] Vitamin D is a principal regulator of calcium homeostasis. However, recent evidence has indicated that vitamin D can have numerous other physiological functions including inhibition of proliferation of a number of malignant cells including breast and prostate cancer cells and protection against certain immune mediated disorders including multiple sclerosis (MS).[3]

Discussion

A protective effect of Vitamin D on multiple sclerosis is supported by the reduced risk associated with sun exposure and use of Vitamin D supplements. Moreover, high circulating levels of Vitamin D have been associated with lower risk of multiple sclerosis. The benefits from vitamin D could either be due to the beneficial effects of vitamin D on the nervous system and/or the benefits of vitamin D for immune system regulation. There are vitamin D receptors in the central nervous system and there is data showing that vitamin D regulates myelin production by the oligodendrocytes as well as other neuronal processes.[4]

One study, measured 1,25 (OH)2 Vitamin D and 25 (OH) Vitamin D levels in multiple sclerosis patients separated into different clinical subgroups according to disease status. In addition, direct effects of 1,25 (OH)2 Vitamin D on ex vivo CD4+ T cells and myelin-peptide specific T cell lines were investigated to gain more insight into putative regulatory mechanisms in the disease pathogenesis. One hundred and thirty-two Hispanic patients with clinically definite multiple sclerosis were studied, 58 with relapsing remitting multiple sclerosis during remission, 34 during relapse and 40 primary progressive multiple sclerosis cases. Sixty healthy individuals matched with respect to place of residence, race/ethnicity, age and gender served as controls.[5] Levels of 25(OH)D3 and 1,25(OH)2D3, measured by ELISA were significantly lower in relapsing–remitting patients than in controls. In addition, levels in patients suffering relapse were lower than during remissions. In contrast, primary progressive patients showed similar values to controls. Proliferation of both freshly isolated CD4+ T cells and MBP-specific T cells was significantly inhibited by 1,25(OH)2D3. Moreover, activated Vitamin D enhanced the development of IL-10 producing cells, and reduced the number of IL-6 and IL-17 secreting cells. Notably, Vitamin D receptor expression was induced by 1,25(OH)2D3 in both activated and resting cells. Interestingly, T cells were able to metabolize 25(OH)D3 into biologically active 1,25(OH)2D3, since T cells express α1-hydroxylase constitutively.[5]

Finally, 1,25(OH)2D3 also increased the expression and biological activity of indoleamine 2,3-dioxygenase, mediating significant increase in the number of CD4+CD25+ T regulatory cells. Collectively, these data suggest that 1,25(OH)2D3 plays an important role in T cell homeostasis during the course of multiple sclerosis, thus making correction of its deficiency may be useful during treatment of the disease.[5]

Another study conducted a randomized trial originally designed to evaluate the impact of early vs delayed interferon beta-1b treatment in patients with clinically isolated syndrome. Serum 25(OH)D concentrations were measured at baseline and 6, 12, and 24 months. A total of 465 of the 468 patients randomized had at least 1 25(OH)D measurement, and 334 patients had them at both the 6- and 12-month (seasonally asynchronous) measurements. Patients were followed up for 5 years clinically and by magnetic resonance imaging. Higher 25(OH)D levels predicted reduced MS activity and a slower rate of progression. A 50-nmol/L (20-ng/mL) increment in average serum 25(OH)D levels within the first 12 months predicted a 57% lower rate of new active lesions, 57% lower relapse rate, 25% lower yearly increase in T2 lesion volume, and 0.41% lower yearly loss in brain volume from months 12 to 60. Similar associations were found between 25(OH)D measured up to 12 months and MS activity or progression from months 24 to 60. In analyses using dichotomous 25(OH)D levels, values greater than or equal to 50 nmol/L (20 ng/mL) at up to 12 months predicted lower disability (Expanded Disability Status Scale score, during the subsequent 4 years. Concluding that among patients with MS mainly treated with interferon beta-1b, low 25(OH)D levels early in the disease course are a strong risk factor for long-term MS activity and progression.[6]

Notable recent findings are that high 25-hydroxyvitamin D (25(OH)D) at the time of a first demyelinating event predicts a lower MS risk , and a decreased risk of MS among offspring whose mothers had high predicted 25(OH)D levels. Recent immunological studies also show modulation of the immune system by vitamin D that may be favorable for preventing or slowing the progression of MS. The demonstration that rare variants in CYP27B1, which encodes the enzyme that converts vitamin D to its active form, are strongly associated with MS risk supports a causal role of vitamin D deficiency as a risk factor for MS.[7]

Widespread seasonal variation in serum 25OHD levels has been reported especially in temperate climates, with low 25OHD levels in winter. Once MS is apparent, low 25OHD levels may aggravate its severity. Living in a temperate climate may cause annually recurring seasonal low serum 25OHD concentrations in MS patients. It is suggested that MS patients living in temperate climates should have their serum 25OHD concentration checked in winter, or use a vitamin D3 supplement.[2]

Conclusion

During the last 5 years the nutrition community has displayed increased interest in studying the effects of vitamin D intakes and status and establishing a connection between vitamin D and MS incidence and symptoms. The evidence for vitamin D sufficiency in reducing MS risk is compelling and the recent literature has provided additional evidence for a causal interpretation. Intervention with vitamin D supplementation could have a substantial impact on reducing disease burden. Future investigations should be focused on refining the dose-response relation between vitamin D levels and MS risk or MS progression, which is critical to plan preventive or therapeutic interventions.

References

1. Kumar, Vinay, Abul K. Abbas, Nelson Fausto, Stanley L. Robbins, and Ramzi S. Cotran. *Robbins and Cotran Pathologic Basis of Disease*. Chapter: 28. 8th Ed. *Philadelphia: Elsevier Saunders*, 2005.
2. B M VanAmerongen, C D Dijkstra, P Lips & C H Polman. Multiple sclerosis and vitamin D: an update. *European Journal of Clinical Nutrition volume 58*, 1095–1109 (2004) doi:10.1038/sj.ejcn.1601952
3. Raghuwanshi, A. , Joshi, S. S. and Christakos, S. (2008), Vitamin D and multiple sclerosis. J. Cell. Biochem., 105: 338-343. doi:10.1002/jcb.21858
4. Cantorna, M. T. (2008), Vitamin D and multiple sclerosis: an update. *Nutrition Reviews*, 66: S135-S138. doi:10.1111/j.1753-4887.2008.00097.x
5. Jorge Correale, María Célica Ysrraelit, María Inés Gaitán; Immunomodulatory effects of Vitamin D in multiple sclerosis, *Brain, Volume 132*, Issue 5, 1 May 2009, Pages 1146–1160, https://doi.org/10.1093/brain/awp033
6. Ascherio A, Munger KL, White R, et al. Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression. *JAMA Neurol*. 2014;71(3):306–314. doi:10.1001/jamaneurol.2013.5993
7. Simon, Kelly Claire, Kassandra L Munger, and Alberto Ascherio. Vitamin D and multiple sclerosis: epidemiology, immunology, and genetics. *Current opinion in neurology* .2012;25(3):246-251. doi:10.1097/WCO.0b013e3283533a7e.