Vitamin D and multiple sclerosis: an update

Margherita T Cantorna

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). Experimental animal models of MS reproduce the beneficial effects of vitamin D and 1,25(OH)$_2$D$_3$. The geographical distribution of MS can be explained by both the hygiene hypothesis and the vitamin D hypothesis. It therefore seems more likely that both hypotheses may be correct and that there are interactions between multiple environmental factors like vitamin D and the rate of infection that might explain the etiology of MS. 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. A need exists for better understanding of the interactions of the environmental factors on MS, communication with the physicians treating MS patients as to the benefits of vitamin D, and clinical interventions with both vitamin D and analogs of 1,25(OH)$_2$D$_3$.

INTRODUCTION

Although classified as a vitamin, vitamin D is not a true vitamin since significant amounts of vitamin D are made in the skin in association with sunlight exposure. The amount of vitamin D made as a result of sunlight exposure depends on a number of factors including skin pigmentation, age, latitude, season, and sunscreen use. Since the sun is an unreliable and difficult to control source of vitamin D, it seems to be inadequate or unreasonable to suggest that vitamin D should be obtained exclusively by exposure to sunlight. There are problems with obtaining vitamin D from the diet as well since, except for in some fish, very little vitamin D is present naturally in the food supply. Nonetheless, vitamin D from either sunlight or diet has been hypothesized to be an important environmental factor that affects the development of a number of chronic diseases including autoimmune diseases like multiple sclerosis (MS) and cancers, especially prostate cancer.

GENES, THE ENVIRONMENT, AND MS

MS is an autoimmune disease of the central nervous system that is of unknown etiology and affects more women than men (2:1 ratio). A number of risk factors for MS have been identified and they can loosely be put into one of two categories – genetic or environmental components.[1,2] Highlighting the role of genetics in the disease is that family members of MS patients are at an increased (20–40%) risk of developing MS and monozygotic twins are at a further increased (additional 10%) risk of developing MS. However, the concordance rate in identical twins is only 25% for MS. Therefore, even though the twins are genetically identical, 75% of the time only one twin develops MS. The environmental factor(s) that explain this anomaly have been difficult to identify and are, therefore, still largely undocumented. Mapping the distribution of MS reveals it is most prevalent in the northern United States, Canada, and the northern parts of Western Europe. Studies that look at populations

Affiliation: *MT Cantorna* is with the Center for Immunology and Infectious Disease, Department of Veterinary and Biomedical Science, The Pennsylvania State University, University Park, Pennsylvania, USA.

Correspondence: *MT Cantorna*, Department of Veterinary and Biomedical Sciences, The Center for Molecular Immunology and Infectious Disease, 115 Henning Bldg., University Park, PA 16802, USA. E-mail: mxc69@psu.edu, Phone: +1-814-863-2819, Fax: +1-814-863-6140.

Key words: hygiene hypothesis, multiple sclerosis, vitamin D

doi:10.1111/j.1753-4887.2008.00097.x

migrating from areas of low to high risk for MS suggest that movement before puberty results in an altered risk for MS development, whereas movement after puberty has no effect.[3] In addition, during the last 50 years there has been a dramatic increase in the incidence of not only MS but other autoimmune diseases and immune-mediated diseases like allergy and asthma. This increase in immune-mediated diseases is likely due to changes in our environment, not genetic changes, which would take much longer to manifest themselves. In addition, it should be noted that there are strong environmental influences on all of the autoimmune diseases and the geographical patterns remain similar, suggesting that there are likely commonalities in the factors regulating these diseases. While it is clear that environmental factors are the likely cause of the shift towards more autoimmunity, the identity of the specific factor or factors have been difficult to determine.

A prevailing hypothesis that explains the odd geography of MS and the increasing incidence of MS and other immune-mediated diseases has been termed the "hygiene hypothesis".[4] This hypothesis suggests that decreased infectious diseases early in life due to vaccination, improvements in sanitation, and prevalent antibiotic use has resulted in a lack of immune system exposure to infections that, in essence, educate the immune system not to respond to the self. The hygiene hypothesis further stipulates that the high rates of infection in third-world countries that populate much of the equator explain the lack of MS and other immune-mediated diseases in those locations. Experimental data to support the hypothesis include animal studies showing that worm infections protect from experimental autoimmune diseases, including MS.[4] Additional experimental data show that infections induce and/or exacerbate these diseases.[5] Nonetheless, it seems clear that infections have roles to play (perhaps some good and some bad) in the development of MS and other immune-mediated diseases.

The production of vitamin D as a result of exposure to ultraviolet light is an additional environmental factor that varies geographically in roughly the same pattern as MS prevalence. In the late 1970s, the first reports of a hypothetical link between vitamin D or sunlight exposure as a factor that affected the development of MS was proposed.[6] In addition, MS patients have been shown to have low levels of circulating vitamin D compared to controls.[7] In the developed world, in addition to vaccination, physical activity and outdoor exposure has decreased. We suggest there has been a shift in lifestyles in the last 50 years that has resulted in both an obesity epidemic in some areas and a decrease in vitamin D exposure through declining quality of the diet and the amount of time spent working and playing outside. We propose a paradigm shift is required in the hygiene hypothesis that would include vitamin D interactions with infectious organisms and/or other environmental exposures to explain the odd geography of MS and the increased incidence of MS in the developed world.

VITAMIN D AND MS BEYOND GEOGRAPHY

Vitamin D and $1,25(OH)_2D_3$ have been shown to suppress the autoimmune response in experimental MS.[8] Vitamin D deficiency accelerates the development of experimental MS compared to normal levels of vitamin D in mice with MS. Unfortunately, no experiment using high doses of vitamin D or $25(OH)D_3$ on experimental MS has been done to date. Instead, $1,25(OH)_2D_3$ treatments have been shown by at least three different groups to suppress the development of experimental MS completely if given prior to disease induction and to block the progression of the disease if given after symptoms develop. In animals, experimental MS is made worse in the absence of vitamin D and is suppressed by active vitamin D treatment.[8]

There is some evidence, beyond the suggestive geographical patterns of MS, to propose a connection between vitamin D and MS in humans. Recent observational studies show that vitamin D supplementation at the highest intake levels (599–714 IU/day) are associated with a 40% decrease in the incidence of MS.[9] These investigators did not account for any vitamin D produced in the skin following sunlight exposure, but they did show that the decreased incidence of MS was associated with levels of circulating vitamin D of 75 nmol/L. In the last 3 years, numerous observational studies in different populations of MS patients have found an association of vitamin D, from supplements, diet, or sunshine, with higher circulating levels of vitamin D and decreased incidence, progression, or symptoms of MS.[9–12] These observational studies clearly and consistently document a positive association between vitamin D and MS.

There is, as yet, still very limited information on the impact of vitamin D supplementation and or $1,25(OH)_2D_3$ treatments on MS. Our group showed that vitamin D supplementation at 1000 IU/day over 6 months led to improvement in circulating vitamin D status (started at 45 nmol/L and ended at 75 nmol/L) and this was associated with an increase in transforming growth factor-β1, which is predicted to be protective for MS.[13] However, symptoms of MS were not reported on and additional studies have been slow to develop. Older studies using fish oil as a source of vitamin D have been reported, but the exact amount of vitamin D was not disclosed.[14,15] These studies were small, and in one case lacked a control group, but the data do suggest a positive association between fish oil-derived vitamin D and a reduction in MS symptoms. In another study,

$1,25(OH)_2D_3$ was given to MS patients and the results showed that $1,25(OH)_2D_3$ was relatively well tolerated and did not exacerbate symptoms in the short term, although elevated serum calcium was problematic.[16] The authors of the $1,25(OH)_2D_3$ intervention concluded that future studies in humans should use some of the many less calcemic analogues under development. More human interventions with vitamin D and various vitamin D metabolites and analogs should be a priority.

HOW VITAMIN D WORKS

The mechanisms underlying the beneficial effects of vitamin D and $1,25(OH)_2D_3$ in experimental MS are beginning to be understood. 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.[17] It is possible that vitamin D exerts some of its beneficial effects in the CNS. Since the effects of vitamin D and $1,25(OH)_2D_3$ extend to other autoimmune diseases that do not occur in the CNS, it seems obvious that even though there may be non-immune targets for vitamin D in the CNS, a common role of vitamin D in regulation of the immune system across the autoimmune diseases must exist.

The immune system has been shown to be an important vitamin D target. In particular, autoimmune diseases seem to be extremely sensitive to the availability of vitamin D. Other immune responses, including the immune response to infectious organisms, do not seem altered by changes in vitamin D and or $1,25(OH)_2D_3$ treatment. Conversely, every experimental model of autoimmunity tested (experimental MS, inflammatory bowel disease, type-1 diabetes, arthritis, lupus, etc.) show sensitivity to vitamin D status and/or suppression of symptoms by $1,25(OH)_2D_3$. This commonality across this family of diseases in different tissues suggests that vitamin D must function to regulate some shared process among these diseases.

In autoimmune disease there is an inappropriate immune-mediated attack against tissues in the body. The data support a model whereby, when vitamin D is low, the development of disease-causing T cells is increased at the expense of other cells that normally would inhibit the process.[18,19] The presence of vitamin D or the use of $1,25(OH)_2D_3$ results in a dampening of the disease-causing cells and a return in the balance of regulatory cells that act to keep auto-reactive cells silent.[19] It should be noted that although vitamin D is an immune system regulator, all immune responses, including the immune response to many infectious organisms, are not suppressed. While there is still a great deal to be learned about these seemingly paradoxical functions of vitamin D in the immune system, it is clear that vitamin D should not be considered an immune suppressant.

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. In addition, great strides have been made towards determining the cellular and molecular mechanisms underlying the effects of vitamin D and vitamin D metabolites on this disease. The challenge is to engage colleagues who treat MS patients in conversations about the proven benefits of modestly increasing vitamin D (bone health) intakes and the potential positive effects of vitamin D on MS disease development. In addition, a need remains to further identify the environmental factors that affect MS, interactions among the environmental factors, the mechanisms of action, and vitamin D and $1,25(OH)_2D_3$ interventions.

Acknowledgment

Declaration of interest. The author has no relevant interests to declare.

REFERENCES

1. Ebers GC, Sadovnick AD. The role of genetic factors in multiple sclerosis susceptibility. J NeuroImmunol. 1994;54:1–17.
2. Giovannoni G, Ebers G. Multiple sclerosis: the environment and causation. Curr Opin Neurol. 2007;20:261–268.
3. Dean G. Annual incidence, prevalence, and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. Br Med J. 1967;2:724–730.
4. Fleming JO, Cook TD. Multiple sclerosis and the hygiene hypothesis. Neurology. 2006;67:2085–2086.
5. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007;61:288–299.
6. Craelius W. Comparative epidemiology of multiple sclerosis and dental caries. J Epidemiol Community Health. 1978;32:155–165.
7. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. Neurology. 1994;44:1687–1692.
8. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci USA. 1996;93:7861–7864.
9. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004;62:60–65.

10. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296:2832–2838.
11. Ozgocmen S, Bulut S, Ilhan N, Gulkesen A, Ardicoglu O, Ozkan Y. Vitamin D deficiency and reduced bone mineral density in multiple sclerosis: effect of ambulatory status and functional capacity. J Bone Miner Metab. 2005;23:309–313.
12. van der Mei IA, Ponsonby AL, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol. 2007;254:581–590.
13. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. J NeuroImmunol. 2003;134:128–132.
14. Nordvik I, Myhr KM, Nyland H, Bjerve KS. Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients. Acta Neurol Scand. 2000;102:143–149.
15. Goldberg P, Fleming MC, Picard EH. Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D. Med Hypotheses. 1986;21:193–200.
16. Wingerchuk DM, Lesaux J, Rice GP, Kremenchutzky M, Ebers GC. A pilot study of oral calcitriol (1,25-dihydroxyvitamin D3) for relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2005;76:1294–1296.
17. Eyles D, Almeras L, Benech P, et al. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol. 2007;103:538–545.
18. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol. 2006;92:60–64.
19. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood). 2004;229:1136–1142.