VITAMIN D3 NEWS FOR MULTIPLE SCLEROSIS PATIENTS

June 5, 2014

Dr. C.E. Hayes, Ph.D., Professor of Biochemistry, U. Wisconsin, Madison, WI

This newsletter's purpose is to provide current information on vitamin D_3 research relevant to multiple sclerosis (MS). It is not medical advice. Medical advice regarding vitamin D_3 and MS must come from your doctor following new Endocrine Society guidelines (1). You may copy and distribute this newsletter.

A critical barrier to developing treatments to halt MS disease progression and repair neurological damage is our limited understanding of the factors that cause MS. The MS disease process appears to involve autoimmunity to myelin components, coupled with non-immune neurodegenerative processes.

Lewis Thomas wrote "For every disease there is a single key mechanism that dominates all others. If one can find it, and then think one's way around it, one can control the disorder." What is the single key mechanism that dominates all others in MS?

The demyelinating disease process appears to develop in individuals carrying genetic risk factors who are exposed to particular environmental factors. MS clustering within families signals a genetic contribution to MS (2). However, 75% of identical twins do not have co-occurrence of MS, and the genetic risk factors identified to date have only a modest influence. Thus, environmental factors play a large, causal role in MS through their interactions with genetic factors (3). The "single key mechanism that dominates all others" must be a disease threshold-setting, environmentally-directed mechanism.

Evidence points to a sunlight-linked factor. High sunlight exposure correlated with low MS risk globally (4). Young immigrants carrying genetic risk factors substantially reduced their MS risk by settling in regions with ample compared to limited winter sunlight (5). After long dark winters in high latitude regions, MS patients experienced a surge in brain lesions (6) and disease relapses (7). Thus, a sunlight-linked factor trumps genetic factors in determining MS risk and disease activity. Curiously, Northern Norwegians who consumed fish as a dietary staple had a lower risk of developing MS than their Southern Norwegian countrymen who consumed less fish (8). Thus, fish consumption compensated for a lack of winter sunlight. If we aspire to control MS, we must identify the factor common to sunlight and fish.

Vitamin D_3 may be that factor, the major conduit for the protective actions of sunlight and fish consumption in MS (9). Sunlight catalyzes vitamin D_3 formation in the skin, and fish oil is a rich source of dietary vitamin D_3. Vitamin D_3 is converted into 25-hydroxyvitamin D_3 (25(OH)D), an inactive hormone precursor, and finally into a hormone, calcitriol. Calcitriol regulates gene activity through a vitamin D receptor (VDR), enabling coordination of important biological processes according to environmental cues.

Could the biological actions of vitamin D_3, calcitriol, and the VDR diminish autoimmunity to myelin components and impede the neurodegenerative processes that drive MS disease? To answer this question, scientists must establish whether the association between vitamin D_3 and MS is strong, consistent, and reproducible, whether a logical time line and plausible mechanisms support a cause-effect relationship, and whether altering vitamin D_3 affects MS risk and/or severity (10). Recent research has addressed all of these questions.

There is a strong, consistent, and reproducible correlation and a logical time line linking low vitamin D_3 status (serum 25(OH)D) and high MS risk, frequent relapses, and rapid disease progression (9). Children who took supplementary vitamin D_3 had a lower risk of MS as adults (11). Among patients with a first event suggestive of MS, low vitamin D_3 status predicted higher MS activity, lesion load, brain atrophy, and clinical progression in a 5 yr study (12). Among MS patients living where serum 25(OH)D levels fluctuate seasonally, a winter drop in 25(OH)D preceded a spring surge in relapses. In adults (13, 14) and pediatric MS patients (15), higher serum 25(OH)D levels (>40 ng/mL) correlated with fewer lesions and relapses. MS patients who began taking vitamin D_3 during a 5 yr study had 33% fewer new MRI lesions for each 10 ng/mL increase in 25(OH)D (14). These studies indicate vitamin D_3 might be a major conduit for environmentally-directed protective mechanisms in MS.

Genetic data also implicate vitamin D. The *CYP27B1* gene encodes the enzyme that converts 25(OH)D into biologically active calcitriol. In rare Canadian families with multiple MS-affected members, 35 of 35 family members with MS had one damaged copy of the *CYP27B1* gene (16). The odds that this inheritance pattern occurred by chance are 1 in a billion. New research confirmed this association in another multi-incident Canadian family (17). Other researchers have not found this correlation, but it may depend on an interaction between the damaged *CYP27B1* gene and low vitamin D status. Vitamin D_3 may also influence the *HLA DRB1*1501* gene, the strongest genetic risk factor for MS (18).

There are plausible biological explanations for the vitamin D_3 - MS link. Growing evidence suggests the vitamin D system is neuroprotective, supporting memory, cognition, neuro-transmission, and neuroplasticity (19). The vitamin D system also opposes autoimmunity and inflammation in the central nervous system (CNS) by reducing autoimmune T cell access to the CNS, increasing autoimmune T cell elimination from the CNS, and promoting induction of the T regulatory cells that maintain immunological self tolerance (9, 20, 21). Animal modeling research also demonstrated that estrogen enabled the vitamin D system to prevent inflammation of the female CNS. Removing estrogen undermined vitamin D_3 protective functions, and replacing estrogen restored them (22). Emerging research suggests that estrogen may also be important for vitamin D's protective functions in women (23, 24). This research has important implications for MS. The transition from relapsing-remitting to secondary progressive MS in women occurs around the time of menopause (25). If estrogen is essential to support vitamin D system functions, then as estrogen declines, the protective benefits of both estrogen and vitamin D_3 may be lost simultaneously. More research is needed to investigate this biological relationship and how it may influence MS progression in women.

Three randomized controlled studies have provided glimpses of vitamin D_3's beneficial effects in MS and optic neuritis patients. MS patients in a Canadian study who took an average of 14,000 IU/day of vitamin D_3 had fewer relapses and less disability progression over one year (26). A Finnish study found the vitamin D_3 group (20,000 IU of vitamin D_3 weekly) had 85% fewer new MRI lesions, and trends toward lower total lesion burden, reduced EDSS, and improved timed 10 foot tandem walk scores over one year (27). An

Iranian study of optic neuritis patients with low 25(OH)D levels found the vitamin D_3 group (50,000 IU of vitamin D_3 weekly) had lower rates of new brain lesions and 68% less risk of developing MS (28). Some studies have not found beneficial effects, but these studies involved few subjects, short observation periods, or vitamin D_2 in place of vitamin D_3. Additional vitamin D_3 studies are underway.

Vitamin D_3 appears to be a major conduit for the protective actions of sunlight and fish consumption, so, it may be beneficial for MS patients with limited sunlight exposure to supplement with vitamin D_3 daily to avoid becoming vitamin D deficient. A blood test for 25(OH)D is needed to determine your vitamin D status (http://www.vitamindcouncil.org/about-vitamin-d/testing-for-vitamin-d/). MS disease activity was lowest in patients whose 25(OH)D levels were greater than 40 ng/mL, so this is a reasonable target level. Several gene variants influence circulating 25(OH)D levels; people with these variants will require more vitamin D_3 than others to achieve 40 ng/mL of 25(OH)D. MS patients can take 14,000 IU/day safely (26). Some evidence indicates vitamin D_2 may be less beneficial so vitamin D_3 is preferred (29). Biological relatives of MS patients, especially sisters and daughters, have an increased risk of MS and may benefit from daily vitamin D_3 supplements.

If vitamin D_3, calcitriol, and the VDR do indeed contribute to protective biological actions like promoting T regulatory cells, eliminating autoimmune T cells, and enhancing neurological repair, and if these are dominant protective mechanisms in MS, then we may be able to control MS through a vitamin D-based strategy. A recent animal modeling study demonstrated that one calcitriol dose plus supplementary vitamin D_3 ameliorated autoimmune demyelinating disease, whereas neither treatment alone accomplished this objective (20). Studies are being designed now to determine whether intermittent calcitriol pulse dosing plus supplementary vitamin D_3 will benefit MS patients. Stay tuned!

References

1. Holick, M. F., N. C. Binkley, H. A. Bischoff-Ferrari, C. M. Gordon, D. A. Hanley, R. P. Heaney, M. H. Murad, and C. M. Weaver. 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96: 1911-1930.
2. Ebers, G. C., D. E. Bulman, A. D. Sadovnick, D. W. Paty, S. Warren, W. Hader, T. J. Murray, T. P. Seland, P. Duquette, T. Grey, and et al. 1986. A population-based study of multiple sclerosis in twins. *N Engl J Med* 315: 1638-1642.
3. Ebers, G. 2013. Interactions of environment and genes in multiple sclerosis. *J Neurol Sci* 334: 161-163.
4. Acheson, E. D., C. A. Bachrach, and F. M. Wright. 1960. Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation and other variables. *Acta Psychiatry (Scandanavia)* 35 (Supplement 147): 132-147.
5. Ebers, G. C. 2008. Environmental factors and multiple sclerosis. *Lancet neurology* 7: 268-277.
6. Meier, D. S., K. E. Balashov, B. Healy, H. L. Weiner, and C. R. Guttmann. 2010. Seasonal prevalence of MS disease activity. *Neurology* 75: 799-806.
7. Soilu-Hanninen, M., M. Laaksonen, I. Laitinen, J. P. Eralinna, E. M. Lilius, and I. Mononen. 2008. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry* 79: 152-157.
8. Swank, R. L., O. Lerstad, A. Strom, and J. Backer. 1952. Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition. *N Engl J Med* 246: 722-728.
9. Hayes, C. E., F. E. Nashold, C. G. Mayne, J. A. Spanier, and C. D. Nelson. 2011. Vitamin D and multiple sclerosis. In *Vitamin D*, Third ed. D. Feldman, J. W. Pike, and J. S. Adams, eds. Elsevier, San Diego, California. 1843-1877.
10. Hill, A. B. 1965. The Environment and Disease: Association or Causation? *Proc R Soc Med* 58: 295-300.
11. Munger, K. L., L. I. Levin, B. W. Hollis, N. S. Howard, and A. Ascherio. 2006. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *Jama* 296: 2832-2838.
12. Ascherio, A., K. L. Munger, R. White, K. Kochert, K. C. Simon, C. H. Polman, M. S. Freedman, H. P. Hartung, D. H. Miller, X. Montalban, G. Edan, F. Barkhof, D. Pleimes, E. W. Radu, R. Sandbrink, L. Kappos, and C. Pohl. 2014. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA neurology* 71: 306-314.
13. Simpson, S., Jr., B. Taylor, L. Blizzard, A. L. Ponsonby, F. Pittas, H. Tremlett, T. Dwyer, P. Gies, and I. van der Mei. 2010. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. *Ann Neurol* 68: 193-203.
14. Mowry, E. M., E. Waubant, C. E. McCulloch, D. T. Okuda, A. A. Evangelista, R. R. Lincoln, P. A. Gourraud, D. Brenneman, M. C. Owen, P. Qualley, M. Bucci, S. L. Hauser, and D. Pelletier. 2012. Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. *Ann Neurol* 72: 234-240.
15. Mowry, E. M., L. B. Krupp, M. Milazzo, D. Chabas, J. B. Strober, A. L. Belman, J. C. McDonald, J. R. Oksenberg, P. Bacchetti, and E. Waubant. 2010. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol* 67: 618-624.
16. Ramagopalan, S. V., D. A. Dyment, M. Z. Cader, K. M. Morrison, G. Disanto, J. M. Morahan, A. J. Berlanga-Taylor, A. Handel, G. C. De Luca, A. D. Sadovnick, P. Lepage, A. Montpetit, and G. C. Ebers. 2011. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. *Annals of neurology* 70: 881-886.
17. Ross, J. P., C. Q. Bernales, J. D. Lee, A. D. Sadovnick, A. L. Traboulsee, and C. Vilarino-Guell. 2014. Analysis of CYP27B1 in multiple sclerosis. *J Neuroimmunol* 266: 64-66.
18. Ramagopalan, S. V., N. J. Maugeri, L. Handunnetthi, M. R. Lincoln, S. M. Orton, D. A. Dyment, G. C. Deluca, B. M. Herrera, M. J. Chao, A. D. Sadovnick, G. C. Ebers, and J. C. Knight. 2009. Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D. *PLoS genetics* 5: e1000369.
19. Deluca, G. C., S. M. Kimball, J. Kolasinski, S. V. Ramagopalan, and G. C. Ebers. 2013. Review: The role of vitamin D in nervous system health and disease. *Neuropathology and applied neurobiology* 39: 458-484.
20. Nashold, F. E., C. D. Nelson, L. M. Brown, and C. E. Hayes. 2013. One calcitriol dose transiently increases Helios+FoxP3+ T cells and ameliorates autoimmune demyelinating disease. *J Neuroimmunol* 263: 64-74.
21. Kang, S. W., S. H. Kim, N. Lee, W. W. Lee, K. A. Hwang, M. S. Shin, S. H. Lee, W. U. Kim, and I. Kang. 2012. 1,25-Dihyroxyvitamin D3 promotes FOXP3 expression via binding to vitamin D response elements in its conserved noncoding sequence region. *J Immunol* 188: 5276-5282.
22. Nashold, F. E., K. M. Spach, J. A. Spanier, and C. E. Hayes. 2009. Estrogen controls vitamin D3-mediated resistance to experimental autoimmune encephalomyelitis by controlling vitamin D3 metabolism and receptor expression. *J Immunol* 183: 3672-3681.
23. Kragt, J., B. van Amerongen, J. Killestein, C. Dijkstra, B. Uitdehaag, C. Polman, and P. Lips. 2009. Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women. *Multiple sclerosis (Houndmills, Basingstoke, England)* 15: 9-15.
24. Correale, J., M. C. Ysrraelit, and M. I. Gaitan. 2010. Gender differences in 1,25 dihydroxyvitamin D3 immunomodulatory effects in multiple sclerosis patients and healthy subjects. *J Immunol* 185: 4948-4958.
25. Tutuncu, M., J. Tang, N. A. Zeid, N. Kale, D. J. Crusan, E. J. Atkinson, A. Siva, S. J. Pittock, I. Pirko, B. M. Keegan, C. F. Lucchinetti, J. H. Noseworthy, M. Rodriguez, B. G. Weinshenker, and O. H. Kantarci. 2013. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 19: 188-198.
26. Burton, J. M., S. Kimball, R. Vieth, A. Bar-Or, H. M. Dosch, R. Cheung, D. Gagne, C. D'Souza, M. Ursell, and P. O'Connor. 2010. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology* 74: 1852-1859.
27. Soilu-Hanninen, M., J. Aivo, B. M. Lindstrom, I. Elovaara, M. L. Sumelahti, M. Farkkila, P. Tienari, S. Atula, T. Sarasoja, L. Herrala, I. Keskinarkaus, J. Kruger, T. Kallio, M. A. Rocca, and M. Filippi. 2012. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry* 83: 565-571.
28. Derakhshandi, H., M. Etemadifar, A. Feizi, S. H. Abtahi, A. Minagar, M. A. Abtahi, Z. A. Abtahi, A. Dehghani, S. Sajjadi, and N. Tabrizi. 2012. Preventive effect of vitamin D3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial. *Acta neurologica Belgica*.
29. Jones, G. 2013. Extrarenal vitamin d activation and interactions between vitamin d2, vitamin d3, and vitamin d analogs. *Annu Rev Nutr* 33: 23-44.