VITAMIN D_3 NEWS FOR MULTIPLE SCLEROSIS PATIENTS

February 8, 2016

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). Medical advice regarding vitamin D_3 and MS must come from your doctor following new Endocrine Society guidelines (1).

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?

Demyelinating disease develops in individuals carrying genetic risk factors who are exposed to particular environmental factors. MS clustering within families signals a genetic contribution (2). However, 75% of identical twins do not have co-occurrence of MS. The influence of the genetic risk factors is so modest that accurately predicting MS based on genetic risk, even between siblings, is impossible (3), and genetic risk factors cannot be changed. The environmental factors exert the strongest influence on MS risk and may be modifiable (4). The "single key mechanism that dominates all others" must be an environmentally-directed mechanism.

Evidence points to a sunlight-linked factor. High sunlight exposure correlated with low MS risk globally (5). Young migrants substantially reduced their MS risk by settling in regions with ample winter sunlight (6). After long dark winters, relapses (7) and brain lesions (8) surged in MS patients. The sunlight-linked factor overcame genetic factors in determining MS risk and disease activity. Curiously, eating fish compensated for limited winter sunlight in Northern Norway (9). If we aspire to control MS, we must identify the factor common to sunlight and fish.

Vitamin D_3 appears to be the protective factor derived from sunlight and fish (10). Sunlight catalyzes vitamin D_3 formation in the skin, and fish oil is a rich vitamin D_3 source. Vitamin D_3 is converted into 25-hydroxyvitamin D_3 (25(OH)D), an inactive hormone precursor. This precursor is converted into a hormone, calcitriol, that regulates cellular genes, enabling cells to coordinate important biological processes according to environmental cues.

Could vitamin D_3 and calcitriol diminish autoimmunity to myelin 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 (11). 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 (10). Children who took supplementary vitamin D_3 had a lower risk of MS as adults (12). 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 (13). 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 (14, 15) and pediatric MS patients (16), 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 (15). These studies indicate vitamin D_3 might be a major conduit for environmentally-directed protective mechanisms in MS.

Genetic data point strongly to low vitamin D status as an MS risk factor. There are several gene variants that reduce 25(OH)D levels. These gene variants caused a 2-fold higher risk of MS for each standard deviation (SD) reduction in the 25(OH)D level (17). The results show that boosting the 25(OH)D level from 25 to 50 nmol/L would reduce MS risk by 50% and boosting it from 50 to 75 nmol/L would reduce MS risk by another 50%. There is another gene variant that blocks the conversion of 25(OH)D into biologically active calcitriol. In rare Canadian families with multiple MS-affected members, 35 of 35 family members with MS had this variant (18). The odds that this inheritance pattern occurred by chance are 1 in a billion. These results confirm that the active hormone calcitriol is needed to reduce MS risk. Vitamin D_3 may also control the *HLA DRB1*1501* gene, the strongest genetic risk factor for MS (19).

There are plausible biological explanations for the vitamin D_3 - MS link. Calcitriol is a neuroprotective hormone; it supports myelin formation, memory, cognition, neuro-transmission, and neuroplasticity (20, 21). The vitamin D system 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 defend against autoimmunity (10, 22, 23). Estrogen and vitamin D_3 may work together to prevent inflammation of the female CNS. In animals, removing estrogen undermined vitamin D_3 protective functions, and replacing estrogen restored them (24). Blocking calcitriol action also undermined estrogen's protective functions (25). The synergy between estrogen and vitamin D_3 may also apply in women (26, 27). The transition from relapsing-remitting to secondary progressive MS in women occurs around the time of menopause (28). As estrogen declines, the protective benefits of vitamin D_3 may be lost. A girl's risk of MS rises at puberty. As estrogen rises, vitamin D_3 appears to be particularly important to reduce MS risk. The last three decades have seen a tripling in new MS cases in girls and young women. During these decades, vitamin D levels have plummeted globally. We don't know if plummeting vitamin D levels are driving the upward trend in new female MS cases. Research into the estrogen-vitamin D interaction is urgently needed to address this question and the question of MS progression in post-menopausal women.

Three randomized controlled trials have shown vitamin D_3's beneficial effects in MS and optic neuritis patients. In a Canadian study, patients who took an average of 14,000 IU/day of vitamin D_3 had fewer relapses and less disability progression over one year (29). In a Finnish study, patients who took 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 walking scores over one year (30). In an Iranian study, optic neuritis patients with low 25(OH)D levels who took 50,000 IU of vitamin D_3 weekly had lower rates of new brain lesions and 68% less risk of developing MS (31). Some studies have not found beneficial effects, but these studies involved few subjects, short observation periods, or vitamin D_2 not vitamin D_3. Additional vitamin D_3 studies are underway.

The evidence for a causal relationship between low vitamin D_3 status and high MS risk is very strong and consistent, and clinical studies have demonstrated beneficial effects of vitamin D_3 in MS patients. It is reasonable to suggest that daily vitamin D_3 supplementation be considered by physicians and MS patients in the MS treatment plan. The place to start is a blood test for 25(OH)D http://www.grassrootshealth.net. A reasonable target level is >40 ng/mL of 25(OH)D. MS disease activity was lowest in patients whose 25(OH)D was greater than 40 ng/mL. Individuals differ in the amount of vitamin D_3 (cholecalciferol) needed to achieve this target. Gradual increases followed by re-testing is a good approach. MS patients can take up to 14,000 IU/day safely (29). Do not use vitamin D_2 (ergocalciferol) (32). Calcium supplements are not needed. Biological relatives of MS patients, especially sisters and daughters, have an increased risk of MS and may benefit from vitamin D_3 supplements.

If vitamin D_3 and calcitriol do indeed carry out protective biological actions like eliminating autoimmune T cells, promoting T regulatory cells, and enhancing myelin formation and neurological repair, and if these are dominant protective mechanisms in MS, then it may be possible to control MS using a vitamin D-based strategy. A recent animal modeling study demonstrated that just one calcitriol dose together with supplementary vitamin D_3 ameliorated autoimmune demyelinating disease, whereas neither treatment alone accomplished this objective (22). Randomized clinical trials are urgently needed to test this combination in MS patients.

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. Isobe, N., V. Damotte, V. Lo Re, M. Ban, D. Pappas, L. Guillot-Noel, I. Rebeix, A. Compston, T. Mack, W. Cozen, B. Fontaine, S. L. Hauser, J. R. Oksenberg, S. Sawcer, and P. A. Gourraud. 2013. Genetic burden in multiple sclerosis families. *Genes Immun* 14: 434-440.
4. Ebers, G. 2013. Interactions of environment and genes in multiple sclerosis. *J Neurol Sci* 334: 161-163.
5. 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.
6. Ebers, G. C. 2008. Environmental factors and multiple sclerosis. *Lancet neurology* 7: 268-277.
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. 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.
9. 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.
10. 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.
11. Hill, A. B. 1965. The Environment and Disease: Association or Causation? *Proc R Soc Med* 58: 295-300.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Mokry, L. E., S. Ross, O. S. Ahmad, V. Forgetta, G. D. Smith, A. Leong, C. M. Greenwood, G. Thanassoulis, and J. B. Richards. 2015. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. *PLoS Med* 12: e1001866.
18. 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.
19. 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.
20. 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.
21. de la Fuente, A. G., O. Errea, P. van Wijngaarden, G. A. Gonzalez, C. Kerninon, A. A. Jarjour, H. J. Lewis, C. A. Jones, B. Nait-Oumesmar, C. Zhao, J. K. Huang, C. Ffrench-Constant, and R. J. Franklin. 2015. Vitamin D receptor-retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. *J Cell Biol* 211: 975-985.
22. 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.
23. 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.
24. 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.
25. Spanier, J. A., F. E. Nashold, C. G. Mayne, C. D. Nelson, and C. E. Hayes. 2015. Vitamin D and estrogen synergy in Vdr-expressing CD4(+) T cells is essential to induce Helios(+)FoxP3(+) T cells and prevent autoimmune demyelinating disease. *J Neuroimmunol* 286: 48-58.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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*.
32. Jones, G. 2013. Extrarenal vitamin d activation and interactions between vitamin d2, vitamin d3, and vitamin d analogs. *Annu Rev Nutr* 33: 23-44.