VITAMIN D NEWS FOR MULTIPLE SCLEROSIS PATIENTS

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This newsletter's purpose is to provide multiple sclerosis (MS) patients with up-to-date information on vitamin D research that is relevant to MS disease. The information in this newsletter is not intended and should not be used as medical advice. Medical advice must come from your health care providers. You may copy and distribute this newsletter freely.

Scientists are searching for cause and effect relationships between genetic and environmental factors and MS. This knowledge will guide strategies to reduce MS risk and disease activity. MS clustering within families and the co-occurrence of MS in 25% of identical twins show that some genes increase MS risk (1). However, 75% of identical twins do not have co-occurrence of MS, and children who migrate to climates with plentiful winter sunlight have a lower risk of MS than children who live in climates where winter sunlight is scarce (2). These observations have focused research on a sunlight-linked protective factor that may reduce MS risk and disease activity.

Vitamin D is the best candidate for the sunlight-linked protective factor in MS (3). High exposure to ultraviolet light (UVL) correlates strongly with low MS risk (4) and low MS disease activity (5). The UVL causes the skin to produce vitamin D (6). To prove that vitamin D is protective in MS, scientists must determine that the association between vitamin D and MS is strong, consistent, and reproducible, that there is a logical time line for the proposed protective effect, that there is a plausible biological explanation for the association that is consistent with all the facts, and lastly, that increasing vitamin D prevents MS and reduces MS disease activity (7). Recent research has satisfied all of these criteria except the criterion of MS prevention, so vitamin D is now widely believed to be a protective factor in MS.

The data correlating low vitamin D (measured as serum 25-hydroxyvitamin D or 25(OH)D) and high MS risk, relapses, and disability are strong, consistent, and reproducible (3). This association exists in the USA, Argentina, Australia, Canada, Finland, Germany, Ireland, the Netherlands, Norway, the UK, and Scotland. There is a logical time line for the proposed protective effect. Data from the USA, Germany, Finland, and Australia show that seasonal changes in UVL and vitamin D occurred a few months before changes in MS disease relapses, consistent with a cause-effect relationship. Recent studies of adult (8) and pediatric MS patients (9) found that each 5 ng/mL increase in serum 25(OH)D correlated with 16% reduction in relapses.

New genetic data have established beyond a doubt that a defect in vitamin D metabolism can cause MS (10). Remarkably, 35 of 35 MS patients in a Canadian study inherited one bad copy of a vitamin D metabolism gene termed *CYP27B1*. The odds that this inheritance pattern occurred by chance alone are less than 1 in a billion. These genetic data leave no doubt that impaired synthesis of the vitamin D hormone imposes a high risk of MS, independently of UV light. Also, the most common genetic risk factor for MS, the *HLA DRB1*1501* gene, appears to be controlled by the vitamin D hormone (11).

There are plausible biological explanations for the vitamin D - MS association that are consistent with all the facts. Research in an animal model of MS has documented a need for vitamin D to eliminate the autoimmune T lymphocytes that are pathogenic in MS. The vitamin D hormone sensitizes these T lymphocytes to death signals that prevent them from causing inflammation in the central nervous system (12-14).

Estrogen may be very important to enable vitamin D to prevent inflammation of the central nervous system. In female mice, removing sources of estrogen undermined the protective functions of vitamin D, and replacing the estrogen restored those protective functions (15, 16). Emerging research suggests that estrogen is also important in women to enable vitamin D to prevent inflammation of the central nervous system (17, 18). This research has implications for MS. When older women reach menopause and begin producing less estrogen, they may lose the protective effects of vitamin D as well as estrogen. The transition from relapsing-remitting to secondary progressive MS (SPMS) occurs around the time of menopause (19). More research is needed to determine if hormone replacement therapy together with vitamin D_3 supplements might prevent the transition from RRMS to SPMS.

The strongest evidence for a protective effect of vitamin D_3 in MS patients came from a Canadian study published in 2010 (20). This study provided a glimpse of what may be possible with vitamin D_3 intervention in MS. RRMS patients were randomized into two

groups, a control group and a vitamin D_3 supplementation group. The supplementation group took vitamin D_3 beginning with 4000 international units (IU) per day, increased their dose to a very high level, and then decreased their dose to 10,000 IU per day over the course of a year. This dose range was safe, since there were no adverse events due to vitamin D_3. Most importantly, 38% of the control group but only 8% of the treatment group had an increase in disability at the end of one year. For the first time, an intervention appears to have slowed the progression of MS disability! A study performed at the University of California San Francisco also found that MS patients who began taking vitamin D3 supplements had fewer relapses and MRI lesions (Mowry et al. ACTRIMS/ECTRIMS Conference, Amsterdam, 2011). Additional vitamin D_3 supplementation studies are underway in the USA and other countries.

What can researchers suggest for MS patients? Patients should request a blood test for 25(OH)D. This should be above 40 ng/mL. If not, vitamin D_3 supplements should be taken with medical supervision 4000 international units per day of vitamin D_3 is a good place to start. *Vitamin D_2 (which is in some prescription forms of vitamin D, e.g. Driscol) should not be used*. It is safe for MS patients to take up to 10,000 IU per day of vitamin D_3 with medical supervision (20). Serum 25(OH)D should be tested again after ~3 months.

A new global multidisciplinary taskforce has been formed to investigate whether vitamin D_3 supplements might reduce the risk of MS among family members of MS patients. Biological relatives of MS patients, especially female relatives like sisters and daughters have an increased risk of MS and should also be tested for 25(OH)D. Wisconsin will be a taskforce study sight. Stay tuned!!

References

1. Gourraud, P. A., J. P. McElroy, S. J. Caillier, B. A. Johnson, A. Santaniello, S. L. Hauser, and J. R. Oksenberg. 2011. Aggregation of multiple sclerosis genetic risk variants in multiple and single case families. *Annals of neurology* 69:65-74.
2. Ebers, G. C. 2008. Environmental factors and multiple sclerosis. *Lancet neurology* 7:268-277.
3. 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.
4. Ponsonby, A. L., R. M. Lucas, and I. A. van der Mei. 2005. UVR, vitamin D and three autoimmune diseases--multiple sclerosis, type 1 diabetes, rheumatoid arthritis. *Photochem Photobiol* 81:1267-1275.
5. 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.
6. Prosser, D. E., and G. Jones. 2004. Enzymes involved in the activation and inactivation of vitamin D. *Trends Biochem Sci* 29:664-673.
7. Hill, A. B. 1965. The Environment and Disease: Association or Causation? *Proc R Soc Med* 58:295-300.
8. Simpson, S., B. Taylor, L. Blizzard, A.-L. Ponsonby, F. Pittas, H. Tremlett, T. Dwyer, P. Gies, and I. A. van der Mei. 2010. Higher 25-hydroxyvitamin D is associated with lower relapse risk in MS. *Annals of neurology* in press.
9. 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.
10. 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.
11. 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.
12. Spach, K. M., L. B. Pedersen, F. E. Nashold, T. Kayo, B. S. Yandell, T. A. Prolla, and C. E. Hayes. 2004. Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis. *Physiol Genomics* 18:141-151.
13. Pedersen, L. B., F. E. Nashold, K. M. Spach, and C. E. Hayes. 2007. 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by inhibiting chemokine synthesis and monocyte trafficking. *J Neurosci Res* 85:2480-2490.
14. Mayne, C. G., J. A. Spanier, L. M. Relland, C. B. Williams, and C. E. Hayes. 2011. 1,25-Dihydroxyvitamin D3 acts directly on the T lymphocyte vitamin D receptor to inhibit experimental autoimmune encephalomyelitis. *European journal of immunology* 41:822-832.
15. 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.
16. Spach, K. M., F. E. Nashold, B. N. Dittel, and C. E. Hayes. 2006. IL-10 signaling is essential for 1,25-dihydroxyvitamin D3-mediated inhibition of experimental autoimmune encephalomyelitis. *J Immunol* 177:6030-6037.
17. 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.
18. 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.
19. Koch, M., E. Kingwell, P. Rieckmann, and H. Tremlett. 2010. The natural history of secondary progressive multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry* 81:1039-1043.
20. 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.