VITAMIN D3 NEWS FOR MULTIPLE SCLEROSIS PATIENTS

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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 this disease. The MS disease process involves 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. 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 (3). Young immigrants carrying known genetic risk factors substantially reduced their MS risk if they settled in regions with ample sunlight compared to regions with little winter sunlight (4). After the long dark winters in high latitude regions, MS patients experienced a surge in brain lesions (5) and disease relapses (6). 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 (7). Thus, fish consumption compensated for a lack of winter sunlight! We must identify the common factor between sunlight and fish if we aspire to control MS.

Vitamin D_3 may be a major conduit for the protective actions of sunlight and fish consumption in MS (8). Sunlight exposure 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). The actions of calcitriol and the VDR allow our bodies to coordinate 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 that the association between vitamin D_3 and MS is strong, consistent, and reproducible, that a logical time line and plausible mechanisms support a cause-effect relationship, and that altering vitamin D_3 affects MS risk and/or severity (9). Recent research has addressed all of these criteria.

Strong, consistent, and reproducible data have correlated low vitamin D_3 status (serum 25(OH)D) with high MS risk, frequent relapses, and rapid disease progression (8). These correlations have been demonstrated 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. In Finland, where serum 25(OH)D levels fluctuate widely from summer to winter, a drop in 25(OH)D preceded a surge in disease relapses. Recent studies of adult (10, 11) and pediatric MS patients (12) found higher serum 25(OH)D levels (>40 ng/mL) correlated with fewer MRI lesions and relapses. Also, individuals who took supplementary vitamin D_3 as children had a reduced risk of MS as adults (13), and 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 (11). These studies indicate vitamin D_3 could be a major conduit for the protective actions of sunlight and fish consumption in MS.

Genetic data also point to the vitamin D pathway. The *CYP27B1* gene encodes the enzyme that converts 25(OH)D into biologically active calcitriol. In rare families with multiple MS-affected members, 35 of 35 family members with MS had one damaged copy of the *CYP27B1* gene (14). The odds that this inheritance pattern occurred by chance are 1 in a billion. Other researchers have not found this correlation. It is possible that an interaction between the *CYP27B1* gene mutation and other genetic factors like an MS susceptibility gene or an environmental factor like low sunlight exposure or a pathogen may determine MS risk. Vitamin D_3 may also influence the strongest genetic risk factor for MS, the *HLA DRB1*1501* gene (15).

There are plausible biological explanations for the vitamin D_3 - MS link. Growing evidence suggests vitamin D_3 supports memory, cognition, neurotransmission, and neuroplasticity (16). Animal modeling research has demonstrated a requirement for vitamin D_3, calcitriol, and the VDR to support T regulatory cells that oppose autoimmunity, reduce access to the central nervous system of pathogenic autoimmune T lymphocytes, and increase pathogenic T lymphocyte elimination, reducing inflammation in the central nervous system (8, 17). Animal modeling research also demonstrated that estrogen is essential in females to enable vitamin D_3, calcitriol, and the VDR to prevent inflammation of the central nervous system. Removing estrogen undermined vitamin D_3 protective functions in female mice, and replacing estrogen restored them (18). Emerging research suggests that estrogen may also be important for vitamin D pathway protective functions in women (19, 20). This research has important implications for MS. The transition from relapsing-remitting to secondary progressive MS in women occurs around the time of menopause (21). If estrogen is essential to support the functions of the vitamin D pathway, then as estrogen production declines, the protective benefits of both estrogen and vitamin D_3 may be lost simultaneously. More research is needed to investigate this biological relationship between estrogen and vitamin D_3 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 patients 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 (22). 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 (23). 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 (24). 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 (22). Some evidence indicates vitamin D_2 may be less beneficial so vitamin D_3 is preferred (25). 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 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 (17). Studies are being designed now to determine whether intermittent calcitriol pulse dosing with supplementary vitamin D_3 will benefit MS patients. Stay tuned!

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