

VITAMIN D₃ NEWS FOR MULTIPLE SCLEROSIS PATIENTS

December 16, 2013

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This newsletter's purpose is to provide current information on vitamin D₃ research relevant to multiple sclerosis (MS). It is not medical advice. Medical advice regarding vitamin D₃ 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 did not consume 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 D₃ may be the major conduit for the protective actions of sunlight and fish consumption in MS (8). Sunlight exposure catalyzes vitamin D₃ formation in the skin, and fish oil is a rich source of dietary vitamin D₃. Vitamin D₃ is converted into 25-hydroxyvitamin D₃ (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 D₃, 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 D₃ and MS is strong, consistent, and reproducible, that there is a logical time line supporting a cause-effect relationship, and that there is a plausible biological explanation for the proposed protective effect (9). Recent research has satisfied all of these criteria.

Strong, consistent, and reproducible data have correlated low vitamin D₃ 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 D₃ as children had a reduced risk of MS as adults (13), and MS patients who began taking vitamin D₃ 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 the vitamin D pathway is 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. These individuals lived in regions with little winter sunlight, and had reduced 25(OH)D and calcitriol levels. Other researchers did not find a correlation between a damaged *CYP27B1* gene and MS, but they studied people living in regions with plentiful sunlight where higher 25(OH)D levels may have allowed the undamaged enzyme to produce enough calcitriol. Other genetic studies suggest that calcitriol may control the strongest genetic risk factor for MS, the *HLA DRB1*1501* gene (15).

There are plausible biological explanations for the vitamin D₃ - MS association. Animal modeling research has demonstrated a requirement for vitamin D₃, calcitriol, and the VDR to enable elimination of the autoimmune T lymphocytes that are pathogenic in MS. Calcitriol sensitized these T lymphocytes to death signals, preventing the cells from causing inflammation in the central nervous system (16-18). Animal modeling research also demonstrated that estrogen is essential in females to enable vitamin D₃, calcitriol, and the VDR to prevent inflammation of the central nervous system. Removing estrogen undermined protective functions of this pathway in female mice, and replacing the estrogen restored those functions (19). Emerging research suggests that estrogen may also be important for vitamin D pathway protective functions in women (20, 21). This research has important implications for MS. The transition from relapsing-remitting to secondary progressive MS in women occurs around the time of menopause (22). 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 D₃ may be lost simultaneously. More research is needed to investigate this biological relationship between estrogen and vitamin D₃ and how it may influence MS progression in women.

Recent studies have provided glimpses of what may be possible with vitamin D₃ supplementation in MS patients. A

Canadian study randomized MS patients into a vitamin D₃ group (10,000 IU of vitamin D₃ daily), and a control group (23). This study established that it is safe for MS patients to take 10,000 IU/day of vitamin D₃. The vitamin D₃ group had fewer relapses and less disability progression than the control group over one year. A Finnish study randomized MS patients into a vitamin D₃ group (28,000 IU of vitamin D₃ weekly) and a control group (24). The vitamin D₃ group had 85% fewer new MRI lesions, and trends toward lower total lesion burden, reduced EDSS, and improved timed 10 foot tandem walk scores compared to controls over one year. An Iranian study randomized optic neuritis patients with low 25(OH)D levels into a vitamin D₃ group (50,000 IU of vitamin D₃ weekly) and a control group (25). The vitamin D₃ group had lower rates of new brain lesions and 68% less risk of developing MS than controls. Vitamin D₃ studies with more MS patients and longer observation periods are underway.

Since vitamin D₃ appears to be a major conduit for the protective actions of sunlight and fish consumption in MS, it may be beneficial for MS patients who live in regions with limited winter sunlight, or who work indoors, to take vitamin D₃ supplements daily to avoid becoming vitamin D deficient. A blood test for 25(OH)D is needed to determine your vitamin D status (see <http://www.vitaminadecouncil.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 D₃ than others to achieve 40 ng/mL of 25(OH)D. MS patients can take 10,000 IU/day safely. Some evidence indicates vitamin D₂ may be harmful so vitamin D₃ is preferred. Biological relatives of MS patients, especially sisters and daughters, have an increased risk of MS and may benefit from daily vitamin D₃ supplements.

If vitamin D₃, calcitriol, and the VDR do indeed perform biological actions like eliminating autoimmune T cells and promoting 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. Testing this prediction was the goal of a recently published animal modeling study (26). The animal research demonstrated that a single calcitriol dose plus supplementary vitamin D₃ ameliorated autoimmune demyelinating disease in mice, whereas neither treatment alone accomplished this objective. It is not certain that this protocol will be translatable from rodents to MS patients. Studies are being designed now to answer this important question. Stay tuned!

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