This newsletter's purpose is to provide current information on vitamin D research relevant to multiple sclerosis (MS). Medical advice regarding vitamin D 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. Cursory, 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 D3 appears to be the protective factor derived from sunlight and fish (10). Sunlight catalyzes vitamin D3 formation in the skin, and fish oil is a rich vitamin D3 source. Vitamin D3 is converted into 25-hydroxyvitamin D3 (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 D3 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 D3 and MS is strong, consistent, and reproducible, whether a logical time line and plausible mechanisms support a cause-effect relationship, and whether altering vitamin D3 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 D3 status (serum 25(OH)D) and high MS risk, frequent relapses, and rapid disease progression (10). Children who took supplementary vitamin D3 had a lower risk of MS as adults (12). Among patients with a first event suggestive of MS, low vitamin D3 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 D3 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 D3 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 D3 may also control the HLA DRB1*1501 gene, the strongest genetic risk factor for MS (19).

There are plausible biological explanations for the vitamin D3 -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 D3 may work together to prevent inflammation of the female CNS. In animals, removing estrogen undermined vitamin D3 protective functions, and replacing estrogen restored them (24). Blocking calcitriol action also undermined estrogen’s protective functions (25). The synergy between estrogen and vitamin D3 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 D3 may be lost. A girl’s risk of MS rises at puberty. As estrogen rises, vitamin D3 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 in girls and young women. Particularly important to reduce MS risk. The last three decades have seen a tripling in new MS cases in girls and young women. Among patients with a first event suggestive of MS, low vitamin D3 status predicted higher MS activity, lesion load, brain atrophy, and clinical progression (13).


