

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.

To reduce the impact of MS, scientists are searching for cause and effect relationships between genetic and environmental factors and MS. This knowledge may lead to strategies to reduce the impact of MS. The clustering of MS in some families and the occurrence of MS in identical twin pairs suggests there are genes that increase MS risk (1). However, MS risk genes probably account for <20% of MS risk, cannot be changed, and can be over-ridden by protective environmental factors (2). Consequently, new research is focusing on protective environmental factors that can be changed and may overcome MS risk genes.

Sunlight exposure and vitamin D are the best candidates for protective environmental factors in MS (3). High exposure to ultraviolet light (UVL) correlates strongly with low MS risk (4). The UVL causes the skin to produce vitamin D (5). Before concluding that UVL and vitamin D are protective in MS, scientists must determine that the association 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 changing the environmental factor changes the disease outcome (6). Recent research has satisfied all of these criteria, so vitamin D is now widely believed to be a protective environmental 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. This association exists in the USA, Argentina, Australia, Canada, Finland, Germany, and the Netherlands (7). There is a logical time line for the proposed protective effect. Data from 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 (8, 9). Recent studies of adult (10) and pediatric MS patients (11) found that each 5

ng/mL increase in serum 25(OH)D correlated with 16% reduction in relapses.

Genetic studies also support a strong association between vitamin D and MS. Alterations in the genes involved in vitamin D hormone synthesis and vitamin D hormone receptor have been implicated in MS risk in Australia, the Netherlands, New Zealand, Norway, Japan, and the UK (12, 13). Also, the strongest genetic risk factor for MS, the *HLA DRB1*1501* gene, appears to be controlled by the vitamin D hormone (14).

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 the protective death signals that are given within the central nervous system to prevent inflammation in this tissue (15, 16). The vitamin D hormone also supports the regulatory T lymphocytes that counteract pathogenic autoimmune T lymphocytes (17).

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 (18, 19). Emerging research suggests that estrogen is also important in women to enable vitamin D to prevent inflammation of the central nervous system (20, 21). This research has implications for MS. When young women begin producing higher amounts of estrogen at puberty, they may become especially dependent on vitamin D to protect them from autoimmunity. The lack of vitamin D may have a greater negative effect on young women than on young men, contributing to the female sex bias in MS. When older women produce lower amounts of estrogen at menopause, they may lose the protective effects of both estrogen and vitamin D. The transition from relapsing-remitting to secondary progressive MS (SPMS) coincided with the menopausal transition (22). More research is needed to determine if estrogen replacement together with vitamin D could prevent the transition to SPMS in older women.

The strongest evidence for a cause-effect relationship between an environmental factor and disease comes from changing the environmental factor

and observing a change in the disease (6). A study published in April 2010 has provided a glimpse of what may be possible with vitamin D intervention in MS (23). RRMS patients were randomized to a control or a treatment group (the study was not blinded). The control patients were allowed to take up to 4000 IU/d of vitamin D₃ and calcium at their discretion. The treatment group was given an escalating dose of vitamin D₃ that began at 4000 IU/d, escalated to 40,000 IU/d, and decreased back to 10,000 IU/d for an average of ~10,000 IU/d over the course of a year. There were no adverse events in either group. 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 (p=0.019). For the first time, an intervention may have slowed the progression of MS disability. The challenge is now to repeat this study in a blinded fashion with larger numbers of participants.

What can researchers suggest for MS patients and their physicians? Every patient should be tested for serum 25(OH)D every 6 mo, especially in winter. The relapse-free zone in the Finnish study was serum 25(OH)D above 50 ng/mL (9), so this is a current target. Vitamin D₃ supplements can be given to increase serum 25(OH)D. Up to 10,000 IU/day of vitamin D₃ has proven to be safe in MS patients (24).

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