## High-Dose Vitamin D Supplementation Reduces Key CNS Inflammatory Markers in MS Patients

**James Meschino DC, MS, ROHP**

Numerous studies show that low levels of vitamin D in the blood are strongly linked to increased risk of developing multiple sclerosis (MS) and that MS patients with low blood levels of vitamin D (25- hydroxycholecalciferol) are more likely to have greater disability and more disease activity. The ground breaking study by E. S. Sotirchos et al, published in the journal *Neurology* in December 2015, showed that MS patients administered high-dose vitamin D (10,400 IU per day) supplementation, over a six month period, had a reduction in the percentage of inflammatory T cells related to MS severity - specifically IL-17+CD4+ and CD161+CD4+ cells.

The study included 40 people with relapsing-remitting MS. Patients in the control group, who were given 800 IU per day of vitamin D, did not show a reduction in these MS inflammatory markers. For the patients ingesting 10,400 IU of vitamin D per day, when the increase in vitamin D levels in the blood over base line levels was greater than 18 ng/ml (45 nmol/L) every additional 5 ng/ml (12.5 nmol/L) increase in vitamin D led to a 1 percent decrease in the percentage of IL-17+CD4+ T cells in the blood. The people taking the low dose did not have any noticeable changes in the percentages of their T cell subsets. The hope is that these changes in inflammatory T cell responses translate into a reduced severity of disease, and other clinical trials are underway to determine if that is the case. However, these findings are quite encouraging, especially considering that no significant side effects were reported by that MS patients administered the high-dose vitamin D supplementation protocol compared with those taking the low-dose protocol.

With respect to optimal vitamin D blood levels for MS patients, researchers are still working to determine what range is most beneficial. At the present time the range of 40 to 60 ng/ml has been proposed as a target. This is equivalent to 100 – 150 nmol/L. Participants taking the high-dose vitamin D protocol reached levels within the proposed target, whereas the group taking the low-dose (800 IU) did not reach the target. It is noteworthy that patients with severe vitamin D deficiency were not included in the study. (1)

## Inflammatory Markers in Multiple Sclerosis

Multiple sclerosis is the most common neurological disease of young adults, afflicting hundreds of thousands of people worldwide. Until recently researchers had highlighted the role of type 1 and type 2 cytokines in the etiology of MS.

The general notion was that a type 1 response (with CD4 T cells of helper type 1, TH1 cells) was associated with a pro-inflammatory, destructive immune reaction, whereas a type 2 response (with TH2 cells) reflected a modulatory, non-pathogenic immune reaction, which may even protect against autoimmune disease caused by TH1-dependent mechanisms.

More recently it has been shown that IL-23 is an upstream modulator of a very important pathogenic signaling pathway way in MS. IL-23 is crucially involved in the expansion of cells producing IL-17, and that IL-17 is produced by TH cells that are distinct from the traditional TH1 and TH2 cell subsets, and have thus been designated as TH17 cells. This rapidly emerging evidence clearly demonstrates that TH17 cells are indeed a T-helper cell subpopulation distinct in differentiation and function from the TH1 and TH2 subsets described previously.

Of great clinical significance is the fact that a systematic analysis of IL-17-positive cells in the brains of MS patients revealed a significant increase in the number of $IL\text{-}17^{+}$ T cells in the active rather than the inactive areas of MS lesions. Another critical finding was the fact that IL-17 immunoreactivity could also be detected in astrocytes and oligodendrocytes in active areas of MS plaques. All of these findings have made it increasingly clear that IL-17 is an essential player in MS, and that IL-17 is likely an important target for future therapeutic interventions to improve MS progression and outcomes. (2) As such, the discovery that high-dose vitamin D supplementation can down regulate the release of IL-17 in MS patients is of great significance. (1)

**Understanding Interleukin-17: A key cytokine in MS**

IL-17 is a signature cytokine of Th17 (T-helper 17) cells and plays critical roles in host defence against bacterial and fungal infections, as well as in the pathogenesis of autoimmune diseases. IL-17 is highly up-regulated at sites of inflammatory tissues of autoimmune diseases and amplifies the inflammation through synergy with other cytokines, such as TNF (tumour necrosis factor) α. Although IL-17 was originally thought to be produced mainly by Th17 cells, a newly defined T-cell subset with a specific differentiation programme and tight regulation, several other cell types (especially innate immune cells) are also found as important sources for IL-17 production.

Mouse genetic studies have demonstrated a critical role for IL-17 in the pathogenesis of variety of inflammatory autoimmune diseases, such as RA (rheumatoid arthritis) and MS (multiple sclerosis). Importantly, promising results have been shown in initial clinical trials of monoclonal antibodies against IL-17 or its receptor (IL-17R) to block IL-17-mediated function in treating autoimmune patients with psoriasis, RA and MS. (3) Human studies have also shown that IL-17 is over expressed in patients with Crohn's disease and that IL-17 induces a pro-inflammatory response in this condition. (4)

**Other Vitamin D Studies In MS Patients and Summary**

Presenting at the American Academy of Neurology in 2009 Dr. Jodie Burton reveled the results of a vitamin D trial in MS patients. This study showed that high doses of vitamin D (14,000 IU per day for one year) dramatically cut the relapse rate in people with multiple sclerosis compared to those given only 1000 IU per day of vitamin D over the same time period. More specifically 16% of 25 MS patients in the high-dose vitamin D group suffered relapsed during the one year period, compared to 40% in the low-dose vitamin D group, which was comprised of 24 MS patients. As well, people taking high-dose vitamin D suffered 41% fewer relapses than the year before the study began, compared with 17% of those taking typical doses (1000 IU – the amount typically recommended to MS patients by neurologists). Also encouraging was the fact that patients taking high doses of vitamin D did not suffer any significant side effects. (5)

Compelling evidence has linked low vitamin D levels with increased risk for MS, and progression of MS in patients suffering from MS. Our understanding of the importance of Vitamin D in immune system modulation continues to unfold with each passing year. Most recently we have learned that vitamin D is capable of down-regulating the over expression of IL-17, a highly implicated cytokine in the pathophysiology of multiple sclerosis. We have preliminary evidence that high-dose vitamin D supplementation (approx. 10,000-14,000 IU per day) can reduce IL-17 levels and significantly reduce relapses in MS patients. This is indeed encouraging, and thus, neurologists may want to reconsider their usual recommendation of 1000 IU vitamin D per day for MS patients by increasing this amount to 10,000-14,000 IU per day, for at least the first year. In these cases monitoring of vitamin D blood levels (25-hydroxycholecalciferol) should be undertaken to ensure that a range of 40-60 ng/ml (100-150 nmol/L) is achieved, while avoiding vitamin D toxicity, which typically can occur at vitamin D blood

levels nearing 100 ng/ml (250 nmol/L). Complementary health practitioners should also be encouraged to discuss these findings with their MS patients and to follow the results of future clinical trials involving vitamin D administration to MS patients.

**References:**


1. Sotirchos E. S., Bhargava P, Eckstein C, Van Haren K, Baynes M. Ntranos A et a**l.**Safety and immunologic effects of high- vs low-dose cholecalciferol in multiple sclerosis**.** *Neurology*, 2015 (http://www.neurology.org/content/early/2015/12/30/WNL.0000000000002316)
2. Gold R, Luhder F. Interleukin-17—Extended Features of a Key Player in Multiple Sclerosis. Am J Pathol. 2008;172(1):8-10
3. Zhu S, Qian Y. IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential. Clin Sci (Lond). 2012;122(11):487-511.
4. Siakavellas SI, Bamias G. Role of the IL-23/Il-17 axis in Crohn's disease. 2012;14(77):253-62
5. http://www.webmd.com/multiple-sclerosis/news/20090428/high-doses-vitamin-d-cut-ms-relapses