If I had clinically isolated syndrome with magnetic resonance imaging diagnostic of multiple sclerosis, I would take vitamin D 10,000 IU daily: Yes

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Proposal

Strong epidemiologic evidence supports a role for vitamin D insufficiency as a risk factor for multiple sclerosis (MS), shown by increasing disease prevalence with increasing latitude, and inverse correlation with duration and intensity of ultraviolet B (UVB) sunlight exposure and vitamin D serum concentration. Moreover, MS risk seems to decrease with migration from higher latitudes to lower ones. The Nurses' Health Study II, in research focused on latitude and sunlight, demonstrated dietary vitamin D supplement use (estimated dose ≥400 IU/day) was associated with 40% less risk of MS development, compared to non users. MS risk among study participants was reduced by approximately half, in women born to mothers with high vitamin D levels in breast milk or taking supplements during pregnancy, compared to women born to mothers whose intake had been low, suggesting that MS risk is related not only to recent vitamin D levels but also to levels present during childhood or in utero. A prospective nested case-control study among US military personnel demonstrated 41% decrease in MS risk in Caucasian individuals, for every 20 ng/ml increase in serum-measured vitamin D levels. Likewise, in patients with pediatric-onset MS or clinically isolated syndrome (CIS) every 10 ng/ml increase in adjusted 25-hydroxyvitamin D3 level was associated with a one-third reduction in subsequent relapse rates.

There is accumulating data documenting the capacity of 1,25 dihydroxyvitamin D3 produced by macrophages, dendritic cells (DCs), T cells and B cells, to contribute physiologically to autocrine and paracrine regulation of both innate and adaptive immune responses, via the vitamin D receptor (VDR) expressed in these types of cells. 1,25 dihydroxyvitamin D3 favors induction of DCs with tolerogenic properties, shaping T cell activation and development. In addition, 1,25 dihydroxyvitamin D3 can have a direct effect on T cells and B cells. On B cells, it inhibits the proliferation of memory B cells, plasma-cell differentiation and immunoglobulin production. Under appropriate conditions, 1,25 dihydroxyvitamin D3 inhibits the proliferation of CD4+ T cells favoring the development of IL-10 producing cells, and also inhibits pro-inflammatory, pathogenic Th1 and Th17 cells inducing differentiation of CD4+CD25+Foxp3+ regulatory T cells. Collectively, vitamin D affects the immune system at different levels, through varied mechanisms conferring an immunosuppressive effect on the whole which may ultimately be applied to treat autoimmune diseases such as MS. However, it is important to note that the majority of these immunological effects have only been demonstrated in animal models, or in vitro experiments, using supra-physiological doses far superior to normal levels.

Altogether, emerging literature has strengthened the association between vitamin D deficiency and increased risk of developing MS. Therefore, intervention with vitamin D supplementation could have an important impact on MS development risk, as well as subsequent disease activity and severity. Nevertheless, this remains unconfirmed without prospective randomized control trials to determine the most efficacious, safe and minimum required dose.

To date, there have been no controlled trials designed to assess whether vitamin D supplementation could benefit individuals with CNS demyelinating diseases. Different investigators have however conducted small studies, primarily to determine the safety of increased vitamin D doses. Given its stability in the serum and superior correlation with vitamin D sufficiency, 25-hydroxyvitamin D3 concentration is considered the best indicator of vitamin D status. Importantly, “normal” vitamin D levels have been determined on the basis of bone-health measures without reference to “extracalcemic” actions of vitamin D. Available data suggest that MS risk is minimized at 25-hydroxyvitamin...
D3 serum levels above 100 nmol/l on average, a concentration that can be achieved by taking 2000–4000 IU/day of vitamin D3. These doses are considered safe and potentially beneficial for other outcomes. On the other hand, based on non-MS clinical trials, the upper limit of safety for 25-hydroxyvitamin D3 is at a concentration of about 200–225 nmol/l, with an unspecified margin of safety beyond this level. In the absence of sunlight, 225 nmol/l is achieved with prolonged consumption of about 10,000 IU/day of vitamin D3.

Only a few clinical trials on vitamin D3 therapy have been completed in individuals with MS. Most data reported in the literature comes from unblinded, uncontrolled study designs. In one recent study, 12 individuals with MS and active Gd-enhancing lesions received dose escalation therapy with vitamin D3 over 28 weeks. Vitamin D3 at 40,000 IU/day generated serum concentrations of vitamin D averaging 155 ng/ml. After five weeks of treatment no toxicities were observed and, although clinical variables remained stable, Gd-enhancing lesions decreased at the end of the study. An extension of this study included 25 treated individuals and 24 controls in an open-label randomized prospective controlled trial. This sample size provided sufficient power for primary endpoints pertaining to safety to be measured. Treated patients received doses of up to 40,000 IU/day, plus 1.2 g of calcium daily, and spent 36/52 weeks on 10,000 IU/day, with mean daily doses of 14,000 IU/day, reaching a serum 25-hydroxyvitamin D3 peak >400 nmol/l. No adverse clinical or biochemical events were reported, despite the high doses of vitamin D3. Although there may have been confounding variables in clinical outcomes, the treated patients appeared to have fewer relapses, as well as a persistent reduction in T cell proliferation in response to stimulation with MS-related antigens and dietary antigens, compared to control subjects; particularly in patients achieving 25-hydroxyvitamin D3 levels ≥100 nmol/l. This study suggests that in individuals with MS, “normal” 25-hydroxyvitamin D3 levels may not be optimal or sufficient to drive benefits at the immunological level. In a third study, 15 MS patients received 20,000 IU/day of vitamin D3 over 12 weeks: there was no control group. Median 25-hydroxyvitamin D3 levels increased to 380 nmol/l, but no adverse events were reported. Although regulatory T cell numbers remained unchanged, the number of IL-10+CD4+ T cells increased and the IFN-γ +CD4+: IL4 + CD4+ T cell ratio decreased, ultimately favoring an anti-inflammatory profile. Building on these studies a larger double-blind, placebo-controlled randomized phase III trial of Vitamin D3 is currently underway. In this add-on study, patients with relapsing–remitting MS receiving subcutaneous interferon β-1a will be treated with escalating doses of up to 14,000 IU/day of vitamin D3, for up to 96 weeks. This dose is expected to elevate 25-hydroxyvitamin D3 levels to over 250 nmol/l. Whether this high level is necessary or even desirable is still unclear. Clearly, further studies should not only focus on classical outcomes like MRI-evidenced changes, relapse rate and disability progression. Other symptoms found in MS and also associated with vitamin D deficiency should be investigated, including depression and cognitive impairment. Inclusion of these parameters could provide a more complete picture of vitamin D supplementation impact on MS progression.

Although optimal dose and vitamin D serum levels have yet to be established, most evidence from the literature on vitamin D supplementation has shown no evidence of toxicity for doses of up to 10,000 IU/day of vitamin D3 for up to five months, or for 25-hydroxyvitamin D3 levels beyond the physiologic range. All published reports on vitamin D toxicity as a result of hypercalcemia involve daily intake levels >40,000 IU which could conservatively be considered the lowest observed adverse effect level. Overall, properly designed and conducted clinical trials are the next step to demonstrate whether vitamin D is an effective treatment to delay time to progression from an initial demyelinating episode to MS, or to treatment of MS, as well as to establish the optimal dose that will benefit patients through immune response modulation without causing toxicity.

Finally, addressing the proposal, I would say “yes it is safe, probably effective and I do not have time to wait for the trials to be done”.

**Disclosures**

JC is a board member of Merck-Serono Argentina, Biogen-Idec LATAM and Merck-Serono LATAM. JC has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina and TEVA-Tuteur Argentina as well as professional travel/accommodation stipends.

**References**


