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Prevention and treatment of MS: studying the effects of vitamin D

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Abstract

Observational studies suggest that adequate vitamin D nutrition may reduce the risk of MS and affect the course of the disease. Inherent limitations in these studies, however, preclude a causal interpretation. Randomized controlled clinical trials are the next step to addressing whether vitamin D prevents MS or can favorably affect the course and progression of MS. Here we briefly review the current literature on vitamin D and MS, both as a risk factor and potential treatment for MS with a focus on the issues and challenges in designing prevention and treatment clinical trials.

Keywords

multiple sclerosis; vitamin D; prevention; treatment; clinical trials

Introduction

Since vitamin D was first proposed as an important factor in MS development,[1] numerous experimental and epidemiological studies have been conducted to answer two key questions: 1) does vitamin D prevent MS, and 2) is vitamin D an effective treatment for MS? While observational studies support a protective role for vitamin D in MS development and progression, their limitations, including proxy measures of vitamin D, recall and selection biases, confounding, and reverse causation, limit the extent to which inverse associations can be attributed specifically to vitamin D. Randomized placebo-controlled clinical trials are considered the gold standard in determining whether there is a cause and effect association between a specific factor and disease, and there is much interest in conducting both prevention and treatment trials for vitamin D and MS. However, issues such as suitable populations, sample size, and appropriate dosing of vitamin D are challenges to conducting these studies. Here we will provide a brief review of the current literature on vitamin D and MS with a focus on the clinical trials literature, as well as the challenges and questions faced in their design.

Vitamin D as a risk factor for development of MS

Observational studies

The latitude gradient for MS prevalence has been well documented, with generally increasing prevalence with increasing distance from the equator; the reduction in risk associated with migration from high to low prevalence areas suggests the primary

determinant is an environmental factor.[2] Vitamin D is a likely candidate because of the strong latitude gradient in the intensity of solar UV radiation, which is the primary source of vitamin D in humans.[2] Observations that individuals born in the spring months are more likely to develop MS [3] and that female offspring of mothers with high dietary vitamin D intake during pregnancy have a lower risk of MS [4] suggest that vitamin D exposure may already be important *in utero*. In case-control studies of sun exposure in Australia,[5] Norway,[6] and the United States,[7] increased sun exposure in childhood/adolescence was associated with a reduced risk of MS; however, MS cases and controls were asked to recall their sun exposure many years in the past and recall bias may affect these results. Further, sun exposure is not a direct measure of vitamin D nutrition and it has immunomodulatory effects outside of the vitamin D pathway that may influence MS risk.[8] The two prospective studies of vitamin D and MS risk that have been conducted eliminate recall bias in the study design and measure vitamin D exposure directly either from diet,[9] or as serum 25-hydroxyvitamin D (25(OH)D) levels, [10] in healthy individuals and follow them for a diagnosis of MS. In both studies, inverse associations between vitamin D nutrition in late adolescence/adulthood and MS were found. Women with an intake of at least 400 IU of supplemental vitamin D per day had a 40% reduced risk of MS as compared to women not taking supplements[9] and healthy, non-Hispanic whites with serum levels of 25(OH)D of 100 nmol/L or greater had a 50% reduced risk of developing MS as compared to those with levels below 75 nmol/L.[10] The prospective design of these two latter studies is a strength because it eliminates recall bias and minimizes the possibility of selection bias, which is a common problem in case-control studies that are not nested within prospective cohorts. Although confounding by other nutrients in the diet study or alternative sun-induced immunosuppressive pathways in the serum study are possible, neither of these possibilities is convincingly supported by available evidence, and a genuine protective effect of vitamin D itself remains the most parsimonious and plausible explanation for the results of both investigations.[2] Additional prospective studies will be important to provide confirmation of these associations in other populations and further elucidate the dose-response or importance of seasonal fluctuations of vitamin D on MS risk; however, a vitamin D-MS prevention trial will be ultimately required to provide the conclusive evidence of a protective effect of vitamin D supplementation that is needed to support a broad public health intervention specific for MS prevention.

Primary prevention trials of vitamin D and MS

There are currently no published or ongoing primary prevention trials on vitamin D and MS. In designing such a trial, there are many important considerations including, but not limited to, which population to target and dose(s) of vitamin D to use. Because MS is a rare disease, it may be most cost-effective to conduct trials among “high-risk” individuals such as first degree relatives of someone with MS, or individuals who have clinically isolated syndrome. Alternatively, because vitamin D may be protective for type 1 diabetes [11], respiratory infections [12], and other diseases, larger, community based trials to evaluate multiple outcomes, including MS, could also be considered. Another issue in designing a vitamin D primary prevention trial for MS is what age group to target. The results of some epidemiological studies suggest that vitamin D may be important for MS prevention in early life,[5] perhaps even *in utero*,[4] but the strongest evidence to date suggests that vitamin D levels during adolescence and adulthood also affect MS risk.[9, 10] This is an important observation, because while a trial starting in early childhood would be theoretically desirable, the large sample size and long duration needed to assess an effect of vitamin D on MS incidence makes it impractical. In terms of the type and dose of vitamin D, cholecalciferol (vitamin D₃—one precursor to 25(OH)D) is probably the optimal choice, as ergocalciferol (vitamin D₂) is not as potent.[13] The dose of cholecalciferol to use should be determined from the available evidence. The only prospective study on levels of serum

25(OH)D and risk of MS found the strongest inverse association in healthy non-Hispanic white individuals with levels of 25(OH)D ≥ 100 nmol/L (range 100–153 nmol/L).[10]--a level that can be reached in most individuals with 2,000 to 4,000 IU/day of cholecalciferol. [14] While higher doses could be considered (cholecalciferol as high as 10,000 IU/day in healthy individuals have been recommended as a safe Upper Intake Level (UL) [14],--increasing serum 25(OH)D to mean levels around 220 nmol/L,[14]) there is no empirical evidence of long term beneficial effects of high-dose vitamin D on MS risk, and thus no rationale for use in a prevention trial.

Vitamin D as a treatment for MS

Observational studies

Seasonal variations in MS relapses have been observed in some, [15–17] but not all,[18] studies, and studies of MRI parameters including gadolinium enhancing lesions[19, 20] and new T2 lesions [21] have also suggested subclinical disease activity may fluctuate by season. Whether seasonal fluctuations in vitamin D specifically influence MS disease activity is not known, but correlations between 25(OH)D and relapses and MRI activity have been found in some ecological and clinical studies. In ecologic studies, mean monthly 25(OH)D levels were inversely correlated with MS relapses in an Australian population, [22] and, in a German study, with MRI activity in MS patients. [19, 23] The main limitation of both these studies, however, is that 25(OH)D was not measured in the MS patients included in the study. The relation between serum 25(OH)D and clinical disease activity has been examined in several clinical investigations. In a study in Finland, MS patients had lower levels of 25(OH)D during relapses than during remissions,[24] but the lower 25(OH)D may have been due to behavioral changes (e.g. remaining indoors, sun avoidance) brought about by the relapse.[25] In an Australian longitudinal study,[26] 145 relapsing-remitting MS patients were followed for an average of 2.3 years and 25(OH)D levels were measured every 6 months and relapses were recorded; every 10 nmol/L increase in serum 25(OH)D level was associated with a 9% reduced risk of relapse. Further, in a model using monthly predicted 25(OH)D, circulating levels around 100 nmol/L were associated with a greater than 80% reduction in the hazard of relapse. While the longitudinal design and repeated measures of 25(OH)D may minimize reverse causation, this explanation cannot be ruled out entirely, as individuals with more active MS may stay indoors, have lower 25(OH)D and, independently, more relapses due to their disease course. The strongest evidence to support vitamin D as an effective MS therapy would come from double-blind, randomized, controlled clinical treatment trials where it could be observed whether manipulation of 25(OH)D levels, through dietary supplementation with vitamin D, affects measures such as relapse rates, EDSS, or MRI parameters.

Clinical treatment trials of vitamin D and MS

To date, there have been no controlled trials designed to assess whether vitamin D supplementation could benefit individuals with MS. Several investigators, however, have conducted small studies, primarily to determine the safety or tolerability of increasing vitamin D doses. None of these studies provide adequate evidence of clinical efficacy, however, because of the small sample sizes and/or lack of adequate control groups. Overall, there are seven trials in which a small number of individuals with MS have been given some form of vitamin D and observed for adverse events and changes in clinical, subclinical, and/or immunological activity.[27–35] (Table 1) In one study,[29] patients were given an escalating dose of calcitriol, the biologically active form of vitamin D, and while a reduction in relapse rates was observed, four of 15 patients (25%) developed hypercalcemia (the two symptomatic cases were attributed to consistent dietary indiscretion). The risk of hypercalcemia with administration of calcitriol makes it less desirable as a treatment drug.

Among the cholecalciferol trials, three were randomized controlled trials [28, 31, 32, 35], while the remaining were uncontrolled treatment trials.[27, 30, 33, 34]

The first experimental study to give MS patients vitamin D,[27] did so in the form of cod liver oil providing approximately 5,000 IU/d over 24 months with no adverse events reported, and the number of relapses observed was lower than expected. The next study was a double-blind randomized, controlled trial[28] in which 17 patients were given a known tolerable and safe dose of 1,000 IU of cholecalciferol per day (22 given placebo) for 6 months, and no significant changes in immunological markers measured were observed (Table 1), though there was a suggestion of a decrease in IL-2 mRNA expression in the treated group. There are several possible explanations of these results including that vitamin D truly has no effect, the 6 month duration was too short to see an effect, or that 1,000 IU/d is too small a dose to have a measurable effect on immunologic activity—over the course of treatment, 25(OH)D levels rose to a mean of only 70 nmol/L. Another double-blind randomized controlled trial has been conducted among 62 Iranian MS patients, 28 of whom were randomized to receive 300,000 IU cholecalciferol/month for 6 months.[35] 25(OH)D levels increased to an average of nearly 150 nmol/L. The authors did not comment on whether any adverse event occurred. No significant differences were observed on clinical parameters, but T cell proliferation was decreased and levels of IL-10 and TGF- β increased after 6 months in the treated vs. untreated groups.

Three trials have been designed to test the safety and tolerability of high-dose (i.e. >10,000 IU/day) cholecalciferol.[30, 31, 33] Two of these studies were conducted in Canada (Table 1), and both employed a dose-escalating approach, gradually increasing the amount of supplemental cholecalciferol from 0 IU/d to a high of 40,000 IU/d for 6 weeks (Table 2). The first was a phase I, uncontrolled trial with 12 MS patients.[30] Average 25(OH)D levels peaked at 386 nmol/L, a value well above the physiological range, and there were no changes in serum or urinary calcium levels, or other adverse events, observed over the 28 week dose escalation. This study was followed by a phase I/II open-label, randomized controlled trial (RCT), with a similar dose-escalation schedule, which included 49 MS patients (25 randomized to the treatment arm) (Table 2). [31] The average 25(OH)D level peaked at 413 nmol/L, and even though the urinary calcium:creatinine ratios significantly rose, no cases of hypercalciuria occurred, and serum calcium levels did not significantly change over the course of the 52 week study; no other adverse events were reported. Because neither trial was blinded nor powered to evaluate MS related outcomes specifically, the reported decline in the mean number of gadolinium enhancing lesions[30] and relapse rates [31] should be interpreted cautiously. (Table 1) The same RCT also evaluated changes in immunological profiles and found a statistically significant decrease in the T-cell proliferative response in the treated group as compared to untreated.[32] In contrast, no significant differences were observed in levels of various cytokines (Table 1). In the third study, conducted in Denmark, 15 MS patients received 20,000 IU/ day of cholecalciferol over 12 weeks; there was no control group. [33] The median 25(OH)D levels increased to 380 nmol/L, but there were no reports of hypercalcemia, hypercalciuria, or other adverse events. The number of regulatory T cells remained stable, and there was only a non-significant improvement in regulatory T cells suppressive function. However, a shift toward a more anti-inflammatory profile in CD4+ T cells was suggested. (Table 1) No significant effects were detected on B cell differentiation, isotype switching or plasma levels of B cells activating factor.[34]

Building on these studies, a few new RCT are now ongoing. The largest is the Supplementation of VigantOL[®] oil versus placebo as Add-on in patients with relapsing-remitting multiple sclerosis receiving Rebif[®] treatment (SOLAR) trial, is a phase II, multicenter, double-blind, randomized controlled trial conducted in Europe and designed to

continue to monitor the safety of high-dose vitamin D₃ in patients with RRMS as well as evaluate cholecalciferol as an add-on treatment to interferon beta-1a.[36] Eligible participants will be 18–50 years old with an EDSS $\leq$ 4.0 and MS duration less than 5 years. Most participants in earlier trials were on some form of disease modifying therapy, and to the extent that the efficacy of these drugs has been established, evaluating vitamin D as an add-on therapy is the most ethical approach. In this trial, 348 MS patients with serum 25(OH)D <150 nmol/L will be randomized to receive either placebo or an escalating dose of cholecalciferol of 7,000 IU/day weeks 1–4 and 14,000 IU/day weeks 5–96, which is projected to increase the average serum 25(OH)D to 395 nmol/L. [36] Primary endpoints of the trial include the proportion of relapse free patients at the end of the study and the mean number of combined unique active lesions at week 48. A similar add-on RCT being conducted in France will evaluate 100,000 IU of cholecalciferol given twice per month (equivalent to ~ 6500 IU/d); 250 MS patients on interferon beta-1a will be randomized to treatment or placebo and followed for 96 weeks with reduction in relapse rates the primary outcome. (www.clinicaltrials.gov; NCT01198132). (Table 3) While this dose should bring the 25(OH)D levels close to the optimal range in most patients, the fluctuations caused by the intermittent administration may have unexpected effects. Two additional, smaller trials of cholecalciferol as add-on treatment in Israel and Finland have been registered with clinicaltrials.gov and details are provided in table 3.

Collectively, the three high-dose safety/tolerability trials increased 25(OH)D levels, on average, to around 400 nmol/L, and the SOLAR trial set the cholecalciferol dose such that average 25(OH)D will also reach this level. Even though these levels, in the short-term, appear to be safe, the rationale behind using such high-doses of cholecalciferol in a treatment trial of MS is perplexing. The longitudinal epidemiologic studies of vitamin D and MS risk [10] and relapse [26] suggest that 25(OH)D may be beneficial for MS at levels as low as 100 nmol/L, which can be reached in most people with 4,000 IU/day.[14] While the high-dose trial investigators argue that providing pharmacologic doses of cholecalciferol will increase 25(OH)D substrate available to immunological cells and increase paracrine effects of vitamin D[30], 25(OH)D levels greater than 200 nmol/L are rarely observed under physiological conditions and there is currently no evidence indicating that doses this high will have beneficial effects on MS patients, and none of the high-dose safety/tolerability studies were properly powered or blinded to assess these outcomes. While the SOLAR trial has been designed to address these issues,[36] at a minimum it would have been desirable to also include a low-dose treatment arm, such as 4,000 IU/day. A high-dose versus placebo trial runs the risk of having null or adverse effects on MS outcomes, which may, in turn, make future trials of lower-dose vitamin D more difficult to conduct.

Conclusions

In summary, the current body of evidence suggests that vitamin D may be important in MS prevention and may provide therapeutic benefit. Where additional observational studies are needed to further understand the nature of the association (dose-response curves, effects of seasonal variation), properly designed and conducted clinical trials are the next step to answering the questions posed earlier: does vitamin D prevent MS and is vitamin D an effecting treatment for MS?

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Table 1

Characteristics and main findings of clinical vitamin D treatment-MS trials

Author, year	Design	n	Duration	Intervention	Main Results	Dose tolerability/safety results
Goldberg, 1986	uncontrolled trial	10	up to 24 months	Vitamin D: 5,000 IU/day (fish oil) Calcium: 16 mg/d/kg body weight Magnesium: 10 mg/d/kg body weight	9 relapses observed vs. 22 expected (p<0.01)	No adverse events reported
Mahon, 2003	double blind randomized, controlled trial	39	6 months	Vitamin D: cholecalciferol 1,000 IU/day Calcium: 800 mg/day	↑ TGF-β-1 serum levels; ↓ IL-2 mRNA (p=0.07) No change in mRNA: TNF-α, IFN-γ, IL-13;	N/A
Wingerchuk, 2005	uncontrolled trial	15	48 weeks	Vitamin D: Calcitriol 0.5 ug/d increased in 0.5 ug/d increments every 2 weeks to target dose of 2.5 ug/d	observed relapse rate lower than baseline; 33% active lesions at baseline vs. 29% end of trial; 27% increased EDSS 1–2 points	At target dose, 2 cases of asymptomatic and 2 cases symptomatic hypercalcemia (symptomatic cases perhaps due to dietary indiscretion)
Kimball, 2007	uncontrolled trial	12	28 weeks	Vitamin D: cholecalciferol 28,000 IU/week incrementally increased to 280,000 IU/week by end of study Calcium: 1,200 mg/day	mean # Gd+ lesions declined (1.75 baseline vs. 0.83, p=0.03); no difference in relapse rates	No hypercalcemia reported and serum calcium levels remained stable over the course of treatment.
Burton, 2010 Kimball, 2011	unblinded randomized, controlled trial	49	52 weeks	Vitamin D: cholecalciferol increased from 4,000 IU/day to 40,000 IU/day over 28 weeks, followed by reduction to 10,000 IU/day for 12 weeks and to 4,000 IU/day for 6 weeks Calcium: 1,200 mg/day	In treated vs. non-treated, non-significant reduction in annualized relapse rate (0.26 vs. 0.45) and proportion of patients experiencing a relapse (0.16 vs. 0.37); T-cell proliferative responses decreased in the treated group (p=0.002), esp. among those with 25(OH)D >100nmol/L Decreased PBMC proliferative responses to MBP and exon-2 seen in treated vs. untreated at 52 weeks. No differences in levels of various cytokines including IL-4, IL-10, IFN-γ/TNF-α	Serum calcium levels remained normal and stable over course of vitamin D treatment despite 25(OH)D levels reaching a high mean of 413 nmol/L; no adverse events reported
Smolders, 2010 Knippenberg, 2011	uncontrolled trial	15	12 weeks	Vitamin D: cholecalciferol 20,000 IU/day	baseline vs. week 12: no difference in # of circulating total T cells or regulatory T cells (total, memory, or naïve); ↑ IL-10 ⁺ CD4 ⁺ T cells; ↓ ratio IFN-γ/IL-4 ⁺ CD4 ⁺ T cell ratio. No changes in total circulating B cells or B cell subsets. Non statistically significant decrease in B cell Activating factor	No hypercalcemia reported and serum calcium levels remained stable over the course of treatment.
Mosayebi, 2011	double blind randomized, controlled trial	62	6 months	Vitamin D: cholecalciferol 300,000 IU/month	baseline vs. 6 months: no difference in EDSS or number of Gd-enhancing lesions; in treated vs. untreated.	not reported

Author, year	Design	n	Duration	Intervention	Main Results	Dose tolerability/safety results
					decrease in T cell proliferation in and significant increase in IL-10 and TGF- β levels. No difference in IFN- γ levels.	

Table 2

Dose-escalation scheme for the safety/tolerability trials of cholecalciferol and MS

	Cholecalciferol (IU/d)	
	Kimball, 2007	Burton, 2010
Study Weeks		
1–2	0	0
3–4	4,000	4,000
5–10	8,000	10,000
11–16	16,000	16,000
17–22	32,000	32,000
23–28	40,000	40,000
29–40	na	10,000
41–48	na	4,000
49–42	na	0

Table 3

Currently ongoing vitamin D treatment trials among MS patients

Randomized Clinical Trials				
	SOLAR	The effects of IFN beta combined with vitamin D on relapsing-remitting multiple sclerosis patients	CHOLINE	Cholecalciferol as an add-on treatment to subcutaneously administered IFN beta-1b for treatment of MS
Locations	Europe (Belgium, Denmark, Estonia, Finland, Germany, Hungary, Latvia, Lithuania, Norway, Switzerland, The Netherlands, Italy)	Israel	France	Finland
Study dates	2/2011–2/2012	10/2010–10/2011	1/2010–12/2013	3/2008–6/2011
Target enrollment	348	100	250	70
Age at recruitment	18–50	18–65	18–65	18–55
Treatment Arms	Active: IFN beta-1a 44 ug sc 3x/wk + 7,000 IU/d cholecalciferol 4 weeks escalating to 14,000 IU/d 92 weeks non-active: IFN beta-1a 44 ug sc 3x/wk +placebo	Active: 800 IU/d cholecalciferol + 75,000 IU cholecalciferol every 3 weeks non-active: 800 IU/d cholecalciferol +placebo solution every 3 weeks	Active: IFN beta-1a 44 ug sc 3x/wk + 100,000 IU cholecalciferol 2x/mo non-active: IFN beta-1a 44 ug sc 3x/wk +placebo	Active: 20,000 IU/week cholecalciferol non-active: once weekly placebo
Endpoints	Primary: mean number of combined unique active lesions on MRI at week 48; proportion of relapse free patients at 96 weeks; Secondary: proportion of relapse free patients at 46 weeks; time to first relapse; relapse rate	Primary: occurrence and severity of IFN beta related flu-like symptoms and injection site reactions. Secondary: EDSS progression, relapse rate, immunological changes	Primary: reduction in relapse rate Secondary: time to first relapse, mean number of relapses per subject, per year; new lesions on MRI	Primary: proportion of patients with P-PTH <20ng/l and 25(OH)D > 85nmol/L at 6 and 12 months; Secondary: number of Gd+ lesions or new lesions at 12 months vs.baseline
Duration	96 weeks	52 weeks	96 weeks	52 weeks
Trial number	NCT 01285401	NCT01005095	NCT01198132	NCT01339676

* **SOLAR:** Supplementation of Vigantol® oil versus placebo as add-on in patients with relapsing-remitting multiple sclerosis receiveing Rebir® treatment

CHOLINE: A multicentre, randomized, double-blind, placebo-controlled Study of the Efficacy of Supplementary Treatment with Cholecalciferol in Patients with Relapsing-Remitting Multiple Sclerosis Treated with Subcutaneous Interferon Beta-1a 44 ug 3 times weekly

[†] target enrollment