

A Systematic Review of Randomized, Double-Blind, Placebo-Controlled Trials Examining the Clinical Efficacy of Vitamin D in Multiple Sclerosis

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Key Words

Multiple sclerosis • Treatment • Systematic review • Vitamin D

Abstract

Background: An association between multiple sclerosis (MS) prevalence as well as MS mortality and vitamin D nutrition has led to the hypothesis that high levels of vitamin D could be beneficial for MS. The purpose of this systematic review is to establish whether there is evidence for or against vitamin D in the treatment of MS. **Methods:** Systematic literature searches were performed to locate randomized, placebo-controlled, double-blind trials measuring the clinical effect of vitamin D on MS in human participants. Data were extracted in a standardized manner, and methodological quality was assessed by the Jadad score. **Results:** Five trials were located that met the selection criteria. Of the 5 trials, 4 showed no effect of vitamin D on any outcome, and 1 showed a significant effect, namely by a reduction in the number of T1 enhancing lesions on brain magnetic resonance imaging. Three studies commented on adverse effects of vitamin D, with gastrointestinal adverse effects being the most frequently reported. The literature is limited by small study sizes (ranging from 23 to 68 patients), heterogeneity of dosing, form of vitamin D tested (vitamin D3 in 4 trials and vitamin

D2 in 1) and clinical outcome measures. Therefore, a meta-analysis was not performed. **Conclusions:** The evidence for vitamin D as a treatment for MS is inconclusive. Larger studies are warranted to assess the effect of vitamin D on clinical outcomes in patients with MS. We further encourage researchers to also test the effect of vitamin D on the health-related quality of life experienced by patients and their families.

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Introduction

Multiple sclerosis (MS) is one of the most common chronic neurological disorders among young adults, especially in high-latitude regions, and the most common cause of non-trauma-related disability in this age group [1–4]. The broad spectrum of symptoms of MS impact considerably upon the health-related quality of life (HRQoL) experienced by patients and their families, to a greater extent than several other chronic diseases [5–14]. It is therefore imperative to focus research efforts on the search for the etiology of this disease. The pathogenesis of MS is complex and likely involves multiple genes and their interactions with environmental factors. Although

an increasing body of evidence suggests that this disease may be mediated by an autoimmune reaction among susceptible people to a widespread pathogen [15, 16] that is ubiquitous in the developed world, there are data which suggest that other nongenetic (environmental) factors, especially vitamin D deficiency, may play a role in MS [17].

Vitamin D is a steroid hormone with pleiotropic effects including calcium homeostasis, immune system modulation and lung tissue remodeling [18, 19]. Humans get vitamin D from exposure to sunlight, from their diet and from diet supplements [18, 19]. Vitamin D is found in two forms, i.e. vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [18, 19]. Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, while vitamin D3 is generated through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin [18, 19]. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D, which is used to determine a patient's vitamin status [18–20].

Epidemiologic evidence supports an association between vitamin D and susceptibility to and severity of autoimmune disorders [18]. In the specific case of MS, correlations of lower MS prevalence, activity and mortality with high levels of vitamin D nutrition have led to the hypothesis that high levels of vitamin D could be beneficial for MS [21, 22]. Most convincingly, the risk of relapse decreased by up to 12% for every 10-nmol/l increase in serum 25-hydroxyvitamin D in a prospective population-based cohort study [23]. However, there are unresolved clinical questions related to vitamin D and MS. Does aggressive vitamin D supplementation in patients with MS change the disease outcome? If so, what would be the optimal dose?

In a 2010 Cochrane review, Jagannath et al. [24] found that the efficacy of vitamin D supplementation in the management of MS was doubtful. Specifically, the evidence for the effectiveness of vitamin D supplementation in MS was only based on an open-label, randomized, prospective, controlled trial with potential high risk of bias [25]. The trial was not powered or blinded to properly address clinical outcomes [25]. Since that time, a number of double-blind, placebo-controlled trials have been conducted. In view of the importance of the subject matter and the absence of a recent comprehensive review of the role of vitamin D in the treatment of MS, we undertook a systematic review with the aim of summarizing the existing evidence for or against the hypothesis that vitamin D may be an efficacious therapy for MS. In this systematic review, we focused on randomized, controlled, dou-

ble-blinded trials, since this design is the best choice to assess therapeutic efficacy while reducing the risks of study bias and confounding factors that influence interpretation of results [26].

Material and Methods

Search Strategy and Information Sources

Searches were performed in August 2012 for randomized, controlled, double-blinded trials of vitamin D supplementation in the management of MS, using PubMed/Medline and the Cochrane Central Register of Controlled Trials. The keywords were different combinations of 'vitamin D treatment' or 'vitamin D therapy' or 'treatment with vitamin D' or 'vitamin D supplementation' with 'multiple sclerosis' or 'MS'. In addition, our own extensive files were searched, including all reviews of vitamin D supplementation in the management of MS. Original articles were obtained, and all reference lists were scanned for further relevant articles. No time limit was applied in our search strategy.

Inclusion and Exclusion Criteria

All articles were included which reported randomized, double-blind, placebo-controlled trials in which subjects with MS were allocated at random to receive either vitamin D or placebo. We only included articles which focused on the treatment effect on clinical [disease progression as determined by the Expanded Disability Status Scale (EDSS) or Multiple Sclerosis Functional Composite, relapse rate, proportion of relapse-free patients and cognitive functioning], HRQoL or neuroimaging parameters.

The search was limited to clinical trials in humans. We also excluded open-label studies and those which were based on self-reported dietary vitamin D intake or whose end points were exclusively percentage change in bone mineral density or laboratory parameters, such as cytokine profile or peripheral blood mononuclear cell proliferative responses, among others. No language restrictions were applied.

Data Extraction

Two investigators (B.P.-M., J.B.-L.) independently reviewed the title and abstract of all citations identified by the initial search strategy and excluded citations that clearly did not meet the inclusion criteria. We retrieved the full text of the remaining studies and both investigators reviewed each study to assess whether it met the inclusion criteria. All differences were settled by discussion. For each study, trial design, randomization, blinding and handling of dropouts were recorded, in addition to inclusion and exclusion criteria, details of treatment and control procedures, main outcome measure and study result. Outcomes included in the systematic review were limited to the clinical efficacy or toxicity of vitamin D in patients with MS. We defined efficacy as the therapeutic effect of vitamin D and toxicity as any unintended adverse consequence of the drug's use. The initial protocol for this review anticipated that results from several studies could be combined in a meta-analysis, but this was precluded by the heterogeneity of the studies.

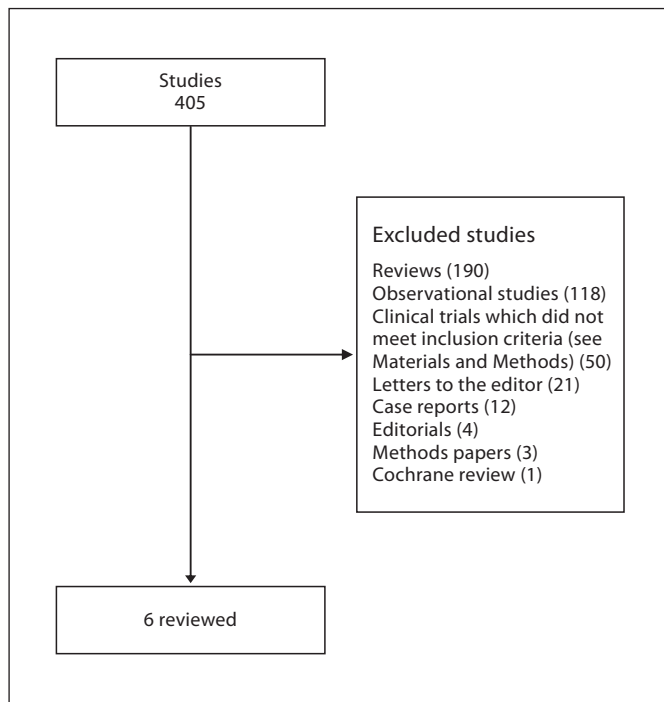


Fig. 1. Identification of studies in the systematic review.

Quality Assessment

The quality of studies was assessed by the system of Jadad et al. [27]. Points were awarded as follows: study described as randomized, 1 point; additional point for appropriate method, 1 point; inappropriate randomization method, deduct 1 point; subject blinded to intervention, 1 point; evaluator blinded to therapy, 1 point; inappropriate method of blinding, deduct 1 point, and description of withdrawals and dropouts, 1 point. The maximum points available were 5. Observer blinding was only scored if specified in the text.

Results

Description of Studies

The electronic search identified a total of 405 publications, of which 6 articles met our inclusion criteria [28–33] (fig. 1). However, the study by Aivo et al. [33] was a substudy of another main trial [31]. Of the 5 trials included, 4 gained the maximum score [29–32], while 1 study scored 2 points (the authors did not mention randomization and blinding procedures, nor the reasons for patient withdrawals and dropouts for each treatment group) [28]. The randomization procedure was reported in sufficient detail to be sure that it was appropriate in 4 studies [29–32]. In 1 study, the randomization procedure was not re-

ported [28]. Likewise, the double-blinding method was appropriately explained in 4 studies [29–32], while in 1 study it was not reported [28]. In all the studies [29–32], except 1 [28], the reasons for patient withdrawals and dropouts were described.

The study size ranged from 23 to 68 patients. All the randomized controlled trials had parallel designs. Only 2 studies reported a power calculation [31, 32]. Two studies did not report a funding source [28, 32]; 1 received an unrestricted grant from a manufacturer of vitamin D [31], and the remaining trials received only the drug and placebo from a manufacturer [29, 30].

The studies were marked by heterogeneity of vitamin D dosing, vitamin D supplementation forms (vitamin D2 or vitamin D3) and outcomes measured (table 1).

Outcomes

Overall, the results of 4 studies [28–30, 32] showed no effect (i.e. supplementation with vitamin D did not result in beneficial effects on the measured MS-related outcomes). One study showed a positive association [31, 33].

In the study of Mosayebi et al. [28], 62 patients were randomized to once-monthly intramuscular vitamin D3 injections (300,000 IU) or placebo intramuscular injections, and EDSS score, mean number of brain gadolinium-enhancing lesions, relapses and T cell function were studied at baseline and at 6 months. No significant differences were found in clinical or magnetic resonance imaging (MRI) parameters in this trial, but lymphocyte proliferation was decreased in the treated patients [28].

Stein et al. [29] tested for a benefit of high-dose (6,000 IU/day) over low-dose (1,000 IU/day) vitamin D2 in patients with clinically active relapsing-remitting MS. There was no between-group difference in the primary MRI-based outcome measures (cumulative number of new gadolinium-enhancing lesions and change in the total volume of T2 lesions). However, there was a higher exit EDSS score ($p = 0.05$) and a higher proportion of patients exhibiting relapse with high-dose vitamin D2 ($p = 0.04$). However, the trial was limited by a small and selected patient sample (23 MS patients) [29]. Nineteen of the patients were receiving either glatiramer acetate or interferon therapy, and 3 patients withdrew, making the ultimate number of comparable patients in each treatment arm very small [29].

Kampman et al. [30] reported outcomes from 62 MS patients in a 96-week trial, which was originally designed to assess the effect of high-dose vitamin D3 supplementation on bone mineral density in persons with MS [34]. A weekly dose of 20,000 IU of vitamin D3 did not affect the

Table 1. Randomized, double-blind, placebo-controlled trials of vitamin D for treatment of MS: study characteristics and results

Reference (year)	Jadad score	Inclusion criteria	Exclusion criteria	Treatment group/controls, n	Intervention	Clinical and/or neuroimaging outcome measures	Clinical and/or neuroimaging results
Mosayebi et al. [28] (2011)	2	patients with MS and at least 1 relapse in the previous 12 months; more than 3 lesions on spinal or brain MRI or both; baseline EDSS score from 0 to 3.5; age from 18 to 60 years	clinically isolated syndrome, progressive MS, MS patients with clinical relapses occurring during the study, drug abuse, use of digitalis or vitamin D supplementation; any condition predisposing to hypercalcemia; nephrolithiasis or renal insufficiency; pregnancy or unwillingness to use contraception; unwillingness to restrict dietary calcium	28/34	300,000 IU of vitamin D3 every month for 6 months	EDSS and brain MRI	no significant difference between the treatment and control groups for the EDSS scores and number of gadolinium-enhancing lesions during the 6-month treatment period
Stein et al. [29] (2011)	5	patients with relapsing-remitting MS; aged >18 years; relapse within the preceding 24 months despite immunomodulatory therapy or declined or could not tolerate such therapy	progressive MS; pregnancy; clinical relapse or systemic glucocorticoid therapy within the prior 30 days; EDSS score >5; current MS treatment other than glatiramer acetate or interferon; hypercalcemia; creatinine >0.2 mM; estimated glomerular filtration rate <60 ml/min; uric acid >sex-matched laboratory reference range	11/12	during 6 months, one group (high-dose D2) received 1,000 IU of vitamin D2 daily plus a high-dose vitamin D2 supplement; the other group (low-dose D2) received 1,000 IU of vitamin D2 daily plus a placebo supplement	EDSS, number of clinical relapses and MRI	no significant treatment differences in the primary MRI end points; follow-up EDSS score after adjustment for baseline EDSS score was higher following high-dose D2 than following low-dose D2 ($p < 0.05$); 4 relapses with high-dose D2 vs. none with low-dose D2 ($p < 0.04$)
Kampman et al. [30] (2012)	5	patients with clinically definite MS according to the McDonald criteria; aged 18–50 years; EDSS score ≤ 4.5	inability to walk ≥ 500 m; history of conditions or diseases affecting bone; pregnancy or lactating during the past 6 months; use of bone-active medications other than intravenous methylprednisolone for treatment of relapses; a history of nephrolithiasis during the previous 5 years; menopause; unwillingness to use appropriate contraception	35/33	20,000 IU of vitamin D3 once a week for 2 years	annualized relapse rate, EDSS, MSFC components, grip strength and fatigue	no significant difference between groups in terms of annualized relapse rate, EDSS score, MSFC components, grip strength or fatigue
Soilu-Hänninen et al. [31] (2012)	5	patients with relapsing-remitting MS (McDonald criteria); aged 18–55 years; interferon- β 1b use for at least 1 month; no neutralizing antibodies to interferon- β ; EDSS score ≤ 5.0 ; using appropriate contraceptive methods (women of childbearing potential)	serum calcium >2.6 mmol/l; serum 25-hydroxyvitamin D >85 nmol/l; primary hyperparathyroidism; pregnancy or unwillingness to use contraception; alcohol or drug abuse; use of immunomodulatory therapy other than interferon- β 1b; known allergy to cholecalciferol or peanuts; therapy with digitalis, calcitonin, vitamin D3 analogues or vitamin D; any condition predisposing to hypercalcemia; sarcoidosis; nephrolithiasis or renal insufficiency; significant hypertension; dysthyroidism in the year before the study began; a history of kidney stones in the previous 5 years; cardiac insufficiency or significant cardiac dysrhythmia; unstable ischemic heart disease; depression; inability to undergo serial MRI scans	32/30	20,000 IU of vitamin D3 once a week for 1 year	annual relapse rate, EDSS score, timed 25-foot walk test and timed 10-foot tandem walk tests, brain MRI and adverse effects	statistically significant reduction in the number of T1 enhancing lesions and trends in MRI burden of disease and EDSS score; no significant differences in adverse events or in the annual relapse rate
Shaygannejad et al. [32] (2012)	5	patients with relapsing-remitting MS (McDonald criteria); aged 15–60 years; stable neurological functioning for at least 1 month prior to study entry; EDSS score ≤ 6 ; serum 25-hydroxyvitamin D level >40 ng/ml; willingness to continue current medications for the duration of the study	progressive MS; evidence of substantial abnormalities in neurological, psychiatric, cardiac, endocrinological, hematologic, hepatic, renal or metabolic functions; use of digitalis; vitamin D supplementation; any condition predisposing to hypercalcemia; nephrolithiasis; renal insufficiency; pregnancy	25/25	0.25 μ g of calcitriol per day, increased to 0.5 μ g/day after 2 weeks and continued for 1 year	EDSS and relapse rate	average EDSS score and relapse rate at the end of the trial did not differ between groups

MSFC = Multiple Sclerosis Functional Composite.

course of the disease as assessed by measures of disease activity, functional tests and the fatigue severity score [30]. The study was not powered to properly address clinical outcomes [30].

Soilu-Hänninen et al. [31] showed a statistically significant reduction in the number of T1 enhancing lesions and trends in T2 burden of disease on MRI and EDSS score in a controlled trial with 20,000 IU/week vitamin D3 for 1 year in relapsing-remitting patients under interferon- β 1b. However, due to the small sample size (62 MS patients), the trial was not powered to address clinical outcomes [31]. The same researchers recently published a subgroup analysis of this trial with 15 patients in the vitamin D arm and 15 patients in the placebo arm who had either at least one relapse during the year preceding the study or enhancing T1 lesions on the baseline MRI scan [33]. They found a statistically significant reduction in the number of T1 enhancing lesions, a smaller T2 lesion volume growth and fewer new/enlarging T2 brain MRI lesions in the vitamin D3-treated than in the placebo-treated patients [33]. The MRI results were therefore slightly more pronounced in this subgroup than in the overall study population [33].

Finally, Shaygannejad et al. [32] found no significant difference in relapse rate or change in EDSS score between 25 MS patients who took placebo and 25 who received adjunct low-dose oral vitamin D [escalating calcitriol (1,25-dihydroxyvitamin D3) doses up to 0.5 μ g/day] during 12 months.

Adverse Effects/Toxicity

Only 1 of the studies that met our inclusion criteria used toxicity (adverse effects) as a primary end point [31]. Furthermore, the methods for surveillance of unintended effects of treatment were not described in any of the studies except the Norwegian trial [31]. Adverse effects were reported in 3 of the 5 studies [30–32]. These were relatively mild, with gastrointestinal adverse effects being the most frequently reported, and included diarrhea, constipation, dyspepsia, fever, fatigue and headache.

Summary Statistics

Because of the heterogeneity of the variable dosing and the different outcome measures used in the 5 studies, we deemed a meta-analysis inappropriate. Thus, no pooled estimates of the effect or risk of therapy are reported. Similarly, combined estimates of dose response were not considered appropriate in light of the wide variability in outcome measures. This heterogeneity and the nature of the outcomes made a funnel plot to assess publication

bias infeasible. Again, due to the small number of patients included, it seems unlikely that small effect can be ruled out.

Discussion

In this review, we tried to elucidate whether there is evidence for or against the clinical efficacy of vitamin D in the treatment of MS following a systematic approach to the randomized, placebo-controlled, double-blind trials published up to August 2012 in PubMed/Medline and the Cochrane Central Register of Controlled Trials databases. Our conclusions are as follows. Firstly, there are only very few studies (5 in total) on the effect of vitamin D on clinical outcomes in MS. Secondly, the literature is marked by small study sizes and heterogeneity of dosing, form of vitamin D tested (vitamin D3 in 4 trials and vitamin D2 in 1) and clinical outcome measures. Issues related to treatment duration were not emphasized in this review because there are no current standards for optimal recommended treatment duration. Given the relative lack of dose-response studies, it is unclear whether any of the studies used an optimal dose, although most were consistent with expert recommendations [17]. However, these studies highlight both the clinical questions and the potential methodological issues that remain to be addressed by future studies. Thirdly, 4 studies showed no effect of vitamin D on any outcome, although 1 [31, 33] showed significant improvement of brain MRI parameters. The reported adverse effects were relatively mild, with gastrointestinal adverse effects being the most frequently reported. Therefore, the available evidence substantiates neither clinically significant benefit nor harm from vitamin D in the treatment of patients with MS.

Furthermore, because all the studies published were relatively small, it is possible that the negative studies in the literature were underpowered to detect an effect. The studies had sample sizes between 23 and 68 participants. Perhaps more problematic was the failure to calculate sample size in 3 of the studies, and thus, these studies were likely underpowered to detect group differences. An alternative explanation for the negative results in these trials, in addition to the small sample sizes, is that the possible protective effect of vitamin D may be attenuated or not present at all in individuals carrying the HLA-DR15 MS risk allele [35]. In other words, there is the possibility that the putative beneficial effect of vitamin D on MS could be masked by subgroups of nonresponders. Furthermore, none of the trials included patients with

progressive MS. It is possible that vitamin D may have differential efficacy according to the different subgroups of MS. We recommend researchers to further stratify by HLA-DR15 status in future clinical trials and include patients with progressive forms of MS.

The results of our systematic review are limited by the availability of studies in the public domain and, specifically, on PubMed. Because of the heterogeneity of studies and the types of outcomes reported, we were unable to formally assess publication bias, although it does seem likely that many small negative studies remain unpublished.

We felt that the quality and heterogeneity of the studies made combining studies in a meta-analysis for an overall estimate of effect inappropriate. Therefore, to fully evaluate the current state of the evidence of the effect of vitamin D on MS outcomes, we decided that a descriptive synthesis of the literature was most appropriate.

The quality of the studies reviewed was rated using the Jadad scoring criteria for potential sources of bias (higher scores indicates higher quality; table 1). Four studies had Jadad scores of 5. All the studies of highest quality, except 1 [31, 33], did not find vitamin D to be significantly superior to placebo.

Two ongoing, high-quality, randomized, placebo-controlled, double-blind trials are currently being conducted [36, 37]. The first one, the SOLAR study, is a 96-week, 3-arm, multicenter, double-blind, randomized, placebo-controlled, phase II trial designed to evaluate the efficacy of vitamin D3 (14,000 IU daily) as add-on therapy to subcutaneous interferon- β 1a in relapsing-remitting MS (n = 174 in both treatment arms) [36]. The second one, the EVIDIMS study, is a German multicenter, stratified, randomized, controlled and double-blind clinical phase II pilot trial [37]. Eighty patients with the diagnosis of definite MS or clinically isolated syndrome who are on stable

immunomodulatory treatment with interferon- β 1b will be randomized to additionally receive either high-dose (average daily dose 10,200 IU) or low-dose (average daily dose 200 IU) vitamin D3 for a total period of 18 months [37]. It is very probable that both trials will contribute substantially to the evaluation of the efficacy of high-dose vitamin D supplementation in MS patients.

In closing, there remains a lack of definitive evidence regarding the clinical efficacy of vitamin D for the treatment of patients with MS. Additional work is needed to clarify the subpopulations most likely to be benefited by vitamin D therapy, the optimal dosing for these subgroups and the most valid and clinically significant outcome measures in these populations. Specifically, we further encourage researchers to test the effect of vitamin D on the HRQoL experienced by patients and their families [5–14]. In the last few years, clinical trials of new pharmacological and nonpharmacological treatments for MS have begun to incorporate HRQoL measures as primary or secondary outcome measures [5–14].

Ultimately, larger randomized placebo-controlled clinical trials of vitamin D in MS with longer follow-up than 1 year will be necessary. Until such studies are completed, clinicians can only continue to judiciously treat and monitor the patients taking vitamin D under their care.

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Disclosure Statement

The authors report no conflicts of interest.

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