Systematic Review

Effect of Vitamin D Supplements on Relapse Rate and Expanded Disability Status Scale (EDSS) in Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis

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Abstract

Background: Multiple sclerosis (MS) is an inflammatory disease while there are controversies regarding the role of vitamin D supplements in controlling relapse and disability improvement during treatment. **Objective:** The goal of this systematic review and meta-analysis was to evaluate the effect of vitamin D supplements on MS-related relapse and the Expanded Disability Status Scale (EDSS). **Methods:** We searched databases to include randomized clinical trials (RCTs) which were published up to October 2018**.** We included RCTs, being single-blinded or double-blinded or open-label trials in which one of the main outcomes was EDSS and/or relapse after vitamin D supplementation. All statistical analyses were performed using RevMan 5.3. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for relapse between treatment arms. The mean difference was calculated for EDSS comparisons. **Results:** Nine articles were included for analysis. Of these nine studies, five compared vitamin D supplement groups with placebo (group 1 studies), and four compared high- and low-dose vitamin D groups. A total of 561 patients were analyzed. Being treated with vitamin D instead of placebo showed no effect on relapse rate (OR = 0.66, 95% CI = 0.28–1.54) as well as EDSS (mean difference = 0.06, 95%CI [-0.31, 0.42]). The results of studies comparing high- vs. low-dose vitamin D interventions showed no significant effect on relapse rate (OR = 1.08, 95%CI [0.29–4.08] as well as final EDSS (mean difference = 0.17, 95% CI = -0.73, 1.07). **Conclusions:** Our findings show that vitamin D supplements (high or low dose) have no significant effect on relapse rate and disability during treatment in MS patients.

Keywords: *Disability, multiple sclerosis, relapse, systematic review, vitamin D*

Introduction

Multiple sclerosis (MS) is an autoimmune chronic demyelinating disease of the central nervous system thought to have an increasing incidence worldwide.[1] It is the one of the most common cause of disability due to neurological disease in young adults.[2]

Environmental factors along with genetics play an important role in disease incidence.[3] Duration and intensity of sunlight exposure, the latitude of birth, and serum vitamin D level are considered to be correlated with the incidence of MS.[4-6] Vitamin D has a significant effect on cytokine profiles, neurological disease development, and regulates inflammation in immune cells[7] as well as regulation of 900 genes.[8,9] It also regulates Th1 and Th2 cell proliferation.[10]

In a nested case-control study using stored serum samples from the U.S. military, the authors concluded that a 50 nmol/L increase in serum vitamin D level was associated with a 50% decreased risk of developing MS.[11] While the literature shows a decreased level of vitamin D during MS relapse as compared to other times in MS cases,[12-14] the role of vitamin D supplements on MS-related relapses is controversial.[15-18] A systematic review and meta-analysis looking at the results of five randomized clinical trials (RCTs), demonstrated that vitamin D supplementation did not affect controlling MS relapses.[19]

In this meta-analysis, we evaluate the effect of vitamin D supplements on MS-related relapse and Expanded Disability Status Scale (EDSS)

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Methods

The protocol of this systematic review has been published.[20]

Literature search

We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, ProQuest, American College of Physicians Journal Club database, Health Technology Assessment Database (The Cochrane Collaboration), and National Health System (NHS), Economic Evaluation Database (The Cochrane Collaboration) and gray literature including the reference of included studies, conference abstracts which were published up to October 2018.

Inclusion and exclusion criteria

We included RCTs, being single-blinded or double-blinded or open-label trials in which one of the main outcomes was EDSS and/or relapse after vitamin D supplementation. Only articles that had been published in the English language were included. Studies comparing high- and low-dose vitamin D therapies were also considered for analysis.

Cohort studies, case-control studies, and any other types of studies were excluded.

Data extraction

Two independent researchers independently assessed the articles. Data on the number of participants in each group, relapse in each treatment arm of the study, final EDSS, study duration, first author, publication year, and sample size were extracted from the included studies. In the case of disagreement, two researchers solved it by consultation with a third reviewer.

Statistical analysis

All statistical analyses were performed using RevMan 5.3 (The Cochrane Community, London, United Kingdom). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for relapse between treatment arms.

We used the inverse variance with a random-effects model.

The mean difference was calculated for EDSS comparisons.

In one study (Stein *et al*.), the authors reported the median and interquartile range (IQR) for the final EDSS which we transformed to mean and SD.

Inconsistency (I2) was calculated to determine heterogeneity.

Risk of bias assessment

We evaluated the risk of potential biases using Cochrane Collaboration's tool for assessing the risk of bias [Figures 1 and 2].[21]

Funnel plots created in Review Manager 5.1 were used to assess publication bias.

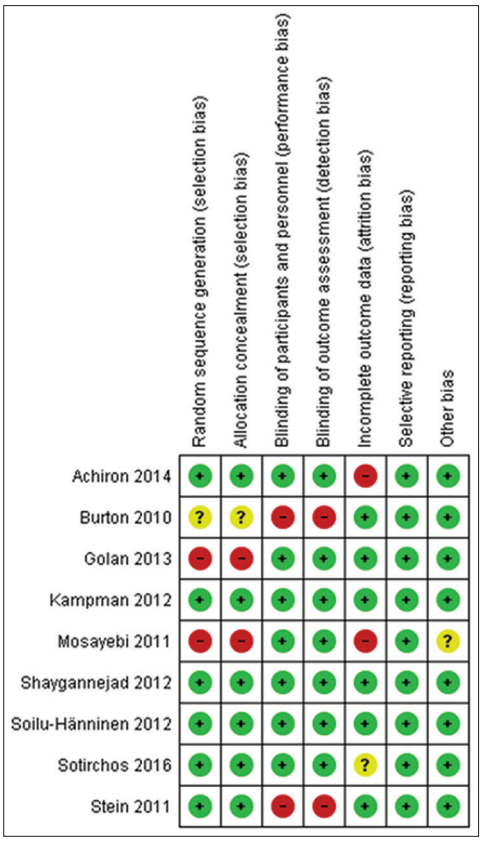

Figure 1: Methodologic quality assessment graph

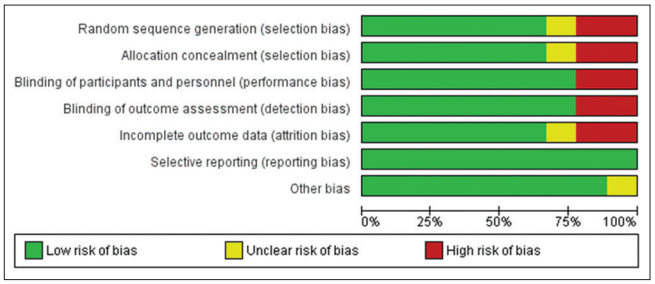

Figure 2: Risk-of-bias assessment for each study included in the meta-analysis

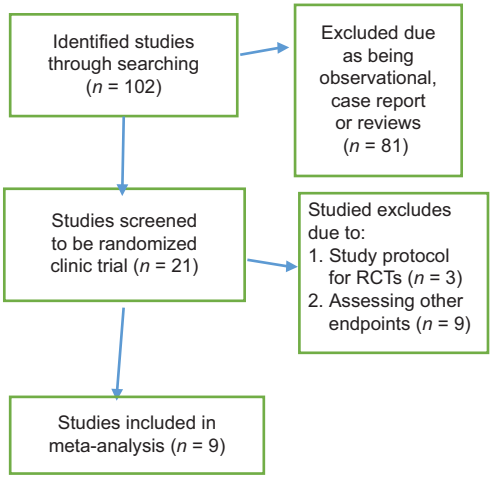

Figure 3: Flow diagram summarizing the selection of eligible studies

A *P* value of less than 0.05 was considered statistically significant.

Results

The literature search found 102 articles that were screened. When discounting observational studies, reviews, case reports, and non-randomized trials, 21 studies remained. Finally, nine articles were included for analysis [Figure 3].

Of these nine studies, five compared vitamin D supplement groups with placebo (group 1 studies), and four compared high- and low-dose vitamin D groups (group 2 studies). Study duration varied among included studies and the included studies were from different countries [Table 1].

One study in group 1 and one in group 2 had no results regarding final EDSS (Achiron *et al*. and Sotirchos[22,23] (the corresponding authors were contacted with no response).

A total of 561 patients were analyzed. Information regarding relapse and final EDSS in group 1 studies are shown in Table 2 and information regarding group 2 studies are shown in Table 3.

Relapse in group 1 studies (vitamin D vs. placebo groups)

Being treated with vitamin D instead of placebo showed no effect on relapse rate during treatment in four studies (one study [Mosayebi *et al*.[24]] had no relapse rate, the corresponding authors were contacted with no response) included for this analysis (OR = 0.66, 95% CI = 0.28–1.54) with no significant heterogeneity ($I2$ = 57%, Chi2 = 7.05, P = 0.07) [Figure 4].

EDSS in group 1 studies (vitamin D vs. placebo groups)

Four studies included in this analysis (one study, Achiron *et al*. had no final EDSS) and the results suggested no

Table 1: Characteristics of included studies

Characteristics	Results
First author and date[22]	Achiron, 2014
Title	Effect of Alfacalcidol on multiple sclerosis-related fatigues: A randomized, double-blind placebo-controlled study
Total number of participants	158
Country	Israel
Intervention	Alfacalcidol (1 mcg/d)
Control	Placebo
Duration	Six consecutive months
First author and date[25]	Shaygannejad, 2012
Title	Effects of Adjunct Low-Dose Vitamin D on Relapsing-Remitting Multiple Sclerosis Progression: Preliminary Findings of a Randomized Placebo-Controlled Trial
Total number of participants	50
Country	Iran
Intervention	0.25 μg adjunct calcitriol per day and increased to 0.5 μg/day after 2 weeks and continued for 12 months
Control	placebo
Duration	1 year
First author and date[18]	Soilu-Hanninen, 2014
Title	A randomized, double-blind, placebo-controlled trial with vitamin D3 as an add on treatment to interferon b-1b in patients with multiple sclerosis
Total number of participants	66
Country	Finland
Intervention	20 mg of cholecalciferol, corresponding to 20 000 IU or 0.5 mg of vitamin D3, once weekly for 1 year
Control	Placebo
Duration	1 year
First author and date[16]	Kampman, 2012
Title	Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomized controlled trial
Total number of participants	68
Country	Norway
Intervention	20,000 IU vitamin D3 (cholecalciferol) once a week
Control	Placebo
Duration	2 years
First author and date[24]	Mosayebi, 2011
Title	Therapeutic Effect of Vitamin D3 in Multiple Sclerosis Patients

Contd...

Table 1: Contd...

Characteristics	Results
Total number of participants	62
Country	Iran
Intervention	300,000 IU/month vitamin D3 IM
Control	Placebo
Duration	6 months
First author and date[23]	Sotirchos, 2015
Title	Safety and immunologic effects of high- vs low-dose cholecalciferol in multiple
Total number of participants	40
Country	USA
Intervention	10,000 IU of cholecalciferol+400 IU cholecalciferol and 1,000 mg calcium.
Control	4,000 IU of cholecalciferol+400 IU cholecalciferol and 1,000 mg calcium
Duration	6 months
First author and date[26]	Golan 2013
Title	Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and immunomodulatory properties
Total number of participants	45
Country	Israel
Intervention	75,000 IU of vitamin D3 solution every 3 weeks in addition to 800 IU of vitamin D3 by daily tablets (total of 4370 IU/d)
Control	One bottle of placebo solution every 3 weeks besides 800 IU of vitamin D3 by daily tablets (total of 800 IU/d)
Duration	1 year
First author and date[27]	Stein, 2011
Title	A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis
Total number of participants	23
Country	Australia
Intervention	1,000 IU vitamin D2 daily plus a high-dose vitamin D2 supplement
Control	(1,000 IU) vitamin D2 daily
Duration	6 months
First author and date[15]	Burton, 2010
Title	A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis
Total number of participants	49
Country	Canada
Intervention	40,000 IU/day over 28 weeks followed by 10,000 IU/day (12 weeks), and further down titrated to 0 IU/day
Control	=<4,000 IU/day of vitamin D
Duration	1 year

Table 2: Number of patients, the number who experienced relapses, and final EDSS in group one studies (vitamin d vs placebo)

First author	Vitamin D group			Placebo group		
	Total number	No of relapses	Final EDSS (mean±SD)	Total number	No of relapses	Final EDSS (mean±SD)
Achiron	80,	8	-	78,	25	-
Shaygannejad	25,	8	1.6±0.7	25,	9	1.94±1.4
Soilu-Hanninen	34	9	1.8±1.2	32	9	1.6±1.3
Kampman	35	6	2.77±0.39	33	4	2.42±0.4
Mosayebi	26	-	2.31±1.3	33	-	2.67±1.25

Table 3: Number of patients, the number who experienced relapses, and final EDSS in group one studies (high vs low dose vitamin D)

First author	High dose group			Low dose group		
	Total number	No of relapses	Final EDSS (mean±SD)	Total number	No of relapses	Final EDSS (mean±sd)
Sotirchos	19	1	-	21	1	-
Golan	24	8	3.3±2.4	21	6	3.6±2.3
Stein	11	4	3±1.48	12	0	2±0.74
Burton	25	4	1.15±1.39	24	9	1.45±1.78

effect of vitamin D supplementation on final EDSS (mean difference = 0.06, 95%CI (-0.31, 0.42).

There was no significant heterogeneity (I2 = 62%, Chi2 = 7.98, *P* = 0.05) [Figure 5].

Relapse in group 2 studies (High- vs. Low-vitamin D groups)

The four studies using high- vs. low-vitamin D interventions showed no significant effect on relapse rate (OR = 1.08, 95%CI (0.29–4.08) with no significant heterogeneity (I2 = 49%, Chi2 = 5.92, *P* = 0.12) [Figure 6].

EDSS in group 2 studies (High- vs. Low-vitamin D groups)

Three out of four studies provided data regarding final EDSS which showed no significant effect (mean difference = 0.17, 95%CI = -0.73, 1.07). The results indicated no significant heterogeneity (I2 = 54%, Chi2 = 4.32, *P* = 0.12) [Figure 7].

Discussion

This meta-analysis showed that neither vitamin D supplements in comparison with placebo nor high- vs. low-dose vitamin D intervention had a significant association with relapse rate during treatment and final EDSS.

In a previous systematic review conducted by James *et al*.,[19] results of five clinical trials were pooled and analyzed. Their results showed that there was no significant association between vitamin D (either low, high, or calcitriol) administration and relapse rate in MS cases.[19] They reported no significant heterogeneity in their subgroup analysis which is as per our findings.

In a recent meta-analysis, Zheng *et al*. assessed the effects of vitamin D supplements on EDSS and annual relapse rate in MS cases.[28] Including six RCTs, they reported no significant effect on EDSS (mean difference = -0.01, 95%C = 0.34, 0.33); however, they found significant effect on annual relapse rate (mean difference = 0.05, 95%CI = 0.01–0.1).[28]

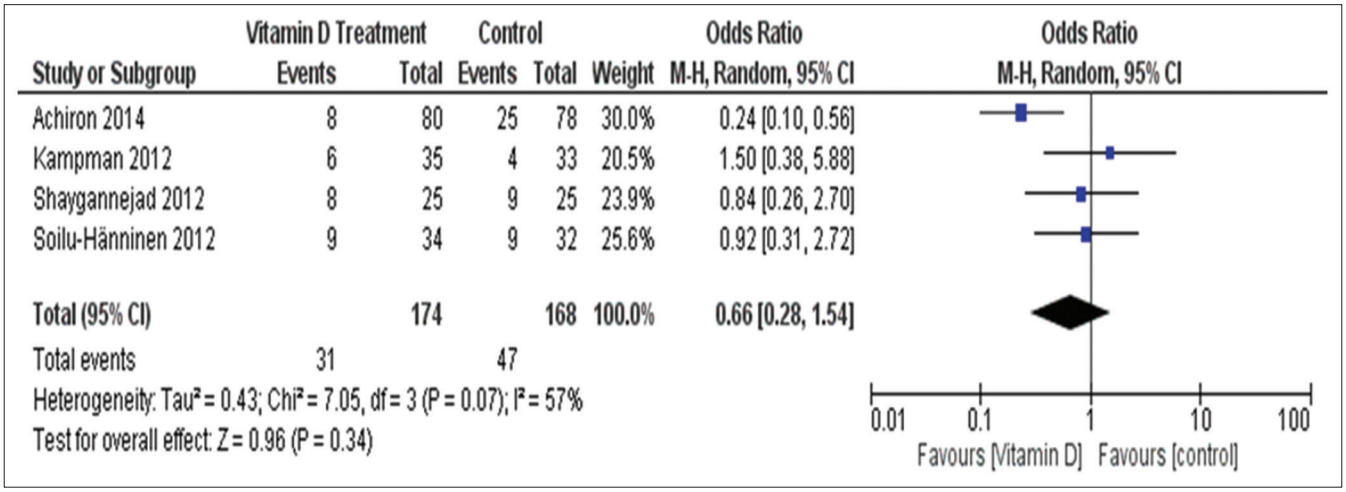

Figure 4: Number of patients who experienced relapses in group 1 studies

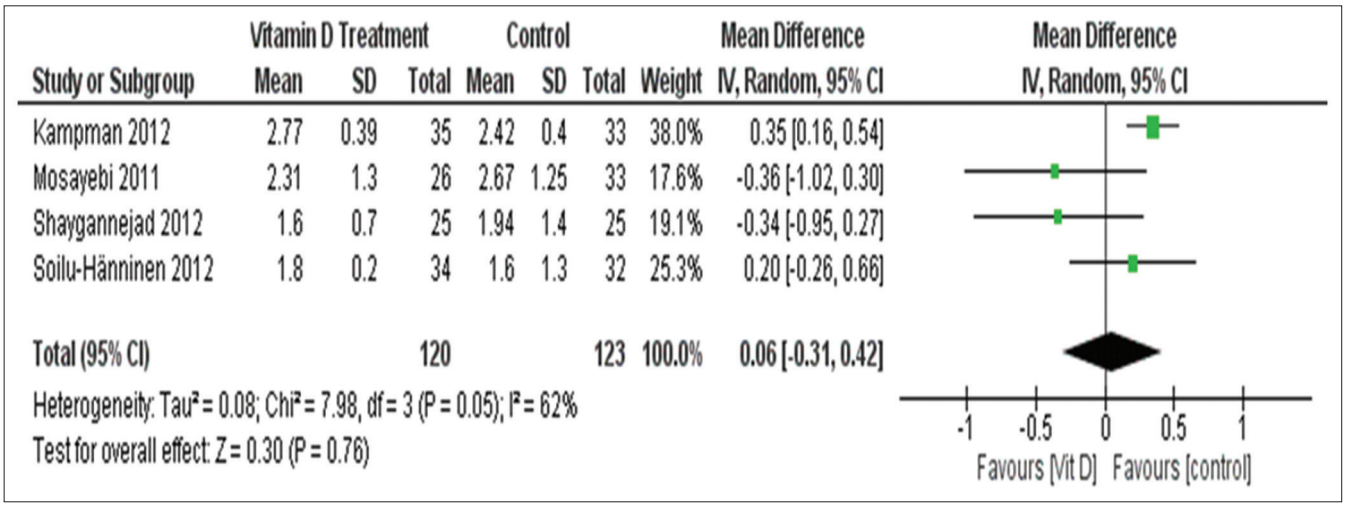

Figure 5: Final EDSS in patients of group 1 studies

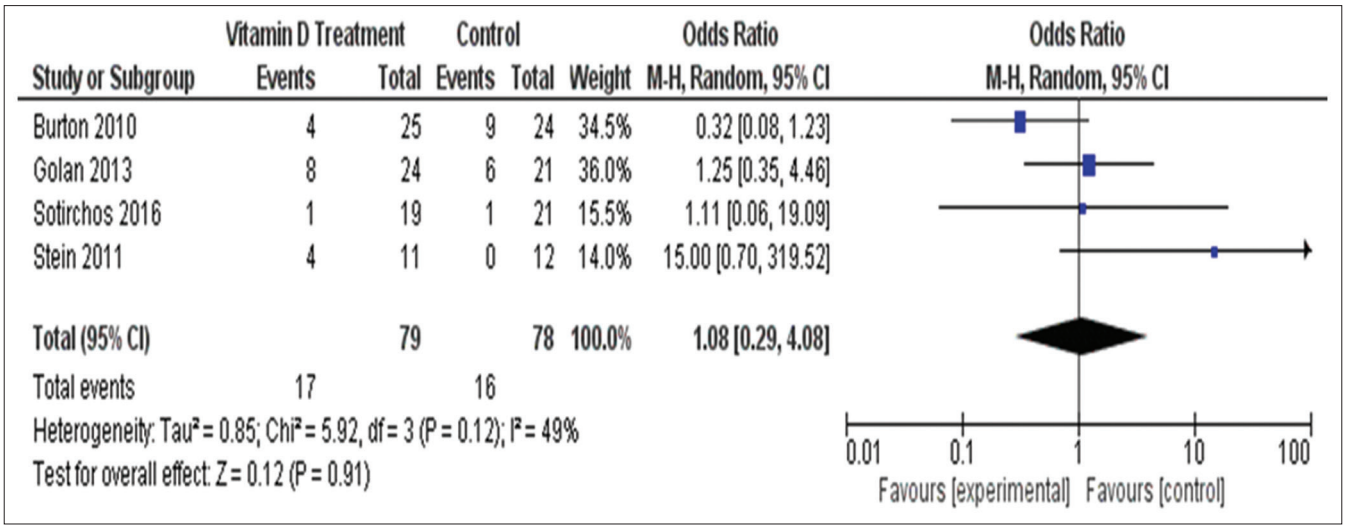

Figure 6: Number of patients who experienced relapses in group 2 studies

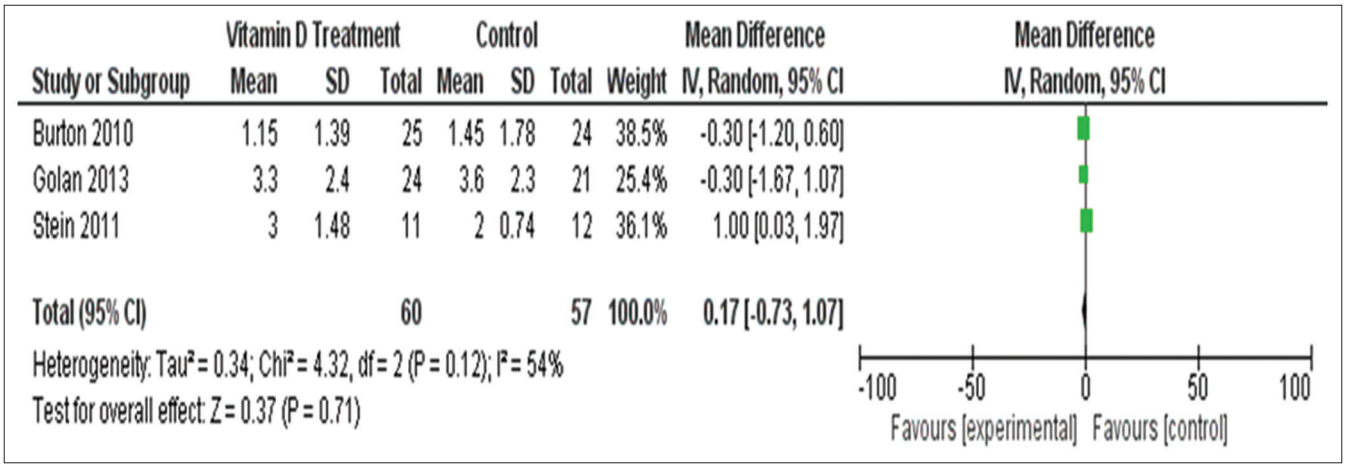

Figure 7: Final EDSS in patients of group 2 studies

This finding could be due to applying the mean difference of annual relapse rate instead of solely looking at relapse numbers.

In one of the included studies in this meta-analysis (Achiron *et al*.),[22] the relapse rate during the study period differed significantly between an intervention (Alfacalcidol 1 mcg/d) and placebo-controlled groups while the others showed no significant differences.

This meta-analysis included studies used different doses of vitamin D supplements in study arms.

There is no consensus regarding the optimal dose of vitamin D supplements for preventing relapse in MS although, Pierrot-Deseilligny *et al*. investigated a plateau effect of vitamin D on the rate of relapse.[29] They suggested that every 10 nmol increase in serum vitamin D level will result in a relapse rate reduction of 13.7%.[29]

Our results also suggest that high-dose vitamin D supplements in comparison with low-dose vitamin D supplements were not associated with better outcomes (reduced relapse rates and a significant decrease of EDSS). Four included studies in this part applied different doses of high- vs. low-dose supplements. We also should consider that duration of administration differed between studies. A delayed vitamin D onset of action is thought to be near 2 months, could explain this diversity. By considering 415 German patients, Embry *et al*. reported a 2-month lag time between vitamin D administration and magnetic resonance imaging (MRI) lesions.[30]

In one of the RCTs of this meta-analysis, 38% of relapses in the vitamin D intervention group occurred during 1 month of administration.[18] Achiron *et al.* claimed that the reduction of relapses in the vitamin D intervention group compared with the placebo group was significant after 4 months of treatment.[22] Shaygannejad *et al*. found that there is no effect on the relapse rate in the 1st year of vitamin D therapy in comparison with placebo in MS.[25] In Kampman *et al*. study, the median time to relapse was 39 and 29 weeks in the vitamin D supplement and placebo groups, respectively ($P = 0.4$).[16]

It may be helpful for future systematic reviews to consider the evaluation of relapses in vitamin D intervention groups after 2 months of administration.

Different factors could affect the effectiveness of vitamin D supplementation on the relapse rate. One factor could be the baseline vitamin D level as sun exposure and nutrition differ among participants of different studies. The results of Kampman *et al*. show relapse in six cases of the intervention vs four of the control group while Golan *et al*. and Stein *et al*. reported higher relapse rates in the high-dose vs low-dose group.[16,26,27]

In the studies included in this meta-analysis, the duration of treatment, and a dose of vitamin D supplements differed along with different formulations. For instance, Stein *et al*. administered vitamin D2 which is thought to have less effectiveness than vitamin D3.[27] It has been also demonstrated that the duration of action and potency of vitamin D2 is less than vitamin D3.[31]

Previous observational studies showed that sunlight exposure, vitamin D supplements, and serum vitamin D levels were associated with a lower risk of MS as well as relapse rate[3,4] but these studies were observational.

Multicentric, large, randomized trials may solve this problem.

Conclusions

Our findings show that vitamin D supplements (high or low dose) have no significant effect on relapse rate and disability during treatment in MS patients.

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Conflicts of interest

There are no conflicts of interest.

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