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REVIEW

Effects of Vitamin D Supplements on IL-10 and INFγ Levels in Patients with Multiple Sclerosis: a Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Vitamin D is one of the considerable environmental factors exhibiting immunomodulatory and anti-inflammatory effects.*

Objective: *To conduct a systematic review and meta-analysis to estimate the effect of vitamin D supplements on IL-10 and INFγ levels in patients with multiple sclerosis.*

Methods: *We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, The Cochrane Library and gray literature, including references of selected studies, conference abstracts which were published up to May 2019. We included single- or double-blinded RCTs or open-label trials in which one of the main outcomes was INFγ and/ or IL-10 levels after vitamin D supplementation. Only articles that had been published in English were included.*

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Results: *The literature search yielded 369 articles, that were monitored by us. After eliminating duplicates, 128 studies remained; from these, we excluded observational studies, reviews, case reports and non-randomized trials, and 33 studies remained. Finally, only three articles were included. The mean difference for INFγ was 268.4 and 95% CI 200.6-336.1. There was no significant heterogeneity (I^2 = 0%, Chi^2 = 0.1, p = 0.7). The mean difference for IL-10 was 398.3 and 95% CI -528.05-1324.8). There was significant heterogeneity (I^2 = 94%, Chi^2 = 31.1 p < 0.001).*

Conclusion: *The results of this systematic review were not satisfactory. More clinical trials are further needed to evaluate the effects of vitamin D supplements on IL-10 and INFγ levels in patients with multiple sclerosis.*

Keywords: multiple sclerosis, systematic review, vitamin D, chemokines.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting the central nervous system and leading to a wide range of disabilities (1). Women are affected more than men and both genetics and environmental factors have roles in disease development (2). T helper 1 cells producing INFγ have been considered to be involved in the disease development (3). On the other hand, IL-10 is a regulatory cytokine controlling inflammatory progressions (4). The exact effects of IL-10 are not clear, while the literature shows that in the relapsing phase of MS, the number of IL-10-positive T cells decrease and promoter polymorphism is related to the disease severity (5, 6).

Vitamin D is one of the considerable environmental factors which has immunomodulatory and anti-inflammatory effects (7, 8). Lower serum levels of this vitamin have been considered as a risk factor of MS along with higher risk of disease activity (8, 9). It is considered that vitamin D modulate the immune system by prohibiting T cell proliferation and inhibiting pro-inflammatory cytokines production such as INFγ as well as regulating the transcription of IL-10 gene resulting in IL-10 level elevation (10-12).

The aim of this systematic review and meta-analysis is to evaluate the effect of vitamin D supplements on IL-10 and INFγ levels in MS, as there is no published systematic review on this specific topic so far.

METHODS

The protocol of this systematic review has been already published (13).

Literature search

We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Ovid, The Cochrane Library and gray literature including reference of the selected studies, conference abstracts which were published up to May 2019.

Inclusion and exclusion criteria

We included single- or double-blinded RCTs or open-label trials in which one of the main outcomes was INFγ and/ or IL-10 levels after vitamin D supplementation. Only articles that had been published in English were included. Studies comparing high and low dose vitamin D therapies as well as 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, INFγ and/ or IL-10 levels in each treatment arm, study duration, first author, publication year and sample size were extracted from the included studies. In case of disagreement, the two researchers searched for a third reviewer's opinion.

Statistical analysis

All statistical analyses were performed using STATA Version 13.0 (Stata Corp LP, College Station, TX, USA).

We used the inverse variance with random effects model.

The mean difference was calculated for comparisons.

Inconsistency (I^2) was calculated to determine heterogeneity.

Risk of bias assessment

We evaluated the risk of potential bias by using a specific tool of Cochrane Collaboration for assessing such risk (14).

A p value less than 0.05 was considered statistically significant.

RESULTS

The literature search found 369 articles that were monitored. After eliminating duplicates, 128 studies remained; from these, we excluded observational studies, reviews, case reports and non-randomized trials, and 33 studies remained. Finally, only three articles were included for analysis (two for INFγ and three for IL-10) (Figure 1). Characteristics of included articles are summarized in Table 1.

The mean difference for INFγ was 268.4 and 95% CI 200.6-336.1.

There was no significant heterogeneity (I^2 =0%, Chi^2 =0.1, p =0.7) (Figure 2).

The mean difference for IL-10 was 398.3 and 95% CI -528.05-1324.8.

There was a significant heterogeneity (I^2 =94%, Chi^2 =31.1 p<0.001) (Figure 3).

The risk of potential bias was evaluated by a specific tool of Cochrane Collaboration for assessing such risk (14) (Figures 4 and 5).

A p value less than 0.05 was considered statistically significant.

DISCUSSION

The result of this systematic review and meta-analysis showed that vitamin D supplements

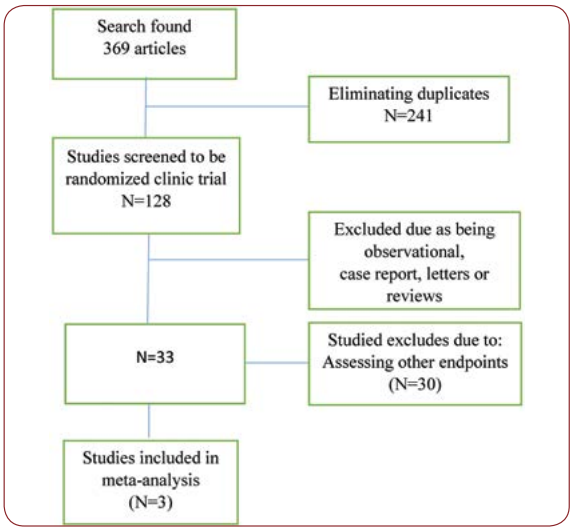

FIGURE 1. Flow diagram summarizing the selection of eligible studies

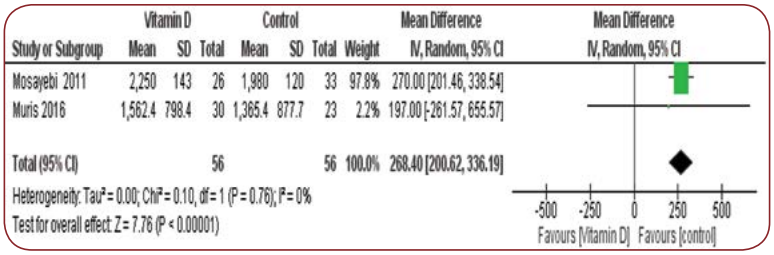

FIGURE 2. Mean difference of INFγ

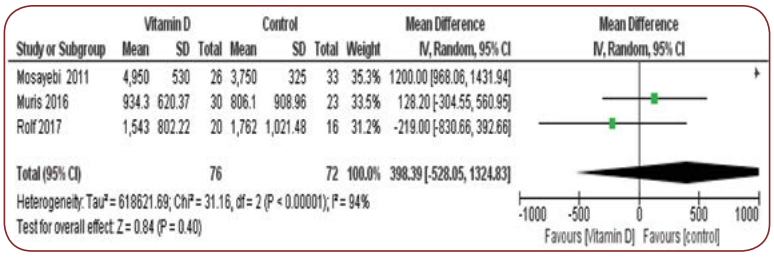

FIGURE 3. Mean difference of IL-10

First author	Publication year	Country	Study duration	No. of patients and dose of vitamin D	No. of placebo group
Mosayebi (15)	2011	Iran	Six months	N=28 300000 IU every month	N=34
Muris (16)	2016	Netherland	52 weeks	N=30 7000 IU for four weeks and 14000 IU for 48 weeks	N=23
Rolf (17)	2017	Netherland	52 weeks	N=20 7000 IU for four weeks and 14000 IU for 48 weeks	N=20

TABLE 1. Characteristics of included studies

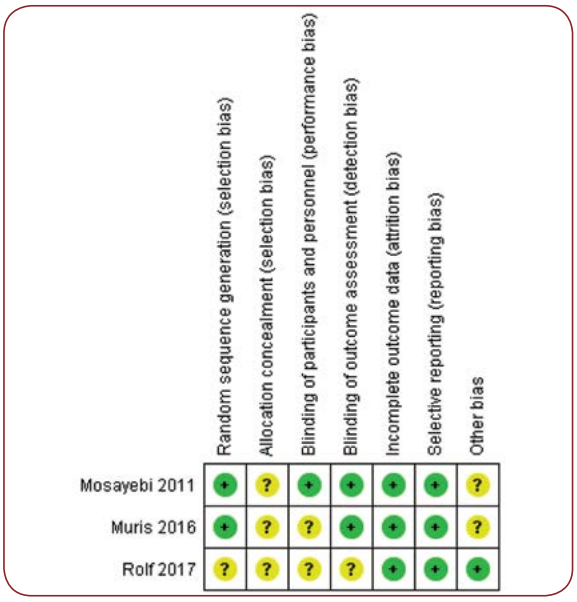

FIGURE 4. Methodologic quality assessment graph

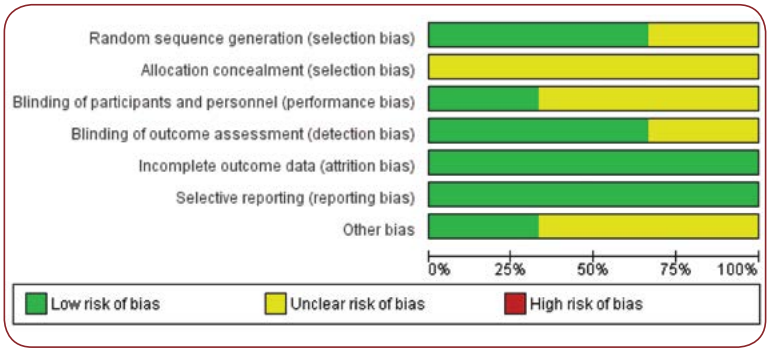

FIGURE 5. Risk-of-bias assessment for each study included in the meta-analysis

resulted in an significant increased level of INFγ (by including two studies) and had no significant effect on IL-10 level when comparing intervention and placebo groups.

In Rolf *et al*'s study, which was included in our systematic review, the vitamin D intervention group received 7000 IU for four weeks and 14000 IU for 48 weeks. According to their results, the mean IL-10 level was not significantly different at baseline and at the end in either the intervention or control group. The mean final levels were not statistically different between groups (final IL-10 was 1762 in the placebo group and 1543 in the vitamin D group) (17).

In Mosayebi *et al*'s study, the intervention group received 300000 IU vitamin D monthly for six months and the mean IL-10 level was reported to be 4950 at the final stage in the intervention group and 3750 in the control group, while the difference was not statistically significant between the two groups, although the level had increased in the intervention group (15).

In Muris *et al*'s study, the intervention group received 7000 IU of vitamin D for four weeks and 14000 IU for 48 weeks; the authors found a mean IL-10 level of 934 in the intervention group and 806 in the control group, while the difference was not statistically significant between the two groups, although the level had increased in the intervention group (16).

Given that the number of included studies for each item was limited, that of the included cases was limited too.

In Mosayebi *et al*'s study, the mean INFγ level decreased in both groups after six months, while the difference between the two groups was not significant (2250 in the intervention group and 1980 in the control group) (15).

In Muris *et al*'s study, the mean INFγ level decreased in both groups, while the difference between groups at the end of the study was not significant (16).

Experimental studies showed that 1,25-OH-vitamin D inhibited Th1 and Th17 cells and promoted Th2 and Treg cells (8, 18). On the other hand, prohibition of dendritic cell proliferation and maturation will result in secretion of IL-10 (19).

Previously, results of *in vitro* studies demonstrated that vitamin D prohibited T-cell proliferation and production of cytokines including IL-2, IL-12, and INFγ (20, 21).

An animal study revealed that 1,25-OH-vitamin D in an experimental autoimmune encephalomyelitis (EAE) model caused suppressed production of INFγ in spleen cells (22).

This systematic review has some limitations. Firstly, the number of included studies was limited. Secondly, we did not evaluate other chemokines.

CONCLUSION

The results of this systematic review was not satisfactory. There is a need for more clinical trials evaluating the effects of vitamin d supplements on IL-10 and INFγ levels in patients with multiple sclerosis. ❑

Conflicts of interest: none declared.
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