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The effects of vitamin D supplementation on expanded disability status scale in people with multiple sclerosis: A critical, systematic review and metaanalysis of randomized controlled trials

Amin Doosti-Irani[a,b], Omid Reza Tamtaji[c], Mohammad Ali Mansournia[d], Majid Ghayour- Mobarhan[e], Gordon Ferns[f], Reza Daneshvar Kakhaki[g], Arash Rezaei Shahmirzadi[h], Zatollah Asemi[c,*]

[a] Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Modeling of Noncommunicable Diseases Research Center, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[c] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran
[d] Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[e] Metabolic Syndrome Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9 PH, UK
[g] Department of Neurology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[h] Student Research Committee, Golestan University of Medical Science, Gorgan, Iran

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ABSTRACT

In this meta-analysis of randomized controlled trials (RCTs), the effects of vitamin D supplementation on the scores for the expanded disability status scale (EDSS) in people with multiple sclerosis (MS) are assessed. The following databases were search up to January 2018: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled by the use of the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI). Six studies were included in this meta-analysis. The findings demonstrated that supplementation with vitamin D alone and vitamin D plus calcium did not affect the EDSS score (WMD -0.11 (-0.33, 0.11); P = 0.32). In addition, subgroup analysis showed that vitamin D supplementation alone, when compared to the use of a placebo, and vitamin D plus calcium supplementation compared with the control did not affect EDSS (WMD -0.13 (-0.30, 0.11); P = 0.29) and (WMD -0.08 (-0.57, 0.41); P = 0.29), respectively. Overall, this meta-analysis indicated that taking vitamin D in people with MS had no significant effect on EDSS.

1. Introduction

Multiple sclerosis (MS) is defined as an immune-mediated inflammation and demyelinating disease of the central nervous system (CNS) and is a major contributor to disability of young people [1,2]. MS is one of the commonest causes of non-traumatic disability in young adults in Western countries [3]. Some observational studies on environmental associations have reported that elevated exposure to sunlight [4], reducing latitude [5], summer outdoor activities and high-dose intake of vitamin D-rich fish oils [6] are each correlated with a decreased risk of progressing MS.

Several observational studies have suggested that circulating levels of vitamin D are a sign of more active disease in subjects with relapsing-remitting multiple sclerosis (RR-MS) [7,8]. In addition, prospective and meta-analyses studies have reported that low circulating levels of vitamin D elevated the risk of mental health disturbances, such as dementia [9], cognitive impairment [10], impaired motor functions [11], and memory decline [12]. Two previous systematic reviews evaluated the relation between vitamin D status and cognitive performance [13,14], but there was insufficient evidence to draw a conclusion. It has been suggested that vitamin D intake in people with MS may influence the regulation of clinical disease activity as well as influencing the progress of disease. In a meta-analysis conducted by James et al. [15], no detectable relationship between vitamin D supplementation and risk of MS relapses was seen. However, the sample size of these trials was small, the quality of different studies was variable, the number of the

* Corresponding Author.
E-mail address: asemi_r@yahoo.com (Z. Asemi).

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studies was small, and the results were inconsistent.

Despite multiple randomized controlled trials (RCTs), we are aware of no meta-analysis of RCTs on the effect of vitamin D administration on EDSS in people with MS. This current meta-analysis was conducted to summarize the available evidence of RCTs to determine the impact of vitamin D administration on EDSS in people with MS.

2. Materials and methods

2.1. Search strategy

Eligible RCTs were identified using Cochrane Library, Embase, Medline, and Web of Science databases for relevant articles published until 2018, and by manually searching the reference list of the retrieved articles. Databases of International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs were also searched for all ongoing trials. Studies retrieved that evaluated the impacts of vitamin D supplementation on parameters of inflammation and oxidative damage by using the following MeSH and text words: patients ["MS"], intervention [("vitamin D3 and/or D2″ OR "vitamin D supplement" OR "vitamin D treatment" AND "supplementation" OR "intake") OR "calcium supplement"], and outcome ["expanded disability status scale (EDSS)"]. Additional manual searches including reference lists of related studies; former review studies were reviewed to increase sensitivity in search strategy. Studies included to this meta-analysis had the following criteria: 1) original trials, 2) human trials, 3) intervention and control groups received of vitamin D and calcium supplementation, and placebo, respectively and 4) the trials reported mean changes or mean difference of body composition and/or metabolic profiles with standard deviation (SD) for the intervention and control groups.

2.2. Data extraction and quality assessment

Two authors (OT, and AD) independently extracted the data and assessed its quality using standard forms and the Cochrane Collaboration risk of bias tool [16,17], respectively. This tool is based on information on the following domains: randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias. When there was disagreement among them, it resolved by third author (ZA). Eligible studies were abstracted: 1) first authors' name 2) publication year 3) age, sex, and body composition and/or metabolic profiles of study participants and associated measures of variance 4) study location 5) number of subjects in the intervention and control groups 6) study design 7) duration of the intervention.

2.3. Data analysis

2.3.1. Heterogeneity and publication biases

The statistical heterogeneity across the results of the included studies was tested using chi-square test [18], and quantified by the I^2 statistic [19]. Publication bias was assessed by the funnel plot and tested for statistical significance using the Egger's test [20].

2.3.2. Summary measures

We calculated the mean difference for the influence of vitamin D supplementation on EDSS for each included studies. The change score approach was used to obtain the effect sizes, because the correlations between baseline and end measurements were more than 1/2 [21]. A meta-analysis was performed to obtain the summary measures for the effect of vitamin D administration on EDSS using the inverse variance method. The random effects model was used to report the pooled mean difference with 95% confidence interval (CI). P-values < 0.05 were considered as statistically significant. Because of the low number of included RCTs and low sample size in the studies, we calculated the power of this meta-analysis [22]. Statistical analyses were performed using both Stata version 11.0 (Stata Corp., College Station, TX) and Review Manager 5.3.

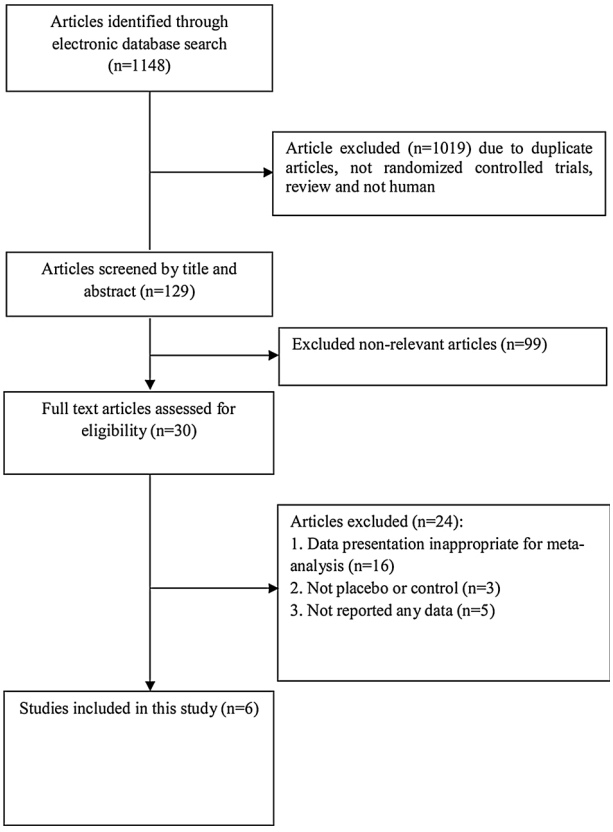

Fig. 1. Literature search and review flowchart for selection of studies.

3. Results

3.1. Description of the included RCTs

Our initial search found 11,487 potential citations. After screening, 6 studies were evidenced to be eligible for meta-analysis. Fig. 1 shows the details of step-by-step study identification and selection. The key characteristics of the RCTs are summarized in Table 1. Trials was published between 2010 and 2013. These 6 selected studies included 331 randomized participants including 166 and 165 participants in the intervention and control groups, respectively.

3.2. Effects of vitamin d supplementation on EDSS

The findings demonstrated that supplementation with vitamin D alone and vitamin D plus calcium did not affect EDSS (WMD -0.11 (-0.33, 0.11); P = 0.32) **(**Fig. 2**).** In addition, sub-group analysis showed that vitamin D administration alone did not influence EDSS (WMD -0.13 (-0.36, 0.11); P = 0.29) and (WMD -0.08 (-0.57, 0.41); P = 0.76), respectively, compared to placebo, and vitamin D plus calcium supplementation.

3.3. Heterogeneity and publication bias

The results of the chi-square test indicated there was considerable heterogeneity across the results of the included RCTs. The overall I^2 for studies assessed the impact of vitamin D administration on EDSS was 88% (P < 0.001). We performed the subgroup analysis based on the comparison groups, the I^2 for vitamin D versus placebo and calcium supplementations were 76% and 94% respectively **(**Fig. 2**).** Results of

Table 1
Characteristics of the studies included in the analysis.

Authors)Ref)	Publication year	Sample size (control/ intervention)	Duration (wk)	Age (years)	Intervention (type and dosage)
Burton et al. [36]	2010	23/24	52	39.9 ± 8.6, 41.1 ± 7.4	Escalating vitamin D3 doses up to 40,000 IU/day over 28 weeks, followed by 10,000IU/day (12 weeks), further downtitrated to 0 IU/day + Calcium 1200 mg/day
Mosayebi et al. [43]	2011	33/26	24	35 ± 9, 37 ± 9	30,0000 IU/ every month
Shaygannejad et al [35].	2012	25/25	48	37.9 ± 7.9, 38.6 ± 8.4	0.25 μg/d vitamin D (calcitriol), increased to 0.5 μg/day after 2 weeks
Soilu-Hänninen et al [44].	2012	30/32	48	35 ± 28.51, 39 ± 27.77	20,000 IU/weeks vitamin D3
Kampman et al [37].	2012	33/35	96	41 ± 28.14, 40 ± 26.29	20,000 IU/weeks vitamin D3 + 500 mg calcium
Golan et al. [45]	2013	21/24	48	44.7 ± 10.7, 43.1 ± 12.3	4370 IU/day Vitamin D

publication bias assessment showed that the included studies in this meta-analysis scattered nearly symmetrically around the null value in the funnel plot. So there was no evidence of publication bias (Fig. 3).

Results of power analysis showed that the power of our meta-analysis was 11%. In order to achieve a power more than 70 percent, we need to at least 15 RCTs with on average 150 participants in each arm of the RCTs.

4. Discussion

This meta-analysis is the first report of the effect of vitamin D supplementation on EDSS among people with MS. This meta-analysis exhibited that consuming vitamin D supplements did not affect EDSS in patients with MS.

4.1. The effect of vitamin D supplementation on EDSS

Previous longitudinal studies have reported increased EDSS scores over time [23,24]. The current meta-analysis showed that vitamin D intake in people with MS did not influence EDDS. Different dosages, co-supplementation with other micronutrients and durations of vitamin D treatment. Multiple observational studies have documented an inverse link between vitamin D concentrations and the risk of MS. In a meta-analysis study by Duan et al. [25], it was found that people with MS had lower levels of 25-hydroxyvitamin D compared with healthy subjects. In another study, Hewer et al. [26] documented that low vitamin D concentrations in people with MS were very common. There is an elevating interest in a range of functions of vitamin D and low circulating vitamin D concentrations play a considerable role in the progress of MS [26,27]. In addition, James et al. [15] performed a meta-analysis on the impact of vitamin D administration on the risk of MS relapses, no detectable association between vitamin D and risk of MS relapses was observed. Furthermore, Pozuelo-Moyano et al. [28] performed a systematic review of vitamin D intake on MS, but the studies included were low their sample size. In addition, the studies included in the current meta-analysis, mean EDSS at study baseline in the treatment and control groups was 1.46–2.61 and 1.23–3.6, respectively. The range of different EDSS may have different responses to vitamin D supplementation. However, mean EDSS improvement in studies included our meta-analysis was not clinically significant. We suggest that higher doses of vitamin D and longer period of intervention might make results clinically significant. Indeed, in previous studies, multiple factors are described to predict response to therapy [29,30], and these predictors vary greatly based on the definition of response used. In a study by Sa et al. [31], it was documented that sub-optimal treatment response appeared to be related only to a more severe EDSS score at study baseline.

In the present meta-analysis, people with MS had received a range of different dosages and formulations of vitamin D. However, the optimum dosage of vitamin D intake for people with MS has not been established, a study done by Pierrot-Deseilligny et al. [31], it was found a plateau effect of the action of vitamin D on the relapse rate in people with MS. Nonetheless, Burton et al. [32] exhibited a trend for the impact of vitamin D on relapse rate with high-dose administration (up to 40,000 IU/day). In addition, variations in formulations of vitamin D used in the different trials would result in variations in the results. Stein et al. [33] demonstrated that high-dose vitamin D2 (6000 IU/day), compared to low-dose supplementation (1000 IU/day), was not effective in reducing MRI lesions in patients with MS. While the efficacy of vitamin D3 supplementation for treatment of MS in adults has been evaluated in a few small non-controlled trials with variable results [34,35], two RCTs conducted over 52 weeks [36,37]. The effect of vitamin D supplementation on EDSS remains unclear. 25(OH)D is present in the central nervous system of MS patients and may be involved in local immune regulatory systems in progressive MS [38]. Response of MS patients to vitamin D administration may depend upon the genetic

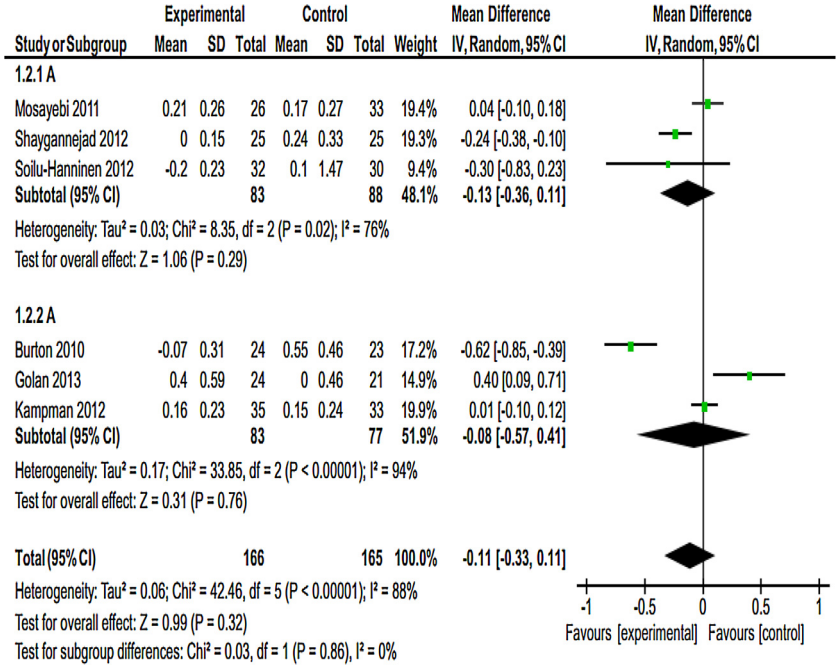

Fig. 2. Meta-analysis of the effects of vitamin D supplementation on expanded disability status scale in patients with multiple sclerosis. 1.2.1A and 1.2.2A the effects of vitamin D supplementation versus placebo and current treatment on expanded disability status, respectively.

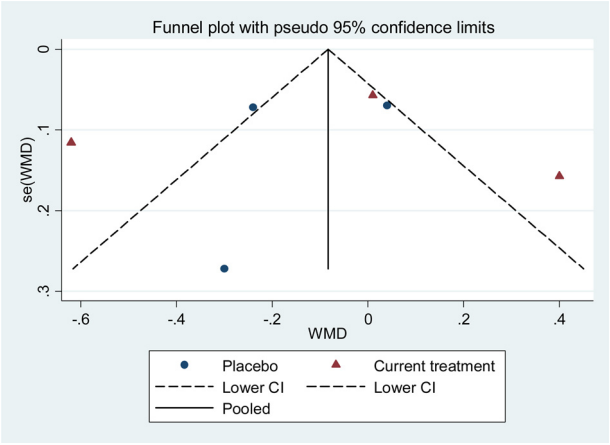

Fig. 3. Funnel plot of vitamin D versus placebo and current treatment to assess the publication bias.

profile of both vitamin D-related genes [39] and major histocompatibility complex (MHC) class II genotype [40]. In addition, it has been reported that in patients with MS, increasing 25-hydroxy vitamin D levels are associated with decreased production of interferon gamma by CD4 + T cells [41]. Bergman et al. [42] demonstrated that long-term supplementation of vitamin D (more than 6 months) was necessary to affect the immune system. This may explain the improvement of EDSS following supplementation with vitamin D.

4.2. Limitations

There are some limitations in our meta-analysis. Firstly, low number of included studies and consequently low sample size in the studies may increase the random error and in addition publication bias. As mean EDSS at baseline in most studies was < 3, we did not perform a distinct statistical approach. In addition, due to low number of included studies, we could not perform subgroup analysis based on duration of intervention.

4.3. Conclusions

Overall, this meta-analysis indicated that in patients with MS, taking vitamin D alone there was no significant effect on EDSS. However, within the RCTs investigating the effect of high-dose vitamin D administration on EDSS in people with MS that have been published so far, there are methodological concerns on formulations of vitamin D, co-supplementation with other micronutrients, different dosage of vitamin D used, and duration of the study and sample size. Therefore, further larger and longer studies addressing these issues should be considered.

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Declaration of Competing Interest

None.

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Not applicable.

References

[1] D. Karussis, The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review, J. Autoimmun. 48–49 (2014) 134–142.
[2] R. Dobson, G. Giovannoni, Multiple sclerosis - a review, Eur. J. Neurol. 26 (1) (2019) 27–40.
[3] Z. Rotstein, R. Hazan, Y. Barak, A. Achiron, Perspectives in multiple sclerosis health care: special focus on the costs of multiple sclerosis, Autoimmun. Rev. 5 (8) (2006) 511–516.
[4] M. Baarnhielm, A.K. Hedstrom, I. Kockum, E. Sundqvist, S.A. Gustafsson, J. Hillert, T. Olsson, L. Alfredsson, Sunlight is associated with decreased multiple sclerosis risk: no interaction with human leukocyte antigen-DRB1*15, Eur. J. Neurol. 19 (7) (2012) 955–962.
[5] S. Simpson Jr, L. Blizzard, P. Otahal, I. Van der Mei, B. Taylor, Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis, J Neurol Neurosurg Psychiatry 82 (10) (2011) 1132–1141.
[6] M.T. Kampman, T. Wilsgaard, S.I. Mellgren, Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle, J. Neurol. 254 (4)

(2007) 471–477.
[7] A. Bettencourt, D. Boleixa, H. Reguengo, R. Samoes, E. Santos, J.C. Oliveira, B. Silva, P.P. Costa, A.M. da Silva, Serum 25-hydroxyvitamin D levels in multiple sclerosis patients from the north of Portugal, J. Steroid Biochem. Mol. Biol. 180 (2017) 137–141.
[8] C. Wang, Z. Zeng, B. Wang, S. Guo, Lower 25-Hydroxyvitamin D is associated with higher relapse risk in patients with relapsing-remitting multiple sclerosis, J. Nutr. Health Aging 22 (1) (2018) 38–43.
[9] S. Afzal, S.E. Bojesen, B.G. Nordestgaard, Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia, Alzheimers Dement. 10 (3) (2014) 296–302.
[10] C. Balion, L.E. Griffith, L. Strifler, M. Henderson, C. Patterson, G. Heckman, D.J. Llewellyn, P. Raina, Vitamin D, cognition, and dementia: a systematic review and meta-analysis, Neurology 79 (13) (2012) 1397–1405.
[11] A.L. Peterson, M. Mancini, F.B. Horak, The relationship between balance control and vitamin D in Parkinson's disease-a pilot study, Mov. Disord. 28 (8) (2013) 1133–1137.
[12] A.L. Peterson, C. Murchison, C. Zabetian, J.B. Leverenz, G.S. Watson, T. Montine, N. Carney, G.L. Bowman, K. Edwards, J.F. Quinn, Memory, mood, and vitamin D in persons with Parkinson's disease, J. Parkinsons Dis. 3 (4) (2013) 547–555.
[13] C. Annweiler, A.M. Schott, G. Berrut, V. Chauvire, D. Le Gall, M. Inzitari, O. Beauchet, Vitamin D and ageing: neurological issues, Neuropsychobiology 62 (3) (2010) 139–150.
[14] K. Barnard, C. Colon-Emeric, Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition, Am. J. Geriatr. Pharmacother. 8 (1) (2010) 4–33.
[15] E. James, R. Dobson, J. Kuhle, D. Baker, G. Giovannoni, S.V. Ramagopalan, The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis, Mult. Scler. 19 (12) (2013) 1571–1579.
[16] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[17] M.A. Mansournia, J.P. Higgins, J.A. Sterne, M.A. Hernan, Biases in randomized trials: a conversation between trialists and epidemiologists, Epidemiology 28 (1) (2017) 54–59.
[18] K. Overvad, B. Diamant, L. Holm, G. Holmer, S.A. Mortensen, S. Stender, Coenzyme Q10 in health and disease, Eur. J. Clin. Nutr. 53 (10) (1999) 764–770.
[19] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7414) (2003) 557–560.
[20] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (1997) 629–634.
[21] J.N. Matthews, Introduction to Randomized Controlled Clinical Trials, Chapman and Hall/CRC, 2006.
[22] M. Borenstein, L.V. Hedges, J.P. Higgins, H.R. Rothstein, Introduction to Meta-analysis, John Wiley & Sons, 2011.
[23] D.K. Tepavcevic, T. Pekmezovic, N. Stojsavljevic, J. Kostic, I.D. Basuroski, S. Mesaros, J. Drulovic, Change in quality of life and predictors of change among patients with multiple sclerosis: a prospective cohort study, Qual. Life Res. 23 (3) (2014) 1027–1037.
[24] C. Chruzander, C. Ytterberg, K. Gottberg, U. Einarsson, L. Widen Holmqvist, S. Johansson, A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life, J. Neurol. Sci. 339 (1–2) (2014) 57–63.
[25] S. Duan, Z. Lv, X. Fan, L. Wang, F. Han, H. Wang, S. Bi, Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis, Neurosci. Lett. 570 (2014) 108–113.
[26] S. Hewer, R. Lucas, I. van der Mei, B.V. Taylor, Vitamin D and multiple sclerosis, J. Clin. Neurosci. 20 (5) (2013) 634–641.
[27] C. Pierrot-Deseilligny, Clinical implications of a possible role of vitamin D in multiple sclerosis, J. Neurol. 256 (9) (2009) 1468–1479.
[28] B. Pozuelo-Moyano, J. Benito-Leon, A.J. Mitchell, J. Hernandez-Gallego, A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis, Neuroepidemiology 40 (3) (2013) 147–153.
[29] J. Rio, C. Nos, M. Tintore, C. Borras, I. Galan, M. Comabella, X. Montalban, Assessment of different treatment failure criteria in a cohort of relapsing-remitting multiple sclerosis patients treated with interferon beta: implications for clinical trials, Ann. Neurol. 52 (4) (2002) 400–406.
[30] J. Rio, J. Castillo, A. Rovira, M. Tintore, J. Sastre-Garriga, A. Horga, C. Nos, M. Comabella, X. Aymerich, X. Montalban, Measures in the first year of therapy predict the response to interferon beta in MS, Mult. Scler. 15 (7) (2009) 848–853.
[31] M.J. Sa, J. de Sa, L. Sousa, Relapsing-remitting multiple sclerosis: patterns of response to disease-modifying therapies and associated factors: a national survey, Neurol. Ther. 3 (2) (2014) 89–99.
[32] S. Kimball, R. Vieth, H.M. Dosch, A. Bar-Or, R. Cheung, D. Gagne, P. O'Connor, C. D'Souza, M. Ursell, J.M. Burton, Cholecalciferol plus calcium suppresses abnormal PBMC reactivity in patients with multiple sclerosis, J. Clin. Endocrinol. Metab. 96 (9) (2011) 2826–2834.
[33] M.S. Stein, Y. Liu, O.M. Gray, J.E. Baker, S.C. Kolbe, M.R. Ditchfield, G.F. Egan, P.J. Mitchell, L.C. Harrison, H. Butzkueven, T.J. Kilpatrick, A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis, Neurology 77 (17) (2011) 1611–1618.
[34] A. Achiron, Y. Barak, S. Miron, Y. Izhak, M. Faibel, S. Edelstein, Alfacalcidol treatment in multiple sclerosis, Clin. Neuropharmacol. 26 (2) (2003) 53.
[35] V. Shaygannejad, M. Janghorbani, F. Ashtari, H. Dehghan, Effects of adjunct low-dose vitamin d on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial, Mult. Scler. Int. 2012 (2012) 452541.
[36] J.M. Burton, S. Kimball, R. Vieth, A. Bar-Or, H.M. Dosch, R. Cheung, D. Gagne, C. D'Souza, M. Ursell, P. O'Connor, A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis, Neurology 74 (23) (2010) 1852–1859.
[37] M.T. Kampman, L.H. Steffensen, S.I. Mellgren, L. Jorgensen, Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial, Mult. Scler. 18 (8) (2012) 1144–1151.
[38] T. Holmoy, S.M. Moen, T.A. Gundersen, M.F. Holick, E. Fainardi, M. Castellazzi, I. Casetta, 25-hydroxyvitamin D in cerebrospinal fluid during relapse and remission of multiple sclerosis, Mult. Scler. 15 (11) (2009) 1280–1285.
[39] S.M. Orton, A.P. Morris, B.M. Herrera, S.V. Ramagopalan, M.R. Lincoln, M.J. Chao, R. Vieth, A.D. Sadovnick, G.C. Ebers, Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis, Am. J. Clin. Nutr. 88 (2) (2008) 441–447.
[40] S.V. Ramagopalan, N.J. Maugeri, L. Handunnetthi, M.R. Lincoln, S.M. Orton, D.A. Dyment, G.C. Deluca, B.M. Herrera, M.J. Chao, A.D. Sadovnick, G.C. Ebers, J.C. Knight, Expression of the multiple sclerosis-associated MHC class II Allele HLA-DRB1*1501 is regulated by vitamin D, PLoS Genet. 5 (2) (2009) e1000369.
[41] M.F. Mrad, N.K. El Ayoubi, M.O. Esmerian, J.M. Kazan, S.J. Khoury, Effect of vitamin D replacement on immunological biomarkers in patients with multiple sclerosis, Clin. Immunol. 181 (2017) 9–15.
[42] P. Bergman, A.C. Norlin, S. Hansen, R.S. Rekha, B. Agerberth, L. Bjorkhem-Bergman, L. Ekstrom, J.D. Lindh, J. Andersson, Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study, BMJ Open 2 (6) (2012).
[43] G. Mosayebi, A. Ghazavi, K. Ghasami, Y. Jand, P. Kokhaei, Therapeutic effect of vitamin D3 in multiple sclerosis patients, Immunol. Invest. 40 (6) (2011) 627–639.
[44] M. Soilu-Hanninen, J. Aivo, B.M. Lindstrom, I. Elovaara, M.L. Sumelahti, M. Farkkila, P. Tienari, S. Atula, T. Sarasoja, L. Herrala, I. Keskinarkaus, J. Kruger, T. Kallio, M.A. Rocca, M. Filippi, A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis, J Neurol Neurosurg Psychiatry 83 (5) (2012) 565–571.
[45] D. Golan, B. Halhal, L. Glass-Marmor, E. Staun-Ram, O. Rozenberg, I. Lavi, S. Dishon, M. Barak, S. Ish-Shalom, A. Miller, 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, BMC Neurol. 13 (2013) 60.