Vitamin D Supplementation on Fatigue in Multiple Sclerosis

Subjects: Clinical Neurology

Contributor: Purificación López-Muñoz, Ana Torres-Costoso, Rubén Fernández-Rodríguez, María José Guzmán-Pavón, Sergio Nuñez de Arenas-Arroyo, Julián Ángel Basco-López, Sara Reina-Gutiérrez

Multiple sclerosis (MS) is an autoimmune and inflammatory chronic disease of the central nervous system that constitutes one of the leading causes of disability among young adults. Multiple sclerosis can produce a variety of symptoms, such as fatigue, blurred vision, optic neuritis, weakness, dizziness, balance disturbances, cognitive decline, and problems with bladder control, as well as an increased risk of depression and anxiety. Fatigue is one of the most common and disabling symptoms and can be described as a subjective lack of physical and/or mental energy that interferes with usual activities.

Keywords: supplements ; disability ; calciferol ; cholecalciferol ; neurological disorders ; tiredness

1. Introduction

In people with multiple sclerosis (MS), fatigue can be central and peripheral, and both types can occur simultaneously. Central fatigue is related to dysfunctions of the central nervous system, especially processes of inflammation, demyelination, and/or neurodegeneration, and peripheral fatigue is related to non-specific factors of the disease or dysfunctions of other body systems [1][2]. Otherwise, fatigue can cause decreased physical activity and concentration, memory disturbances, executive difficulties and feelings of tension, anxiety, or sadness [3]. Furthermore, it is frequently perceived by people as the most debilitating symptom that significantly affects quality of life [3][4]. There are a number of drug treatments for MS-related fatigue; however, to date, there is insufficient evidence to support which ones are most effective [3][5].

Although the etiology of MS is still uncertain, it is likely that the interaction between genetic and environmental factors, along with others, contributes to its appearance [6][7]. Some factors, such as the duration and intensity of sunlight exposure and high-latitude geographical areas, are correlated with the incidence and prevalence of MS [7]. This connection could be due to low ultraviolet radiation exposure and low vitamin D (VD) status in these areas [8][9][10].

Vitamin D is a fat-soluble steroid hormone produced predominantly in response to ultraviolet B (UV-B) irradiation of the skin [11]. The main forms of VD in the diet are ergocalciferol (vitamin D2) of vegetable origin and cholecalciferol (vitamin D3) of animal origin. Vitamin D appears to have an immunomodulatory effect that includes the activation and proliferation of lymphocytes, the differentiation of T cells, and a reduction in inflammatory cytokines [6]. Some studies have confirmed the association between low serum levels of 25-hydroxyvitamin D (25(OH)D) and the risk of MS onset, also constituting a risk factor for disease activity and progression in early stages [6][12]. Likewise, it has been observed that suboptimal levels of VD can contribute to inflammation and axonal degeneration in people with MS [13]. These associations and their effects on immune and central nervous system cells raise the question of whether vitamin supplementation could be used as a therapeutic strategy in MS [7]. Therefore, VD supplementation is an area of great interest because it is a potentially modifiable environmental factor for the development of MS and a possible treatment to reduce the risk of disease activity and progression [11]. However, to date, consensus clinical guidelines on the use of VD in MS do not offer clear recommendations on its effect on the progression and activity of the disease [14][15][16]. The most studied clinical variables in this regard with controversial results are relapse rate [6][10][17][18][19], disability or disease progression [6][10][13][19][20], and the appearance of new magnetic resonance imaging (MRI) lesions [19][21][22]. While some studies have not found a significant positive effect of VD in relation to the relapse rate and disease progression [6][10][13][17][18][19][21], others, such as the study of Camu et al., [22] did find one. On the other hand, regarding the appearance of new MRI lesions, VD has been shown to have a significant positive effect in several studies [19][20][22], although in the Cochrane review by Jagannath et al. [13], this effect was not found. In contrast, the effect of VD supplementation on fatigue has been poorly studied and remains uncertain [23], and considering that fatigue is one of the most disabling symptoms and the one with the greatest

impact on the quality of life of people with MS, it seems pertinent to investigate possible treatments that improve this variable.

2. Effect of Vitamin D Administration on Fatigue

Vitamin D has been administered as a supplement for decades in people with MS since its deficiency can be a pathogenic risk factor and influence the activity of the disease [24][25]. However, to our knowledge, this is the first systematic research with meta-analysis that synthesized the effects of VD supplementation in relation to fatigue, a symptom that affects most people with this disease. Researcher' data show a significant reduction in fatigue in those who received VD supplementation compared to the control group.

In recent years, growing interest has emerged in the potential beneficial effect of VD supplementation on fatigue in people with MS, but the results are controversial. A wide 2018 Cochrane review [13] that evaluated the benefit of VD supplementation to reduce disease activity in relation to fatigue only included the studies of Achiron et al. [26] and Kampman et al. [27], showing contradictory and inconclusive results. The same results were obtained in a 2020 umbrella review [28] that analyzed the evidence for dietary interventions in MS and, regarding fatigue, only included the two mentioned studies [26][27]. On the other hand, in the cross-sectional study of Albrechtsen et al. [29], the intake of VD along with omega-3 fatty acids also showed a trend toward a reduction in fatigue. Similar to this last study, researcher' study data from five clinical trials showed a positive effect of VD supplementation on fatigue in this population.

The study of Achiron et al. [26] showed the best results in terms of a significant reduction in fatigue in the VD group in relation to the control compared to the other studies, which generally showed positive trends or no effect on fatigue. The characteristics that differentiate the study of Achiron et al. from the others are a larger sample size with its 158 participants representing nearly 50% of the total sample and a dose of VD of 280 IU/week (1 mcg/day), much lower than that used in the rest of the studies, which ranged between 20,000 IU [27] and 98,000 IU [30] per week.

Currently, there is no consensus on the optimal dosing of VD intake as adjuvant therapy in MS [6]. People with MS seem to have reduced serological and metabolic responses to VD supplements, which suggests that they may need higher doses than others to achieve clinically relevant effects [31][32]. Supplementation with high doses of VD is generally well tolerated by people with MS [11][33][34]. However, some studies recommend supplementing with VD only in cases of confirmed deficiency [12][35] as well as not exceeding 600 IU/day, since higher doses could increase the risk of toxic side effects [8][12][36][37]. In the meta-analysis by McLaughlin et al. [11], high doses were associated with worse outcomes in general and were even reported to potentially increase the relapse risk. In contrast, other studies suggest that higher doses are more effective than lower doses [12], as reported by a recent cross-sectional study that found a positive association with improvement in quality of life and fatigue [33]. Without having conclusive data on what the optimal dose is for people with MS, it would be advisable to follow the recommendation of consulting with healthcare providers to obtain personalized guidance on VD supplementation according to the specific circumstances and the medical history of each individual [15].

It is necessary to emphasize that the baseline level of 25(OH)D is a very important parameter to consider since VD supplementation is more effective when applied to subjects with low basal levels [38][39]. Although in researcher' meta-regression analysis there were no significant differences in this regard, it is worth highlighting that in most of the studies that provided data, the participants had a baseline normal 25(OH)D level [40], which may have been the reason why no differences were found. Moreover, this may also have influenced the fact that the effect of VD supplementation was not greater.

Furthermore, there is currently interest in disorders of sphingolipid (SL) metabolism in MS, as they play an important role in the regulation of the immune response and inflammation [41][42]. Recently, fingolimod has been used for the treatment of MS, which is an immunomodulatory drug that targets the sphingosine-1-phosphate receptor and helps reduce inflammation and prevent damage to the myelin sheath [43]. Although in the present meta-analysis, only one study reported that some participants were taking this medication [44], it is possible that variations in SL levels among study participants could influence the efficacy of VD supplementation in alleviating fatigue symptoms, as VD is known to affect SL metabolism [45].

Some limitations that might limit the robustness of researcher' estimates should be acknowledged, such as the small sample size of the included studies. Nonetheless, in this systematic research and meta-analysis, a significant effect of VD on fatigue was detected, although RCTs with larger samples would be necessary to confirm these findings. Furthermore, there was wide variability in the duration of the treatment and the dose of VD used among studies, so further research is

necessary to determine the optimal dose to improve fatigue in people with MS and understand the possible benefits and risks associated with these variables. On the other hand, due to the limited data about the type of VD administered, a complementary analysis could not be made to determine its influence on the results. In this regard, most of the studies that provided data used vitamin D3 [27][30][44], which appears to be more effective than vitamin D2 in increasing serum levels of 25(OH)D [46]

References

1. Langeskov-Christensen, M.; Bisson, E.J.; Finlayson, M.L.; Dalgas, U. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. J. Neurol. Sci. 2017, 373, 307–320.
2. Englund, S.; Piehl, F.; Kierkegaard, M. High-intensity resistance training in people with multiple sclerosis experiencing fatigue: A randomised controlled trial. Mult. Scler. Relat. Disord. 2022, 68, 104106.
3. Tarasiuk, J.; Kapica-Topczewska, K.; Czarnowska, A.; Chorąży, M.; Kochanowicz, J.; Kułakowska, A. Co-occurrence of Fatigue and Depression in People with Multiple Sclerosis: A Mini-Review. Front. Neurol. 2022, 12, 817256.
4. Rooney, S.; Wood, L.; Moffat, F.; Paul, L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. Mult. Scler. Relat. Disord. 2019, 28, 276–282.
5. Nourbakhsh, B.; Revirajan, N.; Morris, B.; Cordano, C.; Creasman, J.; Manguinao, M.; Krysko, K.; Rutatangwa, A.; Auvray, C.; Aljarallah, S.; et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: A randomised, placebo-controlled, crossover, double-blind trial. Lancet Neurol. 2021, 20, 38–48.
6. Yuan, X.; Guo, L.; Jiang, C.; Yang, X.; Huang, J. The Effect of Different Administration Time and Dosage of Vitamin D Supplementation in Patients with Multiple Sclerosis: A Meta-Analysis of Randomized Controlled Trials. Neuroimmunomodulation 2021, 28, 118–128.
7. Boltjes, R.; Knippenberg, S.; Gerlach, O.; Hupperts, R.; Damoiseaux, J. Vitamin D supplementation in multiple sclerosis: An expert opinion based on the review of current evidence. Expert Rev. Neurother. 2021, 21, 715–725.
8. Zheng, C.; He, L.; Liu, L.; Zhu, J.; Jin, T. The efficacy of vitamin D in multiple sclerosis: A meta-analysis. Mult. Scler. Relat. Disord. 2018, 23, 56–61.
9. Mokry, L.E.; Ross, S.; Ahmad, O.S.; Forgetta, V.; Smith, G.D.; Leong, A.; Greenwood, C.M.T.; Thanassoulis, G.; Richards, J.B. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. PLoS Med. 2015, 12, e1001866.
10. Ghajarzadeh, M.; Hanaei, S.; Sahraian, M.A.; Mohammadifar, M.; Ramagopalan, S.V. Effect of Vitamin D Supplements on Relapse Rate and Expanded Disability Status Scale (EDSS) in Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis. Int. J. Prev. Med. 2021, 12, 42.
11. McLaughlin, L.; Clarke, L.; Khalilidehkordi, E.; Butzkueven, H.; Taylor, B.; Broadley, S.A. Vitamin D for the treatment of multiple sclerosis: A meta-analysis. J. Neurol. 2018, 265, 2893–2905.
12. Głąbska, D.; Kołota, A.; Lachowicz, K.; Skolmowska, D.; Stachoń, M.; Guzek, D. Vitamin D Supplementation and Mental Health in Multiple Sclerosis Patients: A Systematic Review. Nutrients 2021, 13, 4207.
13. Jagannath, V.A.; Filippini, G.; Di Pietrantonj, C.; Asokan, G.V.; Robak, E.W.; Whamond, L.; Robinson, S.A. Vitamin D for the management of multiple sclerosis. Cochrane Database Syst. Rev. 2018, 9, CD008422.
14. Brum, D.G.; Comini-Frota, E.R.; Vasconcelos, C.C.F.; Dias-Tosta, E. Supplementation and therapeutic use of vitamin D in patients with multiple sclerosis: Consensus of the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology. Arq. Neuropsiquiatr. 2014, 72, 152–156, (In English, In Portuguese).
15. Simpson-Yap, S.; Morahan, J.; Campbell, H.; Luker, T.; Mckay, F.; Chitranjan, A.; Zarghami, A.; Bruce Taylor, B.; Marck, C.; Black, L.; et al. Adapting Your Lifestyle: A Guide for People with MS. MS Research Australia. Available online: https://www.msaustralia.org.au/wp-content/uploads/2021/10/adapting-your-lifestyle-a-guide-for-people-with-ms.pdf (accessed on 31 May 2023).
16. Burgos, R.; Bretón, I.; Cereda, E.; Desport, J.C.; Dziewas, R.; Genton, L.; Gomes, F.; Jésus, P.; Leischker, A.; Muscaritoli, M.; et al. ESPEN guideline clinical nutrition in neurology. Clin. Nutr. 2018, 37, 354–396.
17. Golan, D.; Halhal, B.; Glass-Marmor, L.; Staun-Ram, E.; Rozenberg, O.; Lavi, I.; Dishon, S.; Barak, M.; Ish-Shalom, S.; Miller, A. 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. 2013, 13, 60.

18. Shaygannejad, V.; Janghorbani, M.; Ashtari, F.; Dehghan, H. 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.
19. Langlois, J.; Denimal, D. Clinical and Imaging Outcomes after Vitamin D Supplementation in Patients with Multiple Sclerosis: A Systematic Review. Nutrients 2023, 15, 1945.
20. Hupperts, R.; Smolders, J.; Vieth, R.; Holmøy, T.; Marhardt, K.; Schluep, M.; Killestein, J.; Barkhof, F.; Beelke, M.; Grimaldi, L.M.; et al. Randomized trial of daily high-dose vitamin D3 in patients with RRMS receiving subcutaneous interferon β-1a. Neurology 2019, 93, e1906–e1916.
21. Dörr, J.; Bäcker-Koduah, P.; Wernecke, K.-D.; Becker, E.; Hoffmann, F.; Faiss, J.; Brockmeier, B.; Hoffmann, O.; Anvari, K.; Wuerfel, J.; et al. High-dose vitamin D supplementation in multiple sclerosis—Results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. Mult. Scler. J. Exp. Transl. Clin. 2020, 6, 2055217320903474.
22. Camu, W.; Lehert, P.; Pierrot-Deseilligny, C.; Hautecoeur, P.; Besserve, A.; Deleglise, A.-S.J.; Payet, M.; Thouvenot, E.; Souberbielle, J.C. Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). Neurol. Neuroimmunol. Neuroinflamm. 2019, 6, e597.
23. Miclea, A.; Bagnoud, M.; Chan, A.; Hoepner, R. A Brief Review of the Effects of Vitamin D on Multiple Sclerosis. Front. Immunol. 2020, 11, 781.
24. Sintzel, M.B.; Rametta, M.; Reder, A.T. Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol. Ther. 2018, 7, 59–85.
25. Esteve, I.R.; Lozano, C.W.-B.; Sanz-Valero, J. Efectos del estado nutricional en la enfermedad de la esclerosis múltiple: Revisión sistemática . Nutr. Hosp. 2018, 35, 211–223. (In Spanish)
26. Achiron, A.; Givon, U.; Magalashvili, D.; Dolev, M.; Zaltzman, S.L.; Kalron, A.; Stern, Y.; Mazor, Z.; Ladkani, D.; Barak, Y. Effect of Alfacalcidol on multiple sclerosis-related fatigue: A randomized, double-blind placebo-controlled study. Mult. Scler. 2015, 21, 767–775.
27. Kampman, M.T.; Steffensen, L.H.; Mellgren, S.I.; Jørgensen, L. 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. 2012, 18, 1144–1151.
28. Tredinnick, A.R.; Probst, Y.C. Evaluating the Effects of Dietary Interventions on Disease Progression and Symptoms of Adults with Multiple Sclerosis: An Umbrella Review. Adv. Nutr. 2020, 11, 1603–1615.
29. Albrechtsen, M.; Langeskov-Christensen, M.; Jørgensen, M.; Dalgas, U.; Hansen, M. Is diet associated with physical capacity and fatigue in persons with multiple sclerosis? -Results from a pilot study. Mult. Scler. Relat. Disord. 2020, 40, 101921.
30. Rolf, L.; Muris, A.-H.; Bol, Y.; Damoiseaux, J.; Smolders, J.; Hupperts, R. Vitamin D3 supplementation in multiple sclerosis: Symptoms and biomarkers of depression. J. Neurol. Sci. 2017, 378, 30–35.
31. Bhargava, P.; Steele, S.U.; Waubant, E.; Revirajan, N.R.; Marcus, J.; Dembele, M.; Cassard, S.D.; Hollis, B.W.; Crainiceanu, C.; Mowry, E.M. Multiple sclerosis patients have a diminished serologic response to vitamin D supplementation compared to healthy controls. Mult. Scler. 2016, 22, 753–760.
32. Bhargava, P.; Fitzgerald, K.C.; Calabresi, P.A.; Mowry, E.M. Metabolic alterations in multiple sclerosis and the impact of vitamin D supplementation. JCI Insight 2017, 2, e95302.
33. Ianniello, A.; Sottosanti, A.; Borriello, G.; Vincenti, M. Perception of Quality of Life and Fatigue in Multiple Sclerosis Patients Treated with High-Dose Vitamin D. Clin. Transl. Neurosci. 2023, 7, 12.
34. Amon, U.; Yaguboglu, R.; Ennis, M.; Holick, M.F.; Amon, J. Safety Data in Patients with Autoimmune Diseases during Treatment with High Doses of Vitamin D3 According to the “Coimbra Protocol”. Nutrients 2022, 14, 1575.
35. Haines, S.T.; Park, S. Vitamin D supplementation: What’s known, what to do, and what’s needed. Pharmacotherapy 2012, 32, 354–382.
36. Feige, J.; Moser, T.; Bieler, L.; Schwenker, K.; Hauer, L.; Sellner, J. Vitamin D Supplementation in Multiple Sclerosis: A Critical Analysis of Potentials and Threats. Nutrients 2020, 12, 783.
37. Ross, A.C. The 2011 report on dietary reference intakes for calcium and vitamin D. Public Health Nutr. 2011, 14, 938–939.
38. Berezowska, M.; Coe, S.; Dawes, H. Effectiveness of Vitamin D Supplementation in the Management of Multiple Sclerosis: A Systematic Review. Int. J. Mol. Sci. 2019, 20, 1301.

39. Faqeeh, M.; Alkhotani, A.; Aldoobi, R.; Sheikh, G.; Halabi, R.; Alsharif, W. The effect of Vitamin D in multiple sclerosis: An updated review. Saudi J. Health Sci. 2021, 10, 149–154.
40. Munns, C.F.; Shaw, N.; Kiely, M.; Specker, B.L.; Thacher, T.D.; Ozono, K.; Michigami, T.; Tiosano, D.; Mughal, M.Z.; Mäkitie, O.; et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. Horm. Res. Paediatr. 2016, 85, 83–106.
41. Podbielska, M.; Ariga, T.; Pokryszko-Dragan, A. Sphingolipid Players in Multiple Sclerosis: Their Influence on the Initiation and Course of the Disease. Int. J. Mol. Sci. 2022, 23, 5330.
42. Podbielska, M.; Macala, J.; Jakubiak-Augustyn, A.; Szulc, Z.M.; Fortuna, W.; Budrewicz, S.; Jaskiewicz, E.; Bilinska, M.; Hogan, E.L.; Pokryszko-Dragan, A. Ceramide is implicated in humoral peripheral and intrathecal autoimmune response in MS patients. Mult. Scler. Relat. Disord. 2023, 71, 104565.
43. Gulec, B.; Everest, E.; Gorkey, O.D.; Koc, M.; Tutuncu, M.; Saip, S.; Siva, A.; Uygunoglu, U. Comparison of multiple sclerosis patients with or without rebound activity after fingolimod cessation: Five-year clinical outcomes. Eur. J. Neurol. 2023.
44. Rolf, L.; Damoiseaux, J.; Huitinga, I.; Kimenai, D.; van den Ouweland, J.; Hupperts, R.; Smolders, J. Stress-Axis Regulation by Vitamin D3 in Multiple Sclerosis. Front. Neurol. 2018, 9, 263.
45. Okazaki, T.; Bell, R.M.; Hannun, Y.A. Sphingomyelin turnover induced by vitamin D3 in HL-60 cells. Role in cell differentiation. J. Biol. Chem. 1989, 264, 19076–19080.
46. Balachandar, R.; Pullakhandam, R.; Kulkarni, B.; Sachdev, H.S. Relative Efficacy of Vitamin D2 and Vitamin D3 in Improving Vitamin D Status: Systematic Review and Meta-Analysis. Nutrients 2021, 13, 3328.