Austin Journal of Nutrition and Food Sciences

Open Access

Austin Publishing Group

Special Article – Vitamin D

Effects and Mechanisms of Action of Vitamin D in Multiple Sclerosis

Almeida MR[1], Brasiel PGA[2]* and Dutra SCPL[1]

[1]Department of Nutrition, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil

[2]University Hospital UFJF, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil

***Corresponding author:** Brasiel PGA, Department of Nutrition, University Hospital UFJF, José Lourenço Kelmer Street, s/n – São Pedro, 36036900, Juiz de Fora – MG, Brazil

Received: June 28, 2018; **Accepted:** July 24, 2018; **Published:** July 31, 2018

Abstract

Multiple Sclerosis is a neurological, inflammatory and autoimmune disease characterized by gradual demyelination of axons in the central nervous system and degeneration of neuronal cells. Vitamin D deficiency has been associated with increased risk and worsening of disease activity. Thus, its supplementation has been considered beneficial, demonstrating its effect on increasing serum levels, decreasing disease activity and relapse rates, providing a better quality of life for individuals with Multiple Sclerosis. Studies in animal models and in humans using vitamin D supplementation in Multiple Sclerosis present controversial results. Vitamin D supplementation is related to immunological benefits, acting in the regulation of the immune system, inflammation, recovery of cells of the central nervous system, reduction of relapses and brain lesions, playing an important role in the course of the disease. However, the necessary dose of this vitamin to exert beneficial effects on the activity and progression of Multiple Sclerosis still remain undefined, and there is no consensus regarding the safe and effective dosage to obtain beneficial results in these patients. The purpose of this review is to address the effects of vitamin D supplementation on multiple sclerosis, as well as the mechanisms by which this vitamin acts.

Keywords: Vitamin D; Multiple sclerosis; Supplementation; Immunity

Introduction

Multiple Sclerosis (MS) is a neurological, inflammatory and autoimmune disease, characterized by gradual demyelination of axons in the Central Nervous System (CNS) and neuronal cell degeneration [1].

According to the Atlas of Multiple Sclerosis [2], the estimated number of people with MS increased from 2.1 million in 2008 to 2.3 million in 2013, affecting twice as many women as men, with ages ranging from 20 to 40 years. Currently in Brazil, it is estimated that 35 thousand people are affected by the disease, with a prevalence of 5, 01 to 20 people per 100 thousand inhabitants [2].

Vitamin D, or cholecalciferol, is a steroid hormone, whose primary function is the regulation of calcium homeostasis, formation and bone resorption. In addition to this important function, cholecalciferol has immunomodulatory properties that have been studied in recent years. Vitamin D can be obtained by exposing the skin to sunlight, vitamin and dietary supplements [3-5].

In MS vitamin D deficiency has been associated with increased risk and worsening of disease activity. It has been shown to increase blood levels, decrease disease activity, relapse rates, and immunomodulatory effects, providing a better quality of life in individuals with the disease [6].

In this context, this review aims to study the effects of vitamin D supplementation on multiple sclerosis, as well as the mechanisms by which this vitamin acts.

Ethiopathogeny

MS is an autoimmune disease that reaches the CNS, especially the white matter, causing inflammation and may form multiple lesions or attack a large region of the brain and spinal cord. The lesions are caused by the destruction of the myelin sheath of the neurons, causing the incapacity of the motor conduction [7,8].

According to the Brazilian Association of MS (ABEM), there are three types of MS that vary according to the presence of outbreaks. The mildest and most common type is Relapsing-remitting MS (RRMS), which progresses with outbreaks where symptoms occur suddenly with partial or total recovery. Primary Progressive MS (PPMS) progresses without outbreaks, but the symptoms are progressive accumulated over time. The latter type is Secondary Progressive MS (SPMS), which progresses with slow and progressive symptoms over time in individuals who have the RRMS form [9].

The diagnosis of MS is based on the criteria of McDonald, which uses clinical exams, laboratory tests and demonstration of lesions visualized by nuclear magnetic resonance [10].

In MS, the immune system, especially reactive T lymphocytes, recognize the myelin protein components as pathogenic. These lymphocytes move towards the CNS, crossing the blood-brain barrier after being sensitized in the bloodstream. In the CNS, they are reactivated by the presentation of autogenic peptides by dendritic cells, macrophages and B-lymphocytes, causing an inflammatory cascade with release of cytokines, chemokines, and activation of glial cells and infiltration of other peripheral lymphocytes causing destruction of the myelin sheath [11].

In the pathological process of MS, the CD4 + helper T lymphocyte is the main cell responsible for the release of proinflammatory cytokines such as interferon γ, interleukin 2 and tumor necrosis

Citation: Almeida MR, Brasiel PGA and Dutra SCPL. Effects and Mechanisms of Action of Vitamin D in Multiple Sclerosis. Austin J Nutri Food Sci. 2018; 6(4): 1109.

Table 1: Studies evaluating vitamin D supplementation in Multiple Sclerosis.

REFERENCE	EXPERIMENTAL DESIGN	SUPPLEMENTATION	RESULTS
Guo et al. (2015)	Animal. Experimental Allergic Encephalomyelitis. N: 20 Treatment time: 4 weeks.	Groups: 1- Placebo 2- MS induction. 3- Pretreated with 100 ng/day (before inducing MS). 4- Post treated with 100 ng/day (after developing MS).	Groups: 3- Delay in the progression of MS. 3 and 4 ↑ of the proliferation of neural stem cells, implying improvement of clinical symptoms, repair of neural damage and ↓ in the development of the stages of MS.
Golan et al. (2013)	Humans. ≥ 18 years with RRMS, treated with IFN β. N: 45 Treatment time: 1 year.	Groups: 1- 4.370 IU/day. 2- 800 IU/day.	Groups: 1- ↑ 25(OH)D, ↓ PTH. 2- ↑ IL17. No changes were observed in the flu-like symptoms, levels of IL-10, IFNγ and calcium.
Ashtari et al. (2015)	Humans. 18-55 years with RRMS. N: 89 Treatment time: 12 weeks.	Groups: 1- 50.000 IU every five days. 2- Placebo.	Groups: 1: ↑ 25(OH)D. Positive correlation between vitamin D intake and IL-10. No differences were observed in serum calcium levels for both groups.
Sotirchos et al. (2016)	Humans. 18-55 years with RRMS. N: 40 Treatment time: 6 months.	Groups: 1- 10.000 IU/day. 2- 400 IU/day. + 400 IU/day of vitamin D3 + 1000mg of calcium.	Groups: 1- ↑ 25 (OH) D, ↓ ratio of effector memory CD4 + T cells, ↑ central and naive memory CD4 + T cells. ↓ Production of IL-17 by CD4 + T lymphocytes, a mechanism by which vitamin D3 can show its therapeutic role in MS. 2- No changes were observed.
Holmoy et al. (2017)	Humans. 18-50 years with RRMS. N: 68 Treatment time: 96 weeks.	Groups: 1- 20.000 IU/week. 2- Placebo. + 500 mg/day of calcium.	Groups: 1- ↑ 25(OH)D, ↓ PTH. Supplementation of high doses of vitamin D did not prevent loss of bone mass in subjects with non-deficient MS of this vitamin.

factor α, followed by Th17 with release of interleukin 17 that lead to the formation of CNS lesions, due to the strong inflammatory activity of these cytokines [11].

The lesions are classified as active or chronic. Active lesions are more present in the recurrent remitting phase and are responsible for the destruction of myelin, infiltration of macrophages and perivascular inflammation. Chronic lesions are more frequent in patients who are in advanced stages of the disease, leading to a greater demyelination, with axon reduction and loss of oligodendrocytes. The perceptions of these lesions are important to confirm the diagnosis of MS, according to a criterion established by McDonald [11].

The etiology of MS is not fully understood, but several studies have shown that lifestyle, genetic and environmental factors contribute to the risk of developing the disease. Among the environmental and lifestyle factors that increase their risk are exposure to tobacco smoke, organic solvents, Epstein-Barr virus infection, teenage obesity, low sun exposure and low levels of vitamin D [12].

Vitamin D and multiple sclerosis

Vitamin D can come from two different pathways. The main pathway is the endogenous synthesis of vitamin D3 (cholecalciferol) from its 7-dehydrocholesterol cutaneous precursor that depends on ultraviolet radiation, specifically sun exposure for process activation [13].

The second way of acquiring vitamin D3 and D2 is via the exogenous route from the diet, with the ingestion of foods of animal origin, mainly cold and deep water fish, such as salmon and tuna, fish liver oil, yolk as well as by the ingestion of fortified foods or vitamin supplements [14].

After their synthesis, cholecalciferol (D3) and ergosterol (D2) are bound to the vitamin D binding protein and transported to the liver, where they are hydroxylated by the cytochrome P450 superfamily CYP2R1 to give 25- hydroxyl vitamin D or calcidiol [13,15].

Vitamin D binding protein transports 25 (OH) D to the kidneys, where it undergoes the second hydroxylation step by the enzyme 1-α-hydroxylase, which converts 25 (OH) D to 1,25 dihydroxy vitamin D also called calcitriol, metabolically active molecule of vitamin D [13,16].

The discovery of the specific nuclear receptor of vitamin D in almost all human cells, especially in lymphocytes, has increased the interest for its extra skeletal effect, especially in the immune system, because deficiency of this vitamin is associated not only with bone health but with autoimmune diseases, especially MS [16].

Vitamin D in the immune system has the main function of lowering inflammatory cytokines such as IL-2 and interferon gamma, modulating the differentiation and function of antigen-presenting cells, thereby reducing the activation of auto-reactive T cells. It has an effect on the stimulation of interleukin 4 production by Th2 cells, in the increase of regulatory T cells, especially interleukin-10 (IL-10), important for inhibiting inflammation and decreasing the production of interleukin 17 (IL-17) Th17. These immunomodulatory activities can serve as an endogenous brake to the inflammation present in MS [6,15,17].

One of the immunoregulatory effects of vitamin D that has been shown to be relevant for the pathology of MS is the presence of 1-α-hydroxylase activity, which is responsible for the conversion of vitamin D into its active form in neurons and microglial cells and the presence of a central receptor of vitamin D in the central nervous

system, through which this vitamin can exert local, paracrine and autocrine effects [15].

Vitamin D deficiency has been associated with an increased risk of developing MS, relapses, and increased disease activity. In the present study, it was found that the higher levels of 25 (OH) D are less likely to develop new brain lesions and lower disease activity rates [18].

According to the study by Scott et al. [19] who compared the rate of exacerbations in RRMS patients before and after starting treatment with Natalizumab (a drug used for the treatment of MS), found that both before and after starting treatment with the medication, patients with vitamin D (<20 ng/ml) had higher rates of exacerbations than patients with adequate levels of this vitamin.

Wawrzyniak et al. [20] showed a higher frequency of relapse in patients with RRMS who were in a 25 (OH) D deficiency state (<20 ng/ml) compared to patients with normal levels of 25 (OH) D (>30 ng/ ml).

Other studies have shown that vitamin D status influences the activity of the disease. In the relapse phase of MS, marked by the resurgence of symptoms accompanied by an increase in disease activity, lower vitamin levels were found compared to the remission phase, in which there were no signs of the disease, thus correlating low levels of vitamin D to the course of the disease, with increased symptoms, and which higher levels may exert protective effects and decrease the risk of relapse in individuals with the disease [21].

In MS, cognitive impairment is a common symptom and affects the quality of life of patients. Low levels of 25 (OH) D in serum have been related to a negative effect on cognitive performance. According to Darwish et al, [22] patients with sufficient levels of 25 (OH) D (> 35 ng/ml) presented better cognitive performance than patients with low levels (<25ng/ml).

The optimal serum vitamin D concentrations are quite controversial, with a disagreement between the guidelines. The Scientific Advisory Committee on Nutrition recommends 30nmol/l (12ng/ml) as an adequate value to avoid serious deficiency, while the Institute of Medicine (IOM) recommends the level of 50 nmol/l (20ng/ml). The Endocrine Society indicates 75 nmol/l (30 ng/ml) as an adequate vitamin D level compared to the Vitamin D Council, which indicates levels greater than 100 nmol / day (> 40 ng/ml) [23].

Recommendations for adequate levels of vitamin D are based on the maintenance of calcium homeostasis and bone health, relative to the immune system, it is not known which levels are adequate to increase their effects on immunity and what levels of this metabolite in the blood would be prevention of MS [23].

The toxicity of vitamin D from dietary sources or exposure to sunlight is quite unusual and may occur in cases of high dose supplementation. Its toxicity can be severe and even lethal in individuals repeatedly exposed to high doses, which can cause renal calculi, ectopic soft tissue and vascular calcifications, and lead to death. No consensus has yet been reached on which dosages may be toxic or which safe upper limit for this vitamin [23,24]. According to the IOM the maximum safety dose of vitamin D is 4000 IU/day for healthy adults. No adverse effects were found at doses above this value used for supplementation in MS patients in the reviewed articles [25].

According to the experiment of Kimball et al,. [24] no case of hypercalcemia or hypercalciuria was observed in patients with MS during a 28-week protocol using increasing doses of vitamin D3. Doses ranged from 28,000 to 280,000 IU/week. These doses had no toxicity effect during the 28 weeks of the assay. These data suggest that the dosages commonly used in MS are non-toxic and safe to use.

Effects and mechanisms of action of Vitamin D

Several studies, both in animal models and in humans, have been carried out using vitamin D supplementation in MS, presenting several results. It is difficult to compare and interpret these results, since they use different dosages and treatment times. Table 1 shows the main studies with the use of vitamin D in MS.

Guo et al,. [26] in an animal model of Experimental Allergic Encephalomyelitis (model for the study of MS) showed that vitamin D supplementation (100ng/day) for 4 weeks increased the proliferation of neural stem cells, which help repair the neural damage by demyelination of the axon, decreased lesions, avoided the development of the stages of MS and presented improvements in the clinical symptoms of the disease, since the neural stem cells have the capacity to multiply and to renew itself, triggering important role in the recovery of the injured tissues.

Golan et al,. [27] tested high-dose (4,370 IU/day) and low-dose (800 IU/day) vitamin D supplementation for one year in both sexes with RRMS treated IFN β. The dose of 4,370 IU/day was effective in increasing the serum 25 (OH) D level and lowering the serum levels of parathyroid hormone, which may be beneficial in the prevention of osteoporosis, a common event in MS patients. This dosage did not present significant results in relation to IL-17 levels in these patients. Regarding the dose of 800 IU/day, an increase of IL-17 in this group was found. Based on these results, the study hypothesized that high doses of vitamin D could lead to IL-17 reduction.

Ashtari et al. [28] demonstrated that vitamin D supplementation (50,000 IU/day) in patients with RRMS for 12 weeks increased serum levels of 25 (OH) D and showed a positive correlation with serum levels of interleukin 10 (IL-10) a regulatory cytokine that plays an anti-inflammatory response. The regulatory effect of IL-10 on the immune system is impaired in patients with MS, so the consumption of vitamin D may be beneficial in reducing inflammation in these patients.

Sotichos et al. [29] evaluated vitamin D3 supplementation at doses of 10,000 IU and 400 IU/day in RRMS patients and found that vitamin D3 supplementation at a dose of 10,000 IU/day increased serum 25 (OH) D levels and decreased the production of IL-17 by serum CD4 + T lymphocytes, demonstrating an important mechanism of vitamin D in the pathogenesis of MS, since the expression of IL-17 is increased in blood and lesions during clinical exacerbations of the disease.

According to the immunomodulatory functions found in the literature, vitamin D in MS can act to control inflammation by regulating the immune system, decreasing the production of proinflammatory cytokines, and presenting a role of relevance in MS, since in the disease there is deregulation of the immune system, causing an inflammatory state in the affected patients.

Conclusion

Studies have shown that vitamin D may be associated with immunological benefits, playing a role in regulating the immune system and inflammation, acting on the recovery of CNS cells, reducing relapse rates and brain lesions, and establishing importance in the clinical course of MS. However, there is no consensus regarding the dosage of supplementation that is safe and effective to obtain positive results in patients with the disease. There is also no definition that vitamin D supplementation can prevent MS. More works is needed to establish recommendations for this population.

However, it is important to monitor the serum levels of this vitamin in MS patients, providing better guidance on sun exposure, dietary sources of vitamin D, supplementation, and nutritional education strategies aimed at maintaining adequate serum levels, due to the risk of deficiency in this population.

References

1. Rinaldi AO, Sanseverino I, Purificato C, Cortese A, Mechelli R, Francisci S, et al. Increased circulating levels of vitamin D binding protein in MS patients. Toxins. 2015; 7: 129-137.
2. MSIF. Federação Internacional de Esclerose Múltipla. Atlas do Mapeamento da Esclerose Múltipla no Mundo 2018.
3. Ayuso T, Aznar P, Soriano L, Olaskoaga A, Roldán M, Otano M, et al. Vitamin D receptor gene is epigenetically altered and transcriptionally up-regulated in multiple sclerosis. PLoS One. 2017; 12: 0174726.
4. Marques CDL, Dantas AT, Fragoso TS, Duarte ALBP. A importância dos níveis de vitamina D nas doenças autoimunes. Rev Bras Reumatol. 2010; 50: 67-80.
5. Joshi N, Minz RW. Vitamin D Deficiency as a Risk Factor for Multiple Sclerosis : Evidence from Epidemiology, Animal Model, Genetics, and Immunology. Austin J Mult Scler & Neuroimmunol. 2015; 2: 1016.
6. Goldsmith JR. Vitamin D as an Immunomodulator: Risks with Deficiencies and Benefits of Supplementation. Healthcare. 2015; 3: 219-232.
7. Papaléo RM, Teixeira MJ, Brioschi ML. Infrared thermography to evaluate pain in a multiple sclerosis patient. Case report. Rev dor. 2016; 17: 232-235.
8. Silva VM, Silva DF. Esclerose Múltipla: Imunopatologia, Diagnóstico e Tratamento – Artigo De Revisão. Interfaces Científicas - Saúde e Ambiente. 2014; 2: 81-90.
9. ABEM. São Paulo: Associação Brasileira de Esclerose Múltipla.
10. Errante PR, Ferraz RRN, Rodrigues FSM. Esclerose Múltipla: Tratamento Farmacológico e Revisão De Literatura. UNILUS Ensino e Pesquisa. 2016; 13: 105-117.
11. Siqueira MK, Pires L. Processo epigenéticos envolvidos na fisiopatologia da esclerose múltipla com ênfase na função dos miRNAs. Semina: Ciências Biológicas e da Saúde. 2016; 37: 125-136.
12. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. 2017; 13: 25-36.
13. Castro LCG. O sistema endocrinológico vitamina D. Arq Bras Endocrinol Metab. 2011; 55: 566-575.
14. Mpandzou G, Ait Ben Haddou E, Regragui W, Benomar A, Yahyaoui M. Vitamin D deficiency and its role in neurological conditions: A review. Rev Neurol. 2016; 172: 109-122.
15. Dörr J, Döring A, Paul F. Can we prevent or treat multiple sclerosis by individualized vitamin D supply? EPMA J. 2013; 4.
16. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. Front Immunol. 2017; 7: 697.
17. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev. 2016; 96: 365-408.
18. Fitzgerald KC, Munger KL, Kochert K, Arnason BG, Comi G, Cook S, et al. Association of Vitamin D Levels With Multiple Sclerosis Activity and Progression in Patients Receiving Interferon Beta-1b. JAMA Neurol. 2015; 72: 1458-1465.
19. Scott TF, Hackett CT, Dworek DC, Schramke CJ. Low vitamin D level is associated with higher relapse rate in natalizumab treated MS patients. J Neurol Sci. 2013; 330: 27-31.
20. Wawrzyniak, S, Mikolajewska E, Kuczko-Piekarska E, Niezgodzinska-Maciejek A, Goch A. Association of vitamin D status and clinical and radiological outcomes in a treated MS population in Poland. Brain Behav. 2017; 7: e00609.
21. Luque-Córdoba D, Luque de Castro MD. Metabolomics: A potential way to know the role of vitamin D on multiple sclerosis. J Pharm Biomed Anal. 2017; 136: 22-31.
22. Darwish H, Haddad R, Osman S, Ghassan S, Yamout B, Tamim H et al. Effect of Vitamin D Replacement on Cognition in Multiple Sclerosis Patients. Sci Rep. 2017; 7: 45926.
23. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nat Rev Endocrinol. 2017; 13: 466-479.
24. Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of vitamin D3 in adults with multiple sclerosis. Am J Clin Nutr. 2007; 86: 645-651.
25. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US). 2011; 10: 17226/13050.
26. Gu SG, Wang CJ, Zhao G, Li GY. Role of vitamin D in regulating the neural stem cells of mouse model with multiple sclerosis. Eur Rev Med Pharmacol Sci. 2015; 19: 4004-4011.
27. Golan D, Halhal B, Glass-Marmor L, Staun-Ram E, Rozenberg O, Lavi I et al. 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.
28. Ashtari F, Toghianifar N, Zarkesh-Esfahani SH, Mansourian M. Short-term effect of high-dose vitamin D on the level of interleukin 10 in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Neuroimmunomodulation. 2015; 22: 400-404.
29. Sotirchos ES, Bhargava P, Eckstein C, Van Haren K, Baynes M, Ntranos A, et al. Safety and immunologic effects of high- vs low-dose cholecalciferol in multiple sclerosis. Neurology. 2016; 86: 382-390.
30. Holmøy T, Lindstrom JC, Eriksen EF, Steffensen LH, Kampman MT. High dose vitamin D supplementation does not affect biochemical bone markers in multiple sclerosis - a randomized controlled trial. BMC Neurol. 2017; 17: 67.