Vitamin D3 Supplementation: An Option Associated with The Treatment of Multiple Sclerosis: A Systematic Review and Meta-Analysis

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ABSTRACT

Multiple sclerosis (MS) is a chronic complex neurodegenerative disease. A systematic review and meta-analysis were conducted on observational studies and analytics on impact of Vitamin D supplementation in patients with Multiple Sclerosis. In our research, a total of 457 articles were selected and identified for analysis. This systematic review article and meta-analysis, which included evidence from randomized controlled trials conducted with patients with multiple sclerosis, revealed that Vitamin D3 supplementation is effective as an option associated with the treatment of this disease, and that it also has a diffuse protective role against various remission outbreaks in the health. Doses (50,000 IU/week) are appropriate to restore neuroimmunological parameters when used within 12 weeks.

Keywords: Vitamin D3, Multiple Sclerosis, Neurogenesis, Supplementation, deficiency.

1.0 INTRODUCTION

Multiple sclerosis (MS) is a chronic complex neurodegenerative disease. MS presents destruction of the myelin which develops alterations in the conduction of the nervous impulse with degenerative behavior to which it is often related to autoimmune characteristics [1].

In Brazil, MS has a prevalence rate of 15 cases per 100.000 inhabitants [3-4], on the other hand, in countries as United States of America, Russia and Canada the prevalence increases by around 50-200 cases per 100.000 inhabitants [1-4]. This disease occurs mainly in the adult population from 18 to 55 years [4]. However, it is currently being diagnosed in children and adolescents [3-4]. Women have a higher prevalence [19], around three cases for every two cases for men [04]. It is a disease that impacts on work [01], family, as well as social and economic issues [24]. In Brazil, MS is considered as severe and rare [04]

and its treatment are performed in the Unified Health System (Ministry of Health), which is considered of high cost to the Brazilian government [3]. In Brazil, in some cities such as São Paulo (03), Santos and Campo Grande, the rates of people with MS reach around 15 cases per 100,000 inhabitants [04]. Currently, treatment with Vitamin D3 can be considered as usual for disease [3], although other studies are ongoing [11].

Vitamin D3 is a key hormone for calcium homeostasis, development of a healthy skeleton [16], immune, cardiac and neurological system [18]. Vitamin D is taken orally and after the ingestion process is transported to the liver. In the liver, the hydroxylation of Carbon 25 occurs and thus, it will result in the production of 25-hydroxyvitamin D [25 (OH) D] and thus, this molecular compound is the main circulating vitamin formula used by the body. It is worth mentioning that the mediation of hydroxylation in the liver occurs by several enzymes known as 25-hydroxylase, the most important in the body is CYP2R1 type 1 [01]. And the Vitamin D3 in the immune system is a potent antiproliferative hormone capable of inhibiting proliferation and stimulating cell differentiation [20]. According to studies in neurosciences using Wistar rats [22], Vitamin D3 presents stimulatory actions of modulating neural growth factor and brain development [25].

Vitamin D receptors (VDRs) can be found in some tissues of the body [24], but other actions unrelated to mineral metabolism have been highlighted [23]. As several human brain cells specifically express 1-hydroxylase and VDR [26], some studies [30] claim that vitamin D3 exerts regulatory actions on brain development and functions [30]. However, there is a lack of scientific support for vitamin D3 to be used as adjuvant therapy in the standard treatment of multiple sclerosis [22].

Experimental studies with humans and animals have correlated the mechanism of involvement of Vitamin D3 in MS with differentiated immune modulation of the central nervous system (CNS) [26]. However, Vitamin D3 may interfere with the pathophysiology of Multiple Sclerosis [21], affecting inflamed and healthy tissue [24]. This interference is due to the binding protein of Vitamin D3 (DBP) and Vitamin D receptor (VDR), as well as the presence of metabolic enzymes (CYP27B1) [30] which are present in the central nervous system [28].

VDR and CYP27B1 are expressed in a cellular variety which includes the invading neurons, glial cells and lymphocytes [30]. According to experimental studies, Vitamin D3 plays a modulating role in several pathophysiological processes of Multiple Sclerosis [30], which includes the inflammatory process, demyelination, axonal damage and remyelination [28]. Variations in the risks and benefits to the use of Vitamin D3 have been recorded in relation to the dosage [22]. There is a consensus that the daily intake of 10,000 units (100 ng/ ml in serum) of Vitamin D3 per patient does not present toxic effects in the body [30], which would not cause adverse health effects [24].In the last decades, neuroscience research has revealed conflicting data on the neurological benefits of Vitamin D3, as well as the amount of vitamin D ingested and the time required for patient recovery [22]. The objective of this study was to perform a systematic review and a metanalysis to assess the effectiveness of the impact of Vitamin D3 supplementation on the health-disease process in Multiple Sclerosis in the central nervous system through immunological studies. This research was registered and authorized by the Center of Journals and Disclosure - PROSPERO with the code: CRD42019121732.

2.0 METHODS

2.1 – Protocol - This Systematic Review and meta-analysis was authorized for publication in the "International Prospective Register of Systematic Reviews" with the following code: CRD42019121732.

2.2 – Eligibility Criteria - The eligible studies included in this systematic review and meta-analysis were articles published in peer-reviewed scientific journals; study with randomized, prospective and longitudinal trials; studies that included patients who were supplemented with vitamin D3 at varying doses (4.000 IU –50.000 IU); patients diagnosed with multiple sclerosis and hypovitaminosis D; patients aged ≥ 18 years, sample size ≥ 20 patients, studies that considered a control group and published from 2011 to 2018.

2.3 – Information Sources - The research was carried out in the bibliographic databases Cochrane Library, Medline, US National Library of Medicine and the National Institute Health (PubMed), Latin American and Caribbean Literature in Health Sciences (Lilacs), Scopus, Web of Science and Biblioteca Ciêntifica Online (SCIELO).

2.4 –Search Strategy - This research was carried out from March 2018 to November 2018. The research was conducted in the English and Portuguese languages, and the following terms were used [09]: "Vitamin D3" AND ("Vitamin D3 Supplementation" OR "Vitamin D3 deficiency" AND "Epidemiology OR Vitamin ("OR"), and "Multiple Sclerosis" AND (Adult OR Neurogenesis). Duplicate studies were excluded by two researchers (EMR and MDDL) who selected the relevant titles and abstracts to include them in this study.

2.5 - Selection of Data Collection Studies - The studies were independently reviewed by four authors and the data retrieved (EMR, GGF, MDdL, FJMdR and JECG). Duplicate studies were analyzed according to the previous result and the crossing of included data in order to rule out the risk of bias investigation of the residual effects of the specific methods used. An instrument for data extraction was developed in order to collect the relevant information from the studies used, which included the following information: First author, year of publication, Country, number of participants, published journal, dosage used for vitamin supplementation D3 (4.000 IU – 50.000 IU) and study analysis time. When necessary, contact was made with authors in order to clarify doubts regarding the published data.

2.6 – Quality Assessment - In this systematic review and meta-analysis, studies that performed the analysis of results with treatment group and control group were included without systematic differences between the groups analyzed. The dose administered was considered in the Vitamin D supplementation process in a randomized way to the method used by the study (4.000 IU – 50.000 IU), being considered a high quality study indicator. Studies that did not meet quality control according to the established criteria were not included in this systematic review and meta-analysis. Through the instrument "Down and Black (1998)", a review of the follow-up procedures in the process of oral vitamin D supplementation was carried

out in a randomized way in order to assess whether there was any performance bias in the included study. And it was considered the blinding of the participants in the groups to perform the heterogeneity assessment of the included studies, because these procedures are viable in clinical and randomized research.

2.6 – Data Analysis - The meta-analysis was performed using the random effects model for each outcome variable (vitamin D3 supplementation, clinical improvement and neural regeneration) using the Review Manager 5.3 software. The difference from the standardized average was obtained from the number of participants collected in each selected article and who supplemented vitamin D3. The calculations were performed considering a 95% confidence interval (CI). Inconsistency (I^2) assessed the heterogeneity among the included studies [10]. Heterogeneity was quantified as low, moderate and high, with upper limits of 25%, 50% and 75% [10]. The mean standard deviation in this meta-analysis was obtained using the Software Review Menager 5.3, considering P <0.05 as statistically significant and P> 0.05 as non-significant [10]. The analyzes obtained from the studies included in this review on the impact of vitamin D3 supplementation and the intervention period are identified according to Table 1.

2.7 – Judgment of Clinical Improvement in Signs and Symptoms and Immune Cellular Changes - For the judgment of clinical improvement in signs and symptoms, McDonald's Criteria were established, and an improvement in clinical evolution was established with signs and symptoms of improvement in clinical aspects (Fatigue, sensitive paresthesias, visual, motor, ataxia, sphincter, cognitive and mental) associated with CSF analysis with the search for specific biomarkers. The immunological cellular aspects, on the other hand, established a population analysis in the articles inserted in the T lymphocyte cell population which produced a pattern of anti-inflammatory cytokines (IL-04 and IL-05) in patients and pathogens (CD4 + cells and TH1 autoreactives).

TABLE 1 - Included studies on vitamin D supplementation in patients with multiple sclerosis and intervention period (weeks) according to the dosage administered.

Authors	Dosage of Vitamin D3(weekly dose)	Intervention period(weeks)	Year
Holmoyetal	20.000 UI	98	2017
Rolf et al	14.000UI	48	2018
Rolf et al (b)	4.000UI	16	2018
Smoldersetal	7.000UI	96	2011
Rolf et al	7.000 UI	48	2017
Kovenetal	10.000UI	16	2013
Coccoetal	10.000UI	98	2012
Slavovetal	10.000UI	12	2015
Chaudhurietal	7.000UI	180	2018
Rabeahetal	7.000UI	96	2015
Kouchakietal	50.000UI	12	2018
Hashemietal	50.000 UI	12	2018

3.0 RESULTS AND DISCUSSION

3.1 Clinical characterization of studies

Clinical characterization of studies

In our research, a total of 457 articles were selected and identified for analysis. However, 445 studies were excluded because they met the following criteria: insignificant studies, that is, they do not involve the subject of this research (n = 112), studies with a sample design of less than 20 patients (n = 105), articles whose sample population it was pediatric (n = 85), duplicate articles (n = 75), studies that did not characterize multiple sclerosis with vitamin D3 deficiency (n = 60) and studies without control group analysis (n = 8).

On the other hand, the experimental and randomized clinical studies included in our review totaled 12 articles published in English [19-30].

Of the total articles, only 5 were published in 2018 [19-24], 2 articles were published in 2017 [28, 29] and 5 articles were published from 2011 to 2015 [26-30]. It was verified from the selected studies that the diagnosis of multiple sclerosis was made by imaging methods, which totaled 48.8% of the patients (n = 574) [24-30] (see Table 2).

It was found that all patients received vitamin D3 supplementation with adjuvant therapy with Interferon Beta-1a [30].

The prevalence of hypovitaminosis D3 in the patients analyzed in the twelve studies selected for analysis was 79.8% (n = 458) (TABLE 2).

In the studies evaluated, 88% of patients with multiple sclerosis had a positive response after 12 weeks of vitamin D3 oral supplementation and at a dose equivalent to 50.000 units/week (Figure 03).

Regarding the intervention period with vitamin D3, the benefit of oral supplementation occurred after a frequency of supplementation greater than 12 weeks (Table 1). Seven studies [28-30] had fewer than 50 patients who had no negative implications for the power of the analysis performed by this meta-analysis. Thus, the twelve articles [19-30] were included, totaling 574 patients with multiple sclerosis (TABLE 2).

TABLE 2 - Prevalence of Multiple Sclerosis and Hypovitaminosis D3 in the sample analyzed according to the included studies.

Studies	Adults with EM and hypovitaminosis D3/population Total	Incidence of MS and Hypovitaminosis D3 in Population Sampling.
Holmoyetal	35/48	72,9%
Rolf et al	35/53	66,0%
Rolf et al (b)	25/46	54,3%
Smoldersetal	174/348	50,0%
Rolf et al	30/53	56,6%
Kovenetal	25/30	83,3%
Coccoetal	44/154	28,5%
Slavovetal	23/53	43,3%
Chaudhurietal	56/112	50,0%
Rabeahetal	50/100	50,0%
Kouchakietal	27/53	50,9%
Hashemietal	50//75	66,6%

3.2 Analysis of risk of bias in the included studies

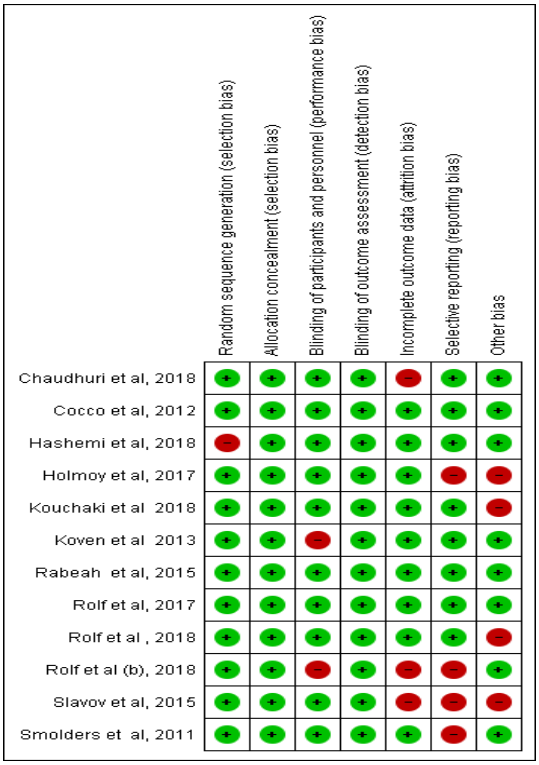
According to Figure 1, it was found that only one study included in this systematic review did not provide adequate descriptions of its methodology used, which did not allow the generation of the random sequence (selection bias) [28].

Ten of the articles included presented a quality bias carried out according to the methodology used in the Refs. [19-24] (FIGURE 1).

Regarding the risk of Cochrane bias, three articles were identified as an obscure risk [19-25], and only one article was considered high risk due to the high dropout rate in the experimental period (FIGURE 1) [30].

The occurrence was observed mainly in the domains: incomplete results, selective reports and other variables (FIGURE 1). It is concluded that, due to the adherence to the quality criteria and the design of the strategic study, the biases in the systematic review process and in the meta-analysis were minimized (FIGURE 1). Some articles included (70%) in this review were from high-income countries [25-30] and, in combination with vitamin D3 supplementation used cholecalciferol (Vigantol) in different doses [19-30].

Figure 1 - Summary of risk of bias assessment.



3.3 Benefits of Vitamin D Use in Multiple Sclerosis and its Anti-Inflammatory Action through Oral Supplementation

Figure 03 - Vitamin D3 and the risk of not presenting clinical improvement in symptoms in multiple sclerosis patients (compared to the control group).

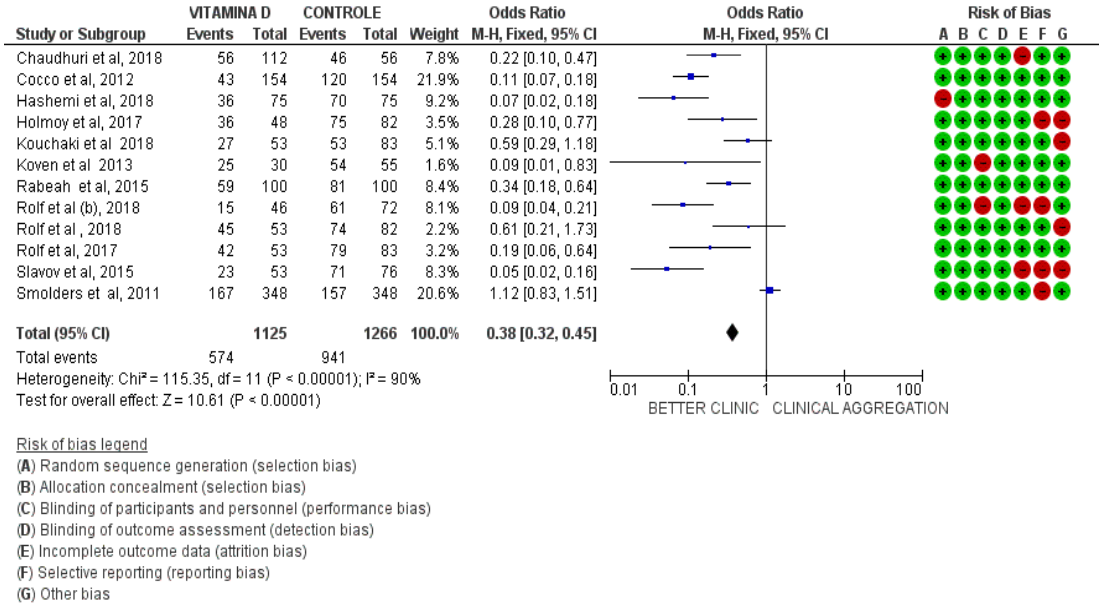


Figure 3 shows a decrease in recurrent episodes of recurrent remission in multiple sclerosis [24-30], totaling 1266 adults evaluated in multiple sclerosis studies (90%), where oral vitamin D

supplementation equivalent to 50.000 IU per week reduced complications related to the disease process ($p < 0.00001$) [25-28].

Vitamin D3 is recognized for its immunomodulatory function and has emerged as an excellent determinant in the etiopathogenesis of multiple sclerosis, considered a chronic and immunomediated disease (Graph 1) [25-30]. In addition, high doses of vitamin D3 reduce CD4 + T cell activation, reporting from direct human data that vitamin D3 may influence cell-mediated immunity [28].

These included studies performed oral vitamin D3 supplementation at different dosages, there were significant differences in the influence of cell-mediated immunity by improving clinical signs with a decrease in recurrent outbreaks (95% CI = 0.38 (0.32 - 0, 45)) [24-30], a significant reduction in IgG levels occurred [21-30], since stimulation of this vitamin D3 receptor causes inhibition of inflammatory cytokines and after 12 weeks of vitamin supplementation D3. In MS patients it is possible to observe and identify the mechanism by which vitamin D3 affects the response of anti-EBNA-1 antibody [22-29]. In addition, there is a significant increase in TCD4 + cells, which correlate with the increase in IL-2RA protein due to vitamin D3 supplementation [23-30].

It should be noted that the use of immunomodulatory treatment does not interfere with the effect of vitamin D3 markers [29], because vitamin D3 in the selected studies was used as adjunctive interferon beta-1a therapy in multiple sclerosis patients [41]. It was possible to detect by magnetic resonance imaging that vitamin D3 associated with Intereferon-Beta-1a treatment significantly reduced the activity of multiple sclerosis [28-30], which was verified by comparing a control group with patients who received only interferon-beta-1a alone [22-30].

The serum analyzes in 12 studies [22-29] were performed using high performance liquid chromatography (HPLC) followed by gold standard mass spectrometry for the analysis of vitamin D3 25-OH serum levels [23].

Blood levels below 30 ng / ml vitamin D should be corrected in patients with multiple sclerosis at any stage to prevent worsening of the disease ($I2 = 90\%$) [25-30]. In the studies analyzed [22-27], it was found that the multiple subtypes of multiple sclerosis showed different prevalence of vitamin D3 deficiency [22-26], since vitamin D3 deficiency is one of the environmental factors associated with worsening of the disease ($p <0.00001$) [22-25].

In fact, high-dose vitamin D3 supplementation in 12-week patients has shown efficacy compared with control groups [28-30]. Treated patients had less remission of outbreaks; On the other hand, a higher proportion of patients had better scale scores, such as the Expanded Disability Statuts Scale [20-26].

3.4 Vitamin D supplementation has benefits in inflammatory biomarkers in preventing neuroimune changes in the central nervous system.

According to the results of Graph 1, it can be seen that as a result of the gradual increase in the dosage of vitamin D3 supplementation, there was a decrease in the inflammatory process in the development of multiple sclerosis in an intervention period of 12 weeks just as there was an increase in neuroimmunological and protective cells of the central nervous system [20-30].

The randomized trials selected in this systematic review and meta-analysis have shown that Vitamin D3 regulates TCD4+ cell responses, promotes T-helper 2 (Th2) production [19-24] and eliminates

T1 (Th1) helper cell production in turn limits Th1-mediated inflammatory responses and tissue damage, while increasing anti-Th2 cell mediation relative to inflammatory responses [20-22].

In fact, the studies of ref. [19-21], when evaluating the TCD4 + cell, demonstrated a decrease in Th1 (interferon - IFN-γ) cytokines [21-24] and increased production of Th2 cytokines (IL-04, IL-05 and IL-10) [22-27] after vitamin D3 supplementation [27-29]. It is emphasized in this study that TCD4+ cells have the ability to convert inactive 25(OH)D to active 1,25-dihydroxy vitamin D (1,25(OH)2D) [24-28].

MS patients with vitamin D3 deficiency (25(OH)D) stated that 12 weeks of oral vitamin D3 supplementation at a dose equivalent to 50.000 units per week showed an increase in IL-10 production and a decrease in Th17 cell frequency in parallel with expected increases in serum 25 (OH) D [28-29].

On the other hand, regarding clinical response (Graph 2 and Graph 3) with altered immunological symptoms, vitamin D3 has an additional effect on T cells [24-29], since cytokines tend to improve or increase the pro- inflammation, especially in patients with multiple sclerosis [24-28].

Vitamin D3 modulates the response of major proinflammatory cytokines such as IL-04, IL-05, IL-06, IL-10, IF-10, IFN-γ and TNF-α [22-25]. Thus, this systematic review and meta-analysis confirmed the sensitivity of these inflammatory biomarkers in the prediction of neuroimmunological changes mainly in the central nervous system [22-29], and highlights in graph 2 that there is an increase in serum 25 (OH) D with selective decrease of the groups. T cells typical of multiple sclerosis [29-30], which can only occur due to protective neural stimulation in the process of progression of proinflammatory lesions in the central nervous system [28-30]. By consensus, this study showed that there is an association between immune deficiency and low vitamin D3. [27-29] (chart 3).

In Graph 2, during the 12-week study period, according to the selected articles [28-30], it can be seen that vitamin D3 supplementation has beneficial effects on an acute phase protein that is synthesized by the liver in response to cytokines, which has the functionality to reflect systemic active inflammation, in this case, C-reactive protein (CRP) and this process occurs due to the total antioxidant capacity of blood biomarkers of oxidative stress. Generally, myelinated brain damage occurs when there is an induction of oligodendrocyte apoptosis through increased IFN-gamma production, which is related to fluctuation of anti-myelin reactivity that occurs due to vitamin D3 deficiency within 12 weeks after supplementation of this vitamin, as observed in Graph 2 and Graph 3 [28-29].

In view of the above evidence, the protective role of vitamin D3 in the treatment of MS is biologically plausible [28] since 1,25 dihydroxyvitamin D3 is present in various immune system cells [24] such as macrophages, activated T cells and B, IL-04, IL-06, IL-08, IL-10 [24-29] and myelin specific [30]. Thus, there is a consensus that the increase in immune system cells occurs by stimulating receptors in the production of inflammatory cytokines [30].

It is noteworthy that 80% (n = 09) of the articles [26-29] selected in this systematic review and meta-analysis highlighted the increased production of regulatory T cells due to vitamin D3 supplementation, characterized by the reduction of IL-2 in mRNA levels in peripheral blood mononuclear cells, promoting the development of regulatory T cells [26-28].

In other words, vitamin D3 supplementation in the health and disease process in sclerosis has a protective role against various remission outbreaks [23-27], because there is a significant reduction in the

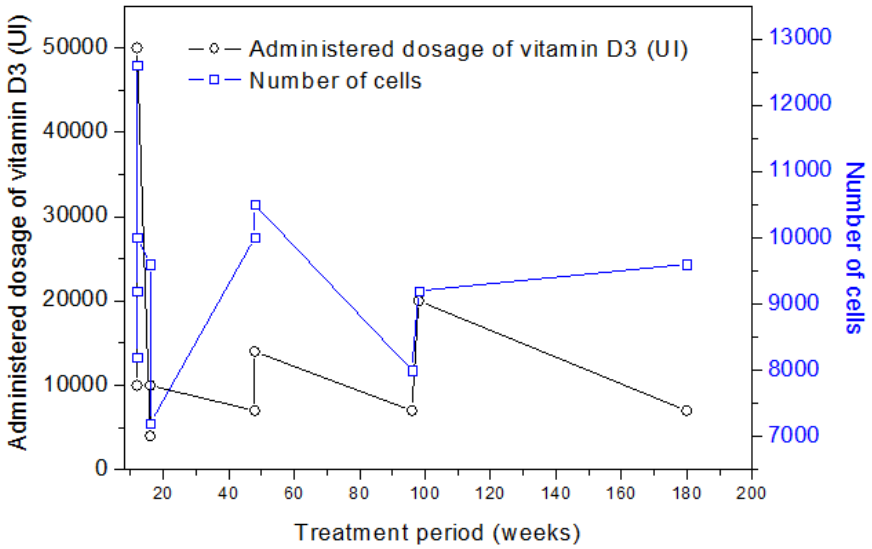
neurofilaments immunopositive axons evidenced in the vitamin D3 supplemented groups when compared to the control group (Figure 3) [27-29].

It is also highlighted in this systematic review and meta-analysis study that high doses of vitamin D3 supplementation influence the axonal regeneration process according to Graph 1 [24-29]. In fact, analyzing the information in Graph 2, it can be seen that the twelve articles analyzed in this review were able to highlight that high-dose vitamin D3 supplementation (50,000 units / week) plays an effective role in immunomodulatory treatment for 12 weeks [22-30] due to reduced inflammatory process in specific immune cells [23-30].

That is, the 12 studies demonstrated the beneficial effect of vitamin D3 supplementation and the intervention time through the chosen dosage [22-24] (Graph 2). In addition, ten articles [24-29] stated that vitamin D3 may influence the process of increased expression of calretinin and calcium binding proteins [29-30]. It should be noted that treatments for multiple sclerosis are immunosuppressive and affect immune function cells that reduce immune activity in the central nervous system [23-28].

The Graph 3 show the effect of Vitamin D3 on serum levels versus dosage administered in patients with multiple sclerosis. It is observed that in the range of 7000 to 20000 (UI) of vitamin D3 dosage there is a decrease in the serum level. However, for dosages above 20000 IU there is an increase in the serum level. This occurs because only supplements with a dosage ≥ 20,000 IU/week influence the concentration of ultra-sensitive C-reactive protein and thus increase blood biomarkers of oxidative stress [30].

Graph 1 – Dosage of Vitamin D supplemented per week according to cellular changes



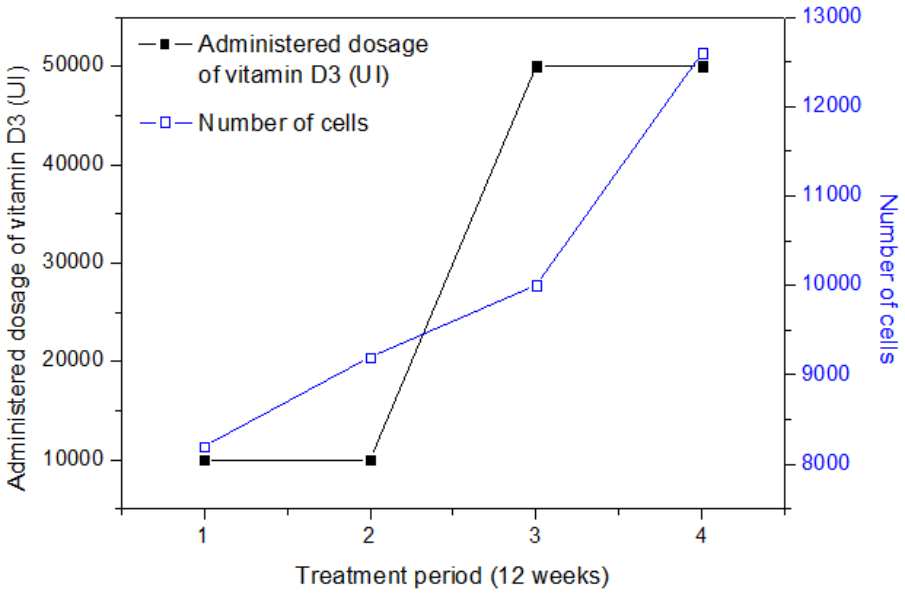
3.5 High dose Vitamin D (50.000 IU/week) in oral supplementation alters TCD4+ cell activation in the central nervous system through immune activity

According to Graph 1, there was no significant adverse event reported in patients assessed in the 12-week period [24-30]. From this review, it was observed that patients with multiple sclerosis treated [28] with doses of 50.000 units (week) of Vitamin D3 reached double the top physiological range without causing hypercalcemia (Graphic 3) [29].

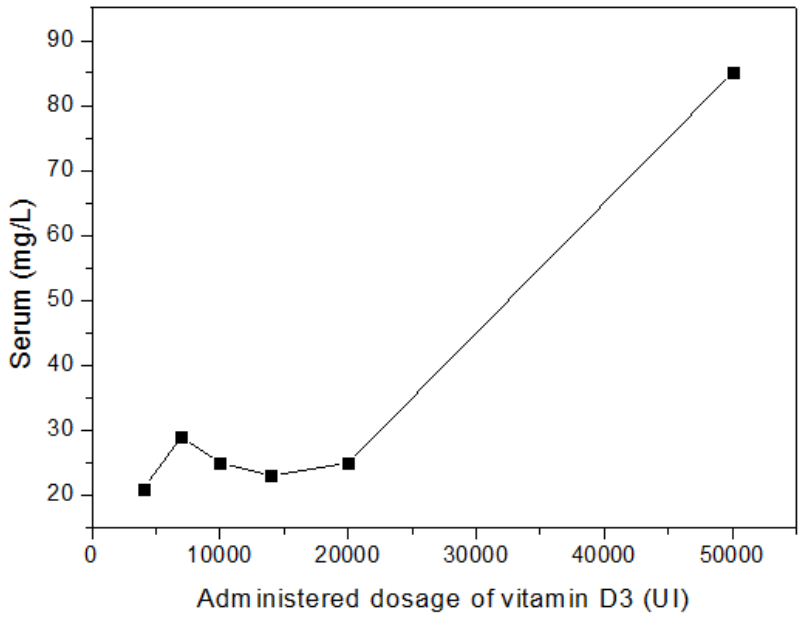
In fact, the results of our meta-analysis prove that Vitamin D3 supplementation promotes phagocytic cell response by stimulating phagocytosis, in Vitamin D3 increases the production of proinflammatory biomarkers such as tumor necrosis factor α (TNF-α) [27-29], interleukin-1β (IL-1β) and IL-6 [29-30].

Generally this process of immune regulation in IL-06 increases due to Vitamin D3 supplementation through anti-inflammatory and pro-inflammatory action which is proven by secretion of various cell types such as lymphocytes, macrophages and monocytes [27-30]. When analyzing vitamin D3 supplementation as a protective factor in patients with multiple sclerosis (Graph 2), the expression of the biomarker thyroxine hydroxylase promotes the bioavailability of some neurotransmitters [24-30], such as noradrenaline, dopamine, and adrenaline [24-29]. Only two articles showed that supplementation by 50.000 IU (week) of Vitamin D3 in the 12-week period influences the concentrations of ultra-sensitive C-reactive protein and increases blood biomarkers of oxidative stress [28-30].

Graph 2-Effect of Vitamin D3 on serum levels of pro-inflammatory and anti-inflammatory markers for 12 weeks in patients with multiple sclerosis.



Graph 03 - Effect of Vitamin D3 on serum levels as dosage administered in patients with multiple sclerosis for weeks.



The development process of this review includes characterization of each selected study [22-24], in which treatment with Vitamin D3 was assigned and participants were monitored daily for adherence and collection of biological material for the quantification of T cell. Different periods were established in each selected study [22-25].

Although the sample size selected in the studies analyzed in this systematic review and metanalysis were relatively small [30], it was found that there was a significant difference in T cells according to the studies in Ref. [26-29]. In fact, oral vitamin D3 supplementation can have an effect on TCD4 + cell activation in the immune system, which reflects on the central nervous system in multiple sclerosis patients with sufficient vitamin D3 supplementation [24-29].

Thus, we highlight that the high dose of Vitamin D3 (50.000 UI/weeks) decreases the activation of TCD4+ cells and provides direct scientific evidence of the role of Vitamin D3 in the central nervous system through immunological activity (Graph 03) [24-29].

In the case of a homogeneous metanalysis regarding the investigation of the best evidence for the intended focus of this research, it is found that the enzymes necessary for the synthesis of the active metabolite of vitamin D3 [22-24], 1,25-dihydroxycolecalciferol (1,25 (OH) 2D3) (27-29) as well as the vitamin D receptor (VDR) are present in the human brain at various sites, such as nucleus accumbens, temporal, orbital and cingulate cortex, tonsil, thalamus, neurons of the hippocampus and olfactory system.

It is important to note that for the survival of migration of developing neurons in these specific brain regions mentioned above there is regulation of neurotrophic signaling through glial cell-derived growth factor [32, 34].

Glial cells are modulators of dopaminergic neural development, survival and functionality [24-29] which are stimulated by Vitamin D3 supplementation. Therefore, according to the regulatory properties of neurotrophic factors, Vitamin D3 supplementation acts as a neuroprotective substance [28-29].

CONCLUSION

This systematic review article and meta-analysis, which included evidence from randomized controlled trials conducted with patients with multiple sclerosis, revealed that Vitamin D3 supplementation is effective as an option associated with the treatment of this disease, and that it also has a diffuse protective role against various remission outbreaks in the health. Doses (50,000 IU/week) are appropriate to restore neuroimmunological parameters when used within 12 weeks.

It is concluded that high doses of Vitamin D3 significantly contribute to the decrease of TCD4+ cells. This study of meta-analysis provides statistical evidence of Vitamin D3's central function on the central nervous system through immunological functionality.

These findings highlight the urgent need for further research and guidance for health professionals regarding the dose and duration of intervention to be administered in the treatment associated with multiple sclerosis.

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