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Effects of different doses of vitamin D supplementation on immune, inflammatory and oxidative stress parameters in the blood serum of patients with multiple sclerosis – a review

Wpływ suplementacji różnych dawek witaminy D na parametry immunologiczne, zapalne oraz parametry stresu oksydacyjnego w surowicy krwi pacjentów ze stwardnieniem rozsianym – praca poglądowa

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Abstract

Multiple sclerosis is a chronic inflammatory disease of the central nervous system associated with demyelination and neurodegeneration. In recent years, vitamin D has gained attention in the medical community following suggestions that there is a correlation between the level of serum vitamin D and the risk of multiple sclerosis, disease progression and activity. The aim of this article was to review recent literature describing the effects of vitamin D supplementation on the immune, inflammatory and oxidative stress parameters in patients with multiple sclerosis. In clinical trials, vitamin D doses ranging from 800 IU/day to 14,000 IU/day were tested. Researchers noticed significant differences in the range of action of vitamin D. However, the overview of studies failed to yield a definite answer concerning an effective dose of vitamin D. We concluded that there was no clear evidence for the impact of vitamin D supplementation on inflammatory parameters in multiple sclerosis patients, even though studies show consistently that the vitamin has an influence on the immune system and contributes to a reduction of pro-inflammatory cytokines. What is more, little is still known about the effects of vitamin D supplementation on oxidative stress, especially with regard to the potential effective dose. Consequently, more research is needed to gain a better understanding of this issue. There is increasing evidence on the significant role of vitamin D in patients with multiple sclerosis but there are as yet no global recommendations regarding the benefits of vitamin D supplementation and the supplementation dose. It is necessary to conduct further studies on the influence of vitamin D on disease activity due to its potential role as an add-on therapy in this group of patients or even as a preventative measure.

Keywords: multiple sclerosis, vitamin D, supplementation, oxidative stress, immune system, cytokines

Streszczenie

Stwardnienie rozsiane jest przewlekłą chorobą zapalną ośrodkowego układu nerwowego związaną z demielinizacją oraz procesami neurodegeneracyjnymi. W ostatnich latach coraz częściej zwraca się uwagę na suplementację witaminy D w związku z sugestiami, że istnieje korelacja między jej stężeniem w surowicy krwi a ryzykiem, progresją i aktywnością stwardnienia rozsianego. Celem artykułu jest przegląd najnowszej literatury opisującej wpływ suplementacji różnymi dawkami witaminy D na parametry immunologiczne, zapalne oraz stresu oksydacyjnego u pacjentów ze stwardnieniem rozsianym. W różnych badaniach klinicznych w grupie chorych ze stwardnieniem rozsianym testowano dawki z zakresu 800–14 000 IU dziennie i zauważono istotne różnice w zakresie działania witaminy D. Przegląd badań nie dał jednoznacznej odpowiedzi co do skutecznej dawki. Autorki niniejszej pracy doszły do wniosku, że nie ma jednoznacznych dowodów na wpływ suplementacji na parametry stanu zapalnego u pacjentów ze stwardnieniem rozsianym, chociaż badania są zgodne co do jej wpływu na układ odpornościowy i redukcję cytokin prozapalnych. Co więcej, wciąż niewiele wiadomo na temat wpływu suplementacji witaminy D

na parametry stresu oksydacyjnego, zwłaszcza biorąc pod uwagę potencjalną skuteczną dawkę, w związku z czym potrzebne są dalsze badania w tym zakresie. Istnieje coraz więcej dowodów na znaczącą rolę witaminy D u osób ze stwardnieniem rozsianym, mimo to nadal nie ma globalnych zaleceń dotyczących zasadności jej suplementacji oraz wielkości suplementowanej dawki. Konieczne jest prowadzenie dalszych badań nad wpływem na aktywność choroby ze względu na potencjalną rolę witaminy D jako terapii uzupełniającej w tej grupie pacjentów.

Słowa kluczowe: stwardnienie rozsiane, witamina D, stres oksydacyjny, układ immunologiczny, cytokiny

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune and progressive inflammatory disease associated with irreversible brain and spinal cord injury. The disease occurs mainly in young people, aged 20–40 years. There are over two million people affected by MS worldwide (Saini et al., 2016). The condition carries serious family, professional and social consequences both for patients and their caregivers.

Currently, MS is considered to be incurable. However, following improvements in pharmacotherapy, it is possible to slow down the progression of the disease and the occurrence of new symptoms. According to researchers, vitamin D (VitD) supplementation seems to be a promising therapeutic strategy in MS patients (Almeida et al., 2018; Berezowska et al., 2019; Jagannath et al., 2018).

The pathomechanism of MS is complex and involves a combination of immunological, genetic and environmental factors. The aetiopathogenesis is associated, among others, with a low VitD status, which affects approximately one billion people worldwide (Alharbi, 2015). It is well established that VitD is an immunomodulator (Gandhi et al., 2021; Yeh et al., 2020). Interestingly, it has also been noted that VitD supplementation may contribute to reducing disease activity (Holmøy and Torkildsen, 2016; Sintzel et al., 2018; Smolders et al., 2019) by lowering the parameters of oxidative stress (OS) in MS patients (Sepidarkish et al., 2019).

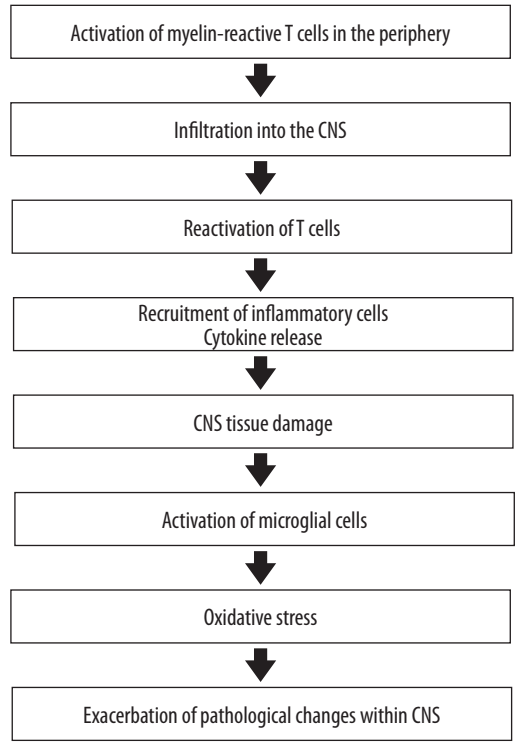
Given the incomplete knowledge of the impact of VitD on the pathogenesis of MS, the analysis of its supplementation, both in terms of the recommended dose and the target serum concentration, seems to be necessary in order to provide MS patients with comprehensive medical care.

In this review, we discuss the influence of VitD supplementation on the immune system, inflammation, and OS parameters in MS patients, focusing on different VitD doses. This literature review summarises the current state of research and is an introduction to a clinical trial comparing the effects of high- and low-dose VitD supplementation in MS patients on inflammatory, immune and OS parameters.

AETIOLOGY OF MS AND THE ROLE OF VitD

One of the main pathogenetic hypotheses of MS associates the development of the disease mainly with the activity of autoreactive T lymphocytes. Antigen-presenting cells present myelin proteins (autoantigens) to T cells, leading to a clonal expansion and autoactivation of T lymphocytes which subsequently cross the blood–brain barrier. In the central nervous system (CNS), they are reactivated, which stimulates a pro-inflammatory response mediated by Th1 and Th17 cells, leading to the damage of the CNS structures. In response to axonal damage, microglial cells are activated. They are an important source of cytokines that mediate inflammatory processes in the CNS and contribute to neurodegeneration. As a result of a prolonged inflammatory process, activated macrophages and microglial structures produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) that cause OS and exacerbate pathological changes in MS (Miller et al., 2013). A simplified diagram of the pathogenesis of MS is presented in Fig. 1.

There is increasing evidence that specific environmental factors may contribute to a higher MS risk and influence the clinical course of the disease in a genetically susceptible population. One of them is hypovitaminosis D (VitD deficiency), which is common in the general population



CNS – central nervous system.

Fig. 1. A simplified diagram of the pathogenesis of MS

worldwide. In addition to the recognised role of VitD in calcium and phosphate metabolism, it is also involved in cell proliferation and differentiation, and participates in the immune and nervous system responses.

There are numerous studies assessing the effect of VitD supplementation on disease activity and clinical condition of MS patients who are known to be at a higher risk of hypovitaminosis D (Boltjes et al., 2021). However, there are as yet no recommendations regarding the dose of supplementation. Based on the literature, VitD supplementation in the group of MS patients was introduced in various doses (ranging from 800 to 14,000 IU/day) and for different periods of time (ranging from 8 to 96 weeks). In conclusion, there are still many uncertainties about the recommended dose and potential benefits of VitD use as an add-on therapy in MS patients.

EFFECTS OF VitD SUPPLEMENTATION ON INFLAMMATION AND THE IMMUNE SYSTEM

As already mentioned, one of the most popular hypotheses about the immune pathology of MS is related to the activation of autoreactive lymphocytes in the secondary lymphoid tissues, which are then reactivated in the CNS.

Inflammation is considered to be mostly driven by T cells that synthesise different cytokines. Some of them are associated with a pronounced pro-inflammatory effect, like interferon γ (INF-γ), tumour necrosis factor α (TNF-α) and interleukins (IL): IL-2, IL-12, IL-15, IL-17, IL-18. In the centres of demyelination, there are also factors that cause anti-inflammatory response, such as IL-4, IL-10, IL-6 or transforming growth factor β (TGF-β) (Feige et al., 2020). Importantly, it has been suggested that dysregulation between the cytokines listed above underlies MS (Muris, 2016).

In addition to various inflammatory pathways leukocyte-endothelial interactions and extracellular matrix alterations are also involved in the pathogenesis of MS. There are markers related to the clinical activity of the disease, including interleukin-1 receptor antagonist (IL-1Ra), osteopontin (OPN), pentraxin 3 (PTX3), soluble tumour necrosis factor receptor 1 (sTNF-R1), and transforming growth factor β 1 (TGF-β1); radiological activity, such as chemokine (C–X–C motif) ligand 16 (CXCL16), matrix metalloproteinase 9 (MMP-9) and osteoprotegerin (OPG), or involved in T cell migration and myelin repair, like activated leukocyte cell adhesion molecule (ALCAM), chemokine ligand (C–C motif) 21 (CCL21), and secreted frizzled-related protein 3 (sFRP3) (Røsjø et al., 2015).

Muris et al. (2016), in their SOLARIUM study, measured the levels of various cytokines in patients with relapsing-remitting multiple sclerosis (RRMS) receiving IFN-β therapy to assess the effects of high-dose VitD supplementation (7,000 IU daily for 4 weeks, followed by 14,000 IU daily up to week 48) on the T helper cell compartment. They concluded that there was no significant effect on the circulating regulatory compartment of immune cells, though they suggested that high doses of VitD could prevent a gradual deterioration or disturbance of (immune) balance, as shown in the placebo group with a decrease in anti-inflammatory cytokine producing Th cells and an increase in the production of pro- and anti-inflammatory cytokines, which was not observed in the VitD group (Muris, 2016; Muris et al., 2016).

Sotirchos et al. (2016), in their randomised double-blind pilot study conducted on 40 patients with RRMS, compared the immunological effect of daily supplementation with 10,400 IU and 800 IU cholecalciferol over a period of six months. In the high-dose group, they observed significantly higher serum 25(OH)D levels and a pleiotropic immunomodulatory effect (Sotirchos et al., 2016). They also found no differences in the levels of 51 cytokines measured at baseline and end line in the mentioned groups. Other researchers drew similar conclusions, establishing that high doses of VitD appeared safe as an add-on therapy (Feige et al., 2020).

What is more, Toghianifar et al. (2015) in a double-blind placebo-controlled study assessing the influence of 50,000 IU of VitD used every five days for 12 weeks in RRMS patients on IFN-β treatment showed a significant positive correlation with the log of IL-17 measures in the intervention group when adjusted by Expanded Disability Status Scale (EDSS) measures, concluding that IL-17 levels exhibited a significant change in RRMS patients.

In addition, Golan et al. (2013), in their randomised double-blind study on 45 subjects with RRMS, administered 800 IU of VitD per day in the low-dose group and 4,370 IU per day in the high-dose group for one year. The researchers observed that the level of IL-17 was increased in patients receiving VitD at low doses, while the high-dose group had a heterogeneous response. They found no significant differences in serum IL-10 and IFN-γ levels between both groups (Golan et al., 2013). The authors hypothesised that high doses of VitD could lead to a reduction of IL-17. Furthermore, reports by Häusler et al. (2019) based on a mice model suggest that VitD used in moderate doses intensifies a direct regulatory effect, while continuous high-dose treatment can increase MS activity by raising the level of T-cell excitatory calcium.

According to some study results, high doses of VitD can also influence other immune parameters. The dose of 20,000 IU of cholecalciferol per week according to the study by Åivo et al. (2015) caused a significant increase in serum TGF-β levels in MS patients using IFN-β-1b. TGF-β is considered to be a pleiotropic cytokine with remarkable immunomodulatory effects and is mainly produced by Treg cells (Hashemi et al., 2020). Røsjø et al. (2015) assessed the influence of VitD supplementation (20,000 IU per week) on 11 serum inflammatory markers, including TGF-β, ALCAM, CCL21, CXCL16, IL-1Ra, MMP-9, OPG, OPN, PTX3, sFRP3, sTNF-R1, in 68 RRMS patients, observing a significant increase in 25(OH)D levels without an effect on inflammation parameters. However, the researchers do not rule out the effect of VitD supplementation on systemic inflammation due to limitations of their study.

In the study by Mahon et al. (2003), six-month supplementation of VitD (1,000 IU/day) in a small group of MS patients resulted in an increase of TGF-β1, which is an important anti-inflammatory cytokine, while the results obtained for IFN-γ, TNF-α and IL-13 were inconclusive in comparison with the placebo group.
In another study, by Mosayebi et al. (2011), a six-month trial in which a total of 62 MS patients received 300,000 IU/month of VitD as an intramuscular injection or placebo also resulted in a significant elevation of the levels of TGF-β and IL-10 in the VitD treatment group, while the amount of IFN-γ did not change after VitD supplementation.
Moreover, Ashtari et al. (2015) observed that 50,000 IU of VitD every five days for 12 weeks causes a significant increase in anti-inflammatory IL-10 levels in the group with RRMS. According to Hashemi et al. (2020, 2018), VitD treatment with 50,000 IU/7 days for eight weeks in MS patients had uplifted the level of anti-inflammatory cytokines (IL-27, TGF-β1, and IL-10), while the concentrations of pro-inflammatory cytokines (IL-17A and IL-6) had decreased.
Burton et al. (2010) also assessed the influence of high-dose VitD supplementation (10,000 IU/day for 12 months) on systemic inflammation. The researchers found a change in MMP-9, tissue inhibitor of metalloproteinase (TIMP-1) and cytokine values, but it was not significant, concluding that there is evidence for immunomodulatory effects (Burton et al., 2010).
The studies reviewed in this report are presented in Tab. 1.
To sum up, taking into account the immunomodulatory properties of VitD described in the literature, the vitamin may be helpful in controlling inflammation through its effects on the immune system and reduction of pro-inflammatory cytokines. Therefore, it may have a significant impact in MS patients, in view of the dysregulation of their immune system responsible for inflammation. The studies presented in this review assessed changes in serum cytokine levels using a variety of parameters, and their results varied. This indicates the need for further research on this subject to determine the usefulness of VitD and its dosage in the treatment of MS.

EFFECTS OF VitD SUPPLEMENTATION ON OS PARAMETERS

In general, OS is associated with a decline of antioxidant defences and an increase of pro-oxidative processes in cells. The CNS is particularly susceptible to the damaging effects of free radicals, including ROS and RNS, derived from the aforementioned imbalance due to the brain's high oxygen demand, low levels of endogenous antioxidants, and high phospholipid levels (Adamczyk and Adamczyk-Sowa, 2016; Hejazi et al., 2014; Padureanu et al., 2019).
To assess antioxidant activity in blood serum, measurements of the activity of superoxide dismutase (SOD), ceruloplasmin (CER), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), or glutathione S-transferase (GST) can be performed; moreover, the nonenzymatic antioxidant status can be assayed with total antioxidant capacity (TAC) and concentration of protein sulfhydryl (PSH). To assess the prooxidative status, total oxidative stress (TOS) or the level of lipid hydroperoxides (LHP) and malondialdehyde (MDA) can be determined (Knapik et al., 2019).
It is well established that OS contributing to oligodendrocyte loss, neuronal damage and myelin degeneration have a key role in the MS pathogenesis (Hejazi et al., 2014; Pădureanu et al., 2020). The OS, mainly ROS and RNS, are claimed to promote an existing in MS inflammatory response – in the inflammation foci within CNS lymphocytes and macrophages secrete pro-inflammatory cytokines, chemokines, nitric oxide (NO) and free radicals which are harmful for neighbouring cells, especially neurons (Gironi et al., 2014; Pegoretti et al., 2020).
Recent studies highlight a significant increase in the OS in MS patients together with a reduction in antioxidant defence (Abdullah et al., 2012; Fahmi et al., 2014; Pădureanu et al., 2019, 2020). Pădureanu et al. (2020), in their study on 36 patients with MS, found that starting at the early stage of disease (RRMS) the activity of the antioxidant enzyme CAT is significantly decreased in comparison with the healthy group, which can be linked to VitD deficiency.
Neurons of the CNS are constantly exposed to low and moderate levels of ROS. In MS and other chronic inflammatory diseases, the production of free radicals exceeds the rate of their elimination through the action of antioxidants (Ortiz et al., 2013). VitD is claimed to have such antioxidant properties, which is explained by structural similarities between VitD and cholesterol and ergosterol. What is more, in body cells VitD binds to its nuclear receptor (vitamin D receptor, VDR) and upregulates the expression of antioxidant systems such as reduced glutathione (GSH), GPx or SOD. Furthermore, it can inhibit ROS secretion (Sepidarkish et al., 2019).
Some researchers have noticed a possible association between VitD level and OS markers. A review of 17 randomised clinical trials performed by Sepidarkish et al. (2019) on the effects of VitD supplementation on the OS status showed that VitD supplementation could significantly decrease the MDA levels as well as enhance antioxidant defence systems (expressed by TAC and GSH) compared to placebo, while it did not affect serum NO. The researchers concluded that VitD doses ranging from 100,000 to 200,000 IU per month had a significant effect on OS parameters (Sepidarkish et al., 2019). Motamed et al. (2022) in their review also analysed the effects of VitD supplementation on OS in a group of pregnant women, showing that it can also be effective in increasing the concentration of TAC and GSH and decreasing the level of MDA.
There are studies suggesting that VitD supplementation can decrease OS parameters in MS patients (Kouchaki et al., 2018). Interestingly, Kouchaki et al. (2018) in a randomised double-blind placebo-controlled study on patients with RRMS assessed the influence of 50,000 IU of VitD biweekly in combination with ω-3 fatty acid capsules daily [500 mg

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Study and year	Total number of patients	Dose of VitD	Duration	Disease modifying therapy (DMT)	Outcome
Muris et al., 2016	23 control/30 treatment (*N* = 53)	Placebo in control 14,000 IU/day in treatment (7,000 IU daily for 4 weeks, then 14,000 IU daily)	48 weeks	IFN-β1a	IL-10, IL-4, IL-5, IFN-γ, IL-17, IL-22, GMCSF, TNF-α, TGF-β
Sotirchos et al., 2016	21 control/19 treatment (*N* = 40)	800 IU/day in control 10,400 IU/day in treatment	6 months	IFN-β (12), glatiramer acetate (10), natalizumab (11), fingolimod (4), abatacept (1), none (2) All received calcium 1 mg/day	51 cytokines (leptin, CXCL5, IL-17F, IFN-β, CXCL1, GM-CSF, IL-13, TNF-α, LIF, IL-1β, VEGF, IL-5, IL-10, CCL2, IFN- γ, IL-12p70, IL-7, IL-2, CCL7, IL-15, IL-4, FGFb, IL-6, CXCL10, PDGFbb, TGF-β, HGF, IL-12p40, IL-1A, SCF, TGF-A, NGF, CXCL9, M-CSF, TNF-β, sFASL, IFN-α, CCL3, IL-1Ra, TRAIL, IL-17, CCL4, G-CSF, resistin, ICAM-1, CCL11, IL-8, VCAM-1, CD40L, CCL5, PAI1)
Toghianifar et al., 2015	45 control/44 treatment (*N* = 89)	Placebo in control 50,000 IU/5 day in treatment	12 weeks	IFN-β	IL-17
Golan et al., 2013	21 low dose/24 high dose (*N* = 45)	800 IU/day in low-dose group 4,370 IU/day in high-dose group	12 months	IFN-β	IL-17, IL-10, IFN-γ
Åivo et al., 2015	29 control/30 treatment (*N* = 59)	Placebo in control 20,000 IU/week in treatment	12 months	IFN-β1b	TGF-β, IFN-γ, IL-17A, IL-2, IL-10, IL-9, IL-22, IL-6, IL-13, IL-4, IL-5, IL-1b, TNF-α
Røsjø et al., 2015	32 control/36 treatment (*N* = 68)	Placebo in control 20,000 IU/week in treatment	96 weeks	IFN-β, glatiramer acetate, natalizumab All received calcium 500 mg/day	ALCAM, CCL21, CXCL16, IL-1Ra, MMP-9, OPG, OPN, PTX3, sFRP3, sTNF-R1, TGF-β1
Mahon et al., 2003	22 control/17 treatment (*N* = 39)	Placebo in control 1,000 IU/day in treatment	6 months	All received calcium 800 mg/day	IFN-γ, TNF-α, IL-13, TGF-β1
Mosayebi et al., 2011	34 control/28 treatment (*N* = 62)	Placebo i.m. in control 300,000 IU/month i.m. in treatment	6 months		IL-10, IFN-γ, TGF-β
Ashtari et al., 2015	45 control/44 treatment (*N* = 94)	Placebo in control 50,000 IU/5 days in treatment	3 months	IFN-β	IL-10
Hashemi et al., 2020, 2018	50 control/25 treatment (control – 25 healthy participants and 25 first-degree relative participants) (*N* = 75)	50,000 IU/week	8 weeks		IL-27, TGF-β1, IL-10, IL-17A, IL-6
Burton et al., 2010	24 control/25 treatment (*N* = 49)	10,000 IU/day*	52 weeks	IFN-β (24), glatiramer acetate (4), none (21) All received calcium 1,200 mg/day	IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, MMP-9, TIMP-1, TNF-α

* Mean dose of VitD (initial escalation and subsequent down-titration 0–40,000–0 IU daily).
i.m. – intramuscular injection.

Tab. 1 The impact of different doses of VitD on the cytokine profile in MS patients

docosahexaenoic acid (DHA) and 106 mg eicosapentaenoic acid (EPA)] for 12 weeks. The authors concluded that the concentrations of serum high-sensitivity C-reactive protein (hs-CRP), TAC, GSH and MDA improved significantly in the supplemented group (Kouchaki et al., 2018).

Interesting findings were reported by Bhargava et al. (2017) in their study on metabolome in MS and the influence of VitD supplementation on metabolic profiles in MS patients in comparison with healthy controls. The researchers found a reduction of OS parameters after 5,000 IU of cholecalciferol daily for 90 days in healthy controls but not in MS patients. In addition, MS patients presented a lower rise in serum 25(OH)D in comparison with the healthy population.

Surprisingly, little is still known about the effect of VitD supplementation on the parameters of OS in MS patients. Further research is needed to explore this issue, with a focus on determining the recommended supplementation dose.

CONCLUSIONS

MS is a multifactorial disease with a complex aetiology. Studies conducted so far warrant the conclusion that VitD plays a significant role in MS.

The overview of studies failed to yield a definite answer concerning an effective dose of VitD. We concluded that there was no clear evidence for the impact of VitD supplementation on inflammatory parameters in MS patients, even though studies show consistently that the vitamin has an influence on the immune system and contributes to a reduction of pro-inflammatory cytokines. What is more, little is still known about the influence of VitD supplementation on OS, especially with regard to the potential effective dose. Consequently, more research is needed to gain a better understanding of this issue.

There is no doubt that patients with hypovitaminosis D should be identified, and VitD deficiency should be corrected by supplementation. Although at the moment there is no definite evidence supporting the use of VitD as a standalone MS therapy, its benefits in supporting traditional therapies of the disease cannot be excluded. This is why it is necessary to conduct further research to determine the influence of VitD on disease activity due to its potential role as an add-on therapy in this group of patients or even as a preventative measure.

Conflict of interest

The authors report no conflicts of interest.

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