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Vitamin D Supplementation in Selected Autoimmune Diseases

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Abstract

Introduction and Objective. In recent years, awareness of the problem of vitamin D deficiency in the human body has been steadily increasing. There is a growing emphasis on investigating the effects of vitamin D supplementation both in the prevention of autoimmune diseases and in the course of existing diseases. The aim of this study is to highlight and discuss the role of vitamin D supplementation in selected autoimmune diseases.

Review methods. The publication is a narrative review. The PubMed electronic database was used to review the literature. To ensure the highest substantive value, the focus was mainly on studies from the last 8 years, with only 6 studies published before 2016, concerning autoimmune diseases.

Results. There are still lots of unknowns when it comes to physiology and the role that vitamin D plays in our body and deepening the knowledge of its functions would definitely help prevent many diseases concerning various systems such as musculoskeletal, immune and nervous systems. Wide range of studies have already proven that appropriate supplementation of vitamin D prevents complications and exacerbations of disorders like rheumatoid arthritis, Hashimoto's thyroiditis, ulcerative colitis, type 1 diabetes and multiple sclerosis. Unfortunately there is no unambiguous evidence of noticeable improvement in the patients suffering from psoriasis after taking vitamin D. There is a huge need for developing guidelines which would establish specific supplementation protocols considering various factors since it is inexplicably difficult to obtain an optimal level of vitamin D in our body.

Summary. The increasing prevalence of autoimmune diseases in the population, their coexistence with vitamin D deficiency, and the scientifically proven impact of this vitamin on the body imply the need for an in-depth analysis of the relationship between its supplementation and the prevention and modification of the course of autoimmune diseases.

Keywords: vitamin D; rheumatoid arthritis; Hashimoto's thyroiditis; ulcerative colitis; psoriasis; type 1 diabetes; multiple sclerosis.

INTRODUCTION

Vitamin D is a group of fat-soluble steroid organic compounds, its metabolic pathway begins in the skin, where, under the influence of sunlight and thermal energy, vitamin D3 is formed, which undergoes double hydroxylation in the liver and kidneys, resulting in its biologically active form - calcitriol (1α,25-dihydroxycholecalciferol) [1, 2]. Vitamin D has a pleiotropic effect on the human body, but plays a fundamental role in the regulation of hormonal and calcium-phosphate metabolism, bone metabolism and modulation of the immune system [3, 4, 5].

A common problem is the deficiency of vitamin D in the body, and knowledge of the mechanism of its synthesis allows us to assume what may be the causes of its deficiency, namely: impaired synthesis in the skin (as a result of low exposure to ultraviolet radiation), reduced absorption in the gastrointestinal tract (a consequence of low supply with food and absorption disorders in the course of some diseases, such as cystic fibrosis), liver and kidney diseases (where changes leading to the synthesis of calcitriol take place) [6, 7, 8, 9].

The multifaceted effects of vitamin D in the body affect the occurrence of various symptoms resulting from its deficiency, which include: musculoskeletal disorders (e.g. rickets, osteomalacia and osteoporosis) and abnormalities in the functioning of the immune system, which leads to an increased risk of autoimmune diseases, such as rheumatoid arthritis, Hashimoto's disease, ulcerative colitis, psoriasis, multiple sclerosis and type 1 diabetes [10, 11, 12, 13].

In clinical practice, prevention of vitamin D deficiency and treatment of existing deficiency play an important role, and its recommended daily intake depends on many factors, primarily age, current body requirements and comorbidities, so these activities include supplementation with preparations containing vitamin D or its metabolites and a balanced diet [14].

The common occurrence of autoimmune diseases, their tendency to co-occur with each other, as well as vitamin D deficiency and its impact on the immune system, prompt the analysis of the impact of vitamin D supplementation on the prevention and course of existing diseases in this group [15].

This paper will discuss the issues of rheumatoid arthritis, Hashimoto's disease, ulcerative colitis, psoriasis, multiple sclerosis and type 1 diabetes.

Rheumatoid arthritis is an inflammatory and chronic rheumatic disease belonging to autoimmune systemic connective tissue diseases, in which the occurrence of antibodies against cyclic citrullinated peptide is characteristic, and it primarily affects joints, leading to their stiffness, pain and deformities [16, 17, 18].

There is also an increased susceptibility to osteoporosis (which may be a side effect of drugs taken, mainly glucocorticosteroids), therefore, in addition to pharmacological treatment and rehabilitation, an appropriate diet and supplementation are also important, because vitamin D in this case can have a beneficial effect on both bone metabolism and the immune system [19, 20, 21].

Hashimoto's disease is an autoimmune disease (characterized by the production of autoantibodies - against thyroperoxidase and against thyroglobulin), which is a common cause of hypothyroidism, in the course of which obesity may occur (which in turn is correlated with vitamin D deficiency), so vitamin D supplementation may have a beneficial effect on reducing inflammation and minimizing complications of Hashimoto's disease [22].
Ulcerative colitis is classified as a non-specific inflammatory bowel disease and is characterized by chronic inflammation of the mucous membrane of the large intestine and rectum, in the course of which vitamin D deficiency may occur as an implication of digestive system disorders, so its supplementation can replenish deficiencies resulting from digestive tract disorders and minimize existing inflammation [23, 24].
Psoriasis is an autoimmune disease that primarily affects the skin, but also nails and joints, and vitamin D, through its beneficial effect on the immune system, can minimize the risk of exacerbations [25, 26].
Multiple sclerosis is a disease classified as an autoimmune disease, in the course of which the myelin sheath around neuronal processes is damaged, which leads to symptoms from the nervous system and the musculoskeletal system, so vitamin D may play a role in supporting the immune system, and therefore potentially protecting neurons [27, 28].
Type 1 diabetes is an autoimmune disease, and the characteristic autoantibodies that predispose to its development are: anti-islet, anti-insulin, anti-tyrosine phosphatases, anti-glutamic acid decarboxylase and anti-zinc [29].
This disease leads to the destruction of beta cells of the pancreatic islets responsible for the production of insulin, which in turn leads to hyperglycemia and the risk of numerous complications, such as reduced immunity, which is why vitamin D, through its beneficial effect on the immune system, can minimize inflammation [30, 31, 32].
As can be seen from the characteristics of the above diseases, vitamin D deficiency can be both the cause of an increased risk of autoimmune diseases and exacerbations of their course, as well as the effect, for example, of obesity and absorption disorders from the gastrointestinal tract, which is why its desired level in the body is important. After discussing all selected autoimmune diseases, the most important information about them will be summarized in two tables (Table 1 and Table 2).

Vitamin D3's Impact on Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 1% of the population. It is more common in women than in men, with women being affected approximately 2-3 times more frequently than men [19, 33]. The disease can manifest at any age, but the peak incidence occurs between the ages of 50 and 75 [19]. The development of the disease is driven by T lymphocytes and pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, which amplify inflammation and result in the deterioration of joint structures. In RA, the immune system attacks the synovial membrane of the joints, leading to pain, swelling, and stiffness [20]. In addition to immune components, genetic and environmental factors play a crucial role in the development of RA. For example, genetic susceptibility, including the presence of certain HLA-DRB1 variants, raises the likelihood of developing the disease. Environmental factors, like smoking, can further enhance the inflammatory response, contributing to disease progression [33, 34].

If left untreated and uncontrolled, inflammation can result in joint damage, loss of function, reduced quality of life and disability. Additionally, complications of RA, such as respiratory and cardiovascular diseases, may increase the risk of premature death [19, 20].

In recent years, increasing scientific interest in the role of vitamin D deficiency in the pathogenesis and progression of autoimmune diseases. Studies show that low levels of vitamin D3 are often found in patients suffering from autoimmune diseases. However, it remains to be elucidated whether this deficiency directly contributes to disease exacerbation and severity, or if it is merely correlated with a higher incidence of these conditions. Vitamin D3 plays a crucial role in regulating the immune response, supporting the proper functioning of the immune system and inhibiting excessive inflammatory response. Vitamin D3 modulates both innate and adaptive immune responses, primarily through Toll-like receptors (TLRs), and influences the activity of T and B lymphocytes. By inhibiting T cell proliferation, vitamin D3 helps reduce the production of pro-inflammatory cytokines such as IL-17 IL-2, which is particularly important in alleviating the symptoms of rheumatoid arthritis. T cells are also a source of RANKL, which leads to the activation of osteoclasts and bone destruction [15, 19, 20, 33].

Moreover, vitamin D3 is crucial for the regulation of calcium homeostasis and the processes of bone mineralization. Its deficiency elevates the risk of osteoporosis and fragility fractures, a concern that is particularly pertinent for patients with rheumatoid arthritis (RA), who frequently undergo glucocorticoid therapy—an intervention that further exacerbates the risk of osteoporosis. Studies conducted worldwide indicate that patients with rheumatoid arthritis frequently have low levels of vitamin D, and this deficiency may be associated with higher disease activity [15, 20].

The meta-analysis conducted by Clasen et al. (2023), which evaluated data spanning from 2014 to 2018, failed to establish a significant correlation between serum vitamin D3 levels and the risk of developing rheumatoid arthritis (RA). The authors emphasized that the small sample size and limited number of studies included may have contributed to the lack of statistical precision. This analysis underscores the critical need for further large-scale, methodologically robust studies to more accurately assess the potential role of vitamin D3 in modulating the risk and pathogenesis of autoimmune disease [33].

The study conducted by Mouterde et al. investigates the association between vitamin D deficiency and disease activity in patients diagnosed with rheumatoid arthritis (RA), as well as the correlation between vitamin D levels and the incidence of disability or radiological progression during the first year of disease onset. The findings indicate that patients with RA exhibit significantly lower serum vitamin D levels, particularly in the initial stages of the disease. Among individuals presenting with vitamin D deficiency, there was a notable exacerbation of disease symptoms, including increased pain and heightened systemic inflammation. This suggests that low serum vitamin D concentrations are correlated with more severe manifestations of RA and a higher frequency of functional impairment, which is corroborated by assessments of the quality of life in affected individuals. Furthermore, the study highlights that low levels of vitamin D3 are associated with accelerated radiographic progression of joint damage. These observations imply that monitoring vitamin D levels may serve as a valuable biomarker for structural changes in RA, underscoring the necessity for early intervention strategies.

The authors advocate for further investigations into vitamin D supplementation as a potential therapeutic approach in the management of RA, particularly for patients in the early stages of the disease [34].

Given the substantial evidence supporting the beneficial effects of maintaining adequate vitamin D3 levels, particularly in alleviating pain and modulating the activity of autoimmune diseases, regular monitoring and correction of vitamin D3 deficiencies should be integral components of rheumatoid arthritis (RA) management. Although growing evidence highlights the benefits of maintaining adequate levels of vitamin D3, unfortunately many unanswered questions still remain. There are currently no definitive guidelines on the optimal dosage of vitamin D3 supplementation for RA patients. Further research is essential to establish the optimal serum levels and supplementation protocols [15, 19]. It is also important to note that many factors influence vitamin D3 levels, including age, diet, season, sun exposure, race, skin color, drug interactions, and comorbidities. Therefore, it is imperative to conduct further research that takes these variables into account and aims to reduce the heterogeneity of findings across different studies [19, 33, 34].

Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder characterized by lymphocyte infiltration of the parenchyma and the presence of antibodies specific to thyroid antigens: anti-thyroperoxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (anti-Tg Ab). HT is currently the leading cause of hypothyroidism. Lower levels of vitamin D have been observed in patients with HT compared to the general population. However, it is not clear whether the lower vitamin D levels in HT patients are a consequence of the disease or potentially a contributing factor [22].

In vitro studies have shown that vitamin D may play an immunomodulatory role, such as inhibiting the differentiation and production of antibodies by B lymphocytes [35], modulating T lymphocyte activity, thereby reducing their ability to induce an autoimmune response [36], decreasing the production of pro-inflammatory cytokines (e.g., IL-17, IL-21), and increasing the production of anti-inflammatory cytokines (e.g., IL-10). The promising in vitro results regarding the immunomodulatory role of vitamin D have led to the hypothesis that vitamin D may influence autoimmune diseases, including HT.

In a randomized double-blind placebo-controlled clinical trial, female patients with HT received 50,000 IU of vitamin D in the vitamin D group and placebo pearls in the placebo group, weekly for 3 months. The study aimed to determine whether vitamin D supplementation affects the levels of anti-TPO Ab, anti-Tg Ab, and thyroid hormone profile (TSH, T3, T4). A significant reduction in anti-Tg Ab and TSH hormone levels was observed in the group receiving vitamin D supplementation compared to the beginning of the study. However, no significant decrease in anti-TPO Ab levels was noted in the vitamin D group compared to the placebo group. No significant changes in T3 and T4 hormone levels in serum were found [22]. The biochemical effect of vitamin D supplementation in HT is shown in Table 1.

In a meta-analysis conducted by J. Zhang et al. [37], it was shown that vitamin D supplementation in patients with HT causes a reduction in anti-TPO Ab and anti-Tg Ab levels. Furthermore, it was demonstrated that supplementation should last at least 3 months. However, the meta-analysis had some limitations.

Firstly, no specific supplementation dose was identified. Additionally, there was significant heterogeneity among the included studies, and the power of the analysis may be limited due to the small number of studies and population size.
Large, well-controlled studies are needed to definitively confirm the hypothesis that vitamin D supplementation may beneficially reduce disease activity in HT patients, due to the immunomodulatory potential of vitamin D. Furthermore, it is necessary to develop guidelines that establish a specific supplementation dose and therapy duration.
Nevertheless, the fact remains that vitamin D supplementation may be recommended for HT patients due to the population-wide deficiency of vitamin D and the fact that vitamin D supplementation therapy is low-cost and has minimal side effects.

Ulcerative colitis

The meta-analysis showed that patients with ulcerative colitis (UC) had significantly lower serum vitamin D levels compared to healthy individuals. Furthermore, the prevalence of vitamin D deficiency was much higher in the UC group than in the control group. This suggests a strong association between the condition and reduced vitamin D levels [38]. Throughout a preclinical study focusing on biopsy samples taken from both inflamed and non-inflamed sections of the colon in patients with UC, researchers observed an upregulation of claudin-1 and claudin-2 proteins in active UC. Treatment with 1,25(OH)2D3 resulted in a reduction in levels of claudin-1 and claudin-2 proteins in both inflamed and non-inflamed tissue. Additionally, claudin-4 and claudin-7 proteins, which were initially downregulated, showed an increase in levels after incubation with 1,25(OH)2D3. Further, incubation with 1,25(OH)2D3 led to decreased levels of IL-13 and IL-6. Researchers suggest that vitamin D could be used as a treatment for active UC [39].
Researchers found that vitamin D supplementation reduces the expression of the CD40L gene in patients with mild-to-moderate UC, which is a key factor in inflammatory pathways [40].
Elevated serum levels of vitamin D were found to be positively correlated with higher ratios of IL-4 plus IL-10 compared to IL-17A plus TNF-α, and IL-4 plus IL-10 compared to IL-6 plus TNF-α. Statistical analysis revealed that higher baseline ratios of IL-4 plus IL-10 to IL-17A plus TNF-α were associated with histologic mucosal healing. Furthermore, an increased ratio of serum IL-4 plus IL-10 to IL-6 plus TNF-α was linked to a reduced risk of clinical relapse and a longer time to relapse [41].
In a controlled trial, ninety patients were randomly assigned to receive either a single intramuscular dose of 300,000 IU vitamin D or a placebo (normal saline). Visfatin, vascular endothelial growth factor (VEGF), and 25(OH)D levels were measured before and 90 days after treatment. Although no significant differences in visfatin and VEGF levels were observed between the groups after supplementation, patients with vitamin D insufficiency showed a smaller increase in visfatin levels in the intervention group compared to the placebo. An inverse correlation was also found between serum 25(OH)D and visfatin in patients with vitamin D insufficiency, suggesting that vitamin D may play a role in modulating visfatin levels in this subgroup [42].
In a prospective, double-blinded, randomized pilot trial involving 18 patients diagnosed with UC and hypovitaminosis D, oral vitamin D3 supplementation was administered at dosages of 2000 IU and 4000 IU. This intervention yielded a spectrum of advantageous outcomes.

After a ninety-day period of oral vitamin D3 supplementation, both groups experienced an increase in their vitamin D levels. The increase was notably higher in the 4000 IU group compared to the 2000 IU group. After the treatment period, 40% of UC patients in the 4000 IU group achieved normal vitamin D levels (>30 ng/ml), compared to 12% in the 2000 IU group. Additionally, the quality of life, as measured by SIBDQ, improved across all UC patients after the ninety-day vitamin D3 supplementation. This improvement was statistically significant in the 4000 IU group, but not in the 2000 IU group.Following 90 days of vitamin D3 supplementation, both treatment groups showed a decrease in overall disease activity scores. The 4000 IU group experienced a greater reduction, although this change was not statistically significant. Similar outcomes were observed in the measurement of CRP levels [43]. The study results suggest that using even higher doses of vitamin D3 may be beneficial for patients with UC.

In a study involving ninety patients with mild to moderate UC, participants were given either a single injection of 300,000 IU of vitamin D3 or a placebo. After 90 days, researchers found no significant differences in asymmetric dimethylarginine (ADMA) levels between the two groups. The study also revealed that baseline ADMA levels did not show any correlation with vitamin D, erythrocyte sedimentation rate (ESR), or high-sensitivity C-reactive protein. Even after adjusting for body mass index and conducting subgroup analyses based on gender and vitamin D levels, the results remained unchanged. The study concluded that high-dose vitamin D3 supplementation did not have a significant impact on ADMA levels in mild to moderate UC patients [44].

In a meta-analysis of seven studies involving 539 participants, it was found that vitamin D supplementation led to significant improvements in serum vitamin D levels, ESR, CRP, and calcium (Ca) levels. Specifically, the supplementation resulted in increased serum vitamin D levels, decreased ESR, reduced CRP, and increased Ca levels. Subgroup analysis indicated that vitamin D supplementation at a dose of ≥ 300,000 IU/day was particularly effective in raising serum vitamin D levels. Additionally, high-dose supplementation over a short period also showed efficacy in improving serum vitamin D levels [45].

Within a meta-analysis of 10 studies involving 1,077 patients, it was determined that the combination of vitamin D with mesalazine is effective in the treatment of UC. This approach has been shown to improve the Mayo score, intestinal barrier function and reduce inflammatory markers [46]. Table 1 demonstrates the impact of vitamin D supplementation in UC.

To sum up, vitamin D supplementation appears to offer significant benefits in UC by modulating inflammatory markers, strengthening intestinal barrier function, and aiding in disease management. Moreover, it enhances the quality of life for patients. However, further research is necessary to comprehensively elucidate the therapeutic role of vitamin D in UC and refine treatment approaches [38, 39, 40, 41, 42, 43, 44, 45, 46].

Psoriasis

An adequate level of vitamin D in the body has a significant impact on modulating the immune response. Sufficient intake of this vitamin can, therefore, reduce the risk of developing chronic diseases and their exacerbations, prevent infections, and ultimately lower mortality rates [12].

One of the chronic autoimmune diseases is psoriasis, which is characterized by the presence of a generalized inflammatory state, primarily affecting the skin, nails, and joints [25].

Skin lesions in psoriasis are characterized by increased proliferation of epidermal keratinocytes, accompanied by an inflammatory infiltrate. The epidermis naturally serves as an indirect source of endogenous vitamin D. Significant correlations have been observed between low levels of vitamin D and the occurrence of psoriasis. Appropriate supplementation has become an important aspect of therapeutic strategies. However, evidence supporting its beneficial effect [47].

It has been suggested that vitamin D supplementation should be considered in populations at high risk of vitamin D deficiency, which often include patients with psoriasis. The purpose of such supplementation is not only to alleviate the clinical severity of the disease [48].

After reviewing the impact on the operating system, it is believed that additional extension may be introduced to the risk of disease flare-ups [26]. However, to determine an effective dosage, it is necessary to design a study involving a large number of subjects [48].

Serum vitamin D levels are significantly lower in patients with psoriasis compared to healthy individuals. It remains unclear whether low levels of 25(OH)D are a consequence of psoriasis or a contributing factor to its development. According to a recent meta-analysis, vitamin D supplementation did not significantly improve the Psoriasis Area and Severity Index (PASI) score despite long-term supplementation [47].

Type 1 diabetes

Type 1 diabetes is a chronic disease, which occurs 1 in 250 people, that is caused by an immune response against B cells in pancreas [49]. More than 90% patients that were recently diagnosed with type 1 diabetes had present antibodies against specific B cell proteins. That leads to decreased production of insulin and has an impact on glucose levels inside body cells that can often lead to hyperglycemia [29]. Loss of cells whose main function is to produce insulin can be measured by level of C-peptide. Because immunology reaction is responsible for this deprivation, there are studies carried out to provide solutions, for e.g. use of otelixizumab and teplizumab, that their effect can contribute to finding new ways of approaching treatment for diabetes [31].

There are multiple reasons that can be involved in starting an immune response such as: viral infections, genetics, metabolism. However to this day we can’t point out only one cause. Researchers are still finding correlations between diabetes and factors of different surroundings [49].

Vitamin D takes part in regulating maturity of the immune system. It has an important role in development mechanisms that can protect us from infectious diseases, and also stabilize the autoimmune response [50]. Vitamin D has an impact on producing anti-inflammatory cytokines such as IL-4, IL-10 and TGF-**β**. Additionally, in the article by Singh et al., studies were conducted which showed vitamin D causes downregulation expression of CatG, which is participating in antigen presentation of proinsulin and CD4+ T cells in nonobese diabetic mice [51].

Vitamin D insufficiency can promote the onset of diabetes type 1 and is usually found in patients that are recently diagnosed. Researchers found that an accurate level of vitamin D can protect patients from developing T1D.

According to study conducted by Gabbay et al. on 38 patients after administration cholecalciferol 2000 IU/d to patient that had remaining function of pancreatic **β**-cells, that are at the starting point of diabetes type 1, there were promising results of stimulation of C-peptide during first year of supplementation and revealed a particularly smaller decline after 18 months with cholecalciferol compared to placebo [52].
Studies were conducted that concentration of 25D vitamin form has a more beneficial impact on detaining from C-peptide deficiency than 1,25D vitamin form. Because of the late diagnosis of T1D there is loss of almost every B cell so it is suggested that preventive supplementation of vitamin D has to be taken under consideration [53].
Moreover vitamin D has a forthright impact on stimulation of insulin secretion and can cut down insulin resistance through minimisation of inflammation through deactivation of cytokines and encourage calbindin production [54].
During the analysis of studies on vitamin D supplementation for delaying type 1 diabetes, many publications emphasized the need for further research involving larger cohort groups and varying diabetes onset.

Multiple sclerosis
Multiple sclerosis is a chronic and progressive, demyelinating disease of the central nervous system. It occurs mainly in young adults, between the ages of 20 and 40. It is an autoimmune disorder. In multiple sclerosis the immune system attacks myelin in the central nervous system. The essence of the disease is diffuse damage to the brain and spinal cord involving atrophy of the myelin sheaths of nerve fibers (demyelination), resulting in varied neurological symptoms in the form of flares and slow progression of the disease.
The diagnosis of multiple sclerosis is based on a detailed history, neurological examination and additional tests. One of the laboratory tests used in diagnosing multiple sclerosis is cerebrospinal fluid analysis. The most valuable diagnostic method is magnetic resonance imaging (MRI) of brain and spinal cord. It allows visualization of demyelinating lesions, which are the basis for the diagnosis of the disease, assessment of its progression, activity and treatment results.
Treatment of multiple sclerosis (MS) primarily focuses on treating relapses, relieving symptoms, and using disease-modifying therapies. In Poland, therapies available include interferon β1a, interferon β1b, and glatiramer acetate. Glucocorticosteroids are regarded as the most effective for treating relapses and reducing their duration.
Due to the relationship between the risk of developing multiple sclerosis and climate zone - where the risk increases the further one is from the equator - the role of vitamin D is being highlighted more frequently. Research suggests that adequate vitamin D supplementation has a protective effect, lowering the risk of developing the disease and, in patients with MS, reducing both the frequency of relapses and the severity of the condition.
Studies indicate that vitamin D can modulate immune function by suppressing T cell proliferation, promoting regulatory T cell activity, and affecting the production of inflammatory cytokines. s. This potential to modulate the immune response has led to increased interest in the role of vitamin D supplementation in multiple sclerosis, a disease with a well-established autoimmune component [55]. Given the immunomodulatory effects of vitamin D and its high rate of deficiency in MS patients, prescribing vitamin D is a remarkable issue in MS.

There is a correlation between the level of serum vitamin D and MS risk and disease activity. The level of serum vitamin D affects the risk of developing MS and also modifies disease activity in MS patients. Higher levels of vitamin D are associated with reduced risk for developing multiple sclerosis (MS), and with reduced clinical activity in established MS. Research conducted on two large cohorts of women in the Nurses' Health Study found that higher dietary intake of vitamin D (approximately 700 IU per day) was associated with a 33% lower incidence of multiple sclerosis compared to those with lower intake. Additionally, women who took vitamin D supplements (over 400 IU per day) had a 41% reduced risk of developing MS compared to non-users [56].

Research on vitamin D levels is becoming increasingly important, especially in light of the results of the studies. The BEYOND and BENEFIT studies revealed that higher levels of vitamin D may affect disease activity, and that appropriate monitoring of these levels may be key to improving patients' conditions.

The BEYOND study, which included patients with established multiple sclerosis, found that higher levels of 25(OH)D were inversely correlated with the number of active MRI lesions, and that a 50 nmol/L increase in 25(OH)D levels was associated with a 31% lower incidence of new lesions. This study had a large group of participants and a diverse population, but was limited by a relatively short follow-up period. The authors noted that the lowest MS activity occurred in patients with 25(OH)D levels above 100 nmol/L, suggesting that many people with MS may have suboptimal levels of this vitamin [56].

The BENEFIT study was designed to evaluate the effect of early treatment with interferon beta-1b in patients with clinically isolated syndrome (CIS). CIS, or Clinically Isolated Syndrome, is the first neurological episode that may suggest the development of multiple sclerosis (MS). It is characterized by the onset of neurological symptoms that last at least 24 hours, but do not yet meet the criteria for a full diagnosis of MS. The BENEFIT study involved a large group of participants and regular measurements of serum vitamin D (25(OH)D) levels for five years. The results indicate that low 25(OH)D levels in the early phase of the disease are a strong risk factor for long-term MS activity. In the group of patients treated with early access to interferon, a stronger association was found between vitamin D levels and disease activity. Increasing 25(OH)D levels by 50 nmol/L reduced the number of active MRI lesions by 55% [56].

Analyses from the BENEFIT and BEYOND studies suggest that higher vitamin D levels may predict a lower risk of conversion to full-blown MS and lower disease activity. Patients with higher 25(OH)D levels had fewer new active MRI lesions and slower disease progression. In addition, early treatment with interferon beta-1b may act synergistically with vitamin D levels in reducing disease severity. These findings underscore the importance of monitoring and optimizing vitamin D levels in patients with early MS.

Researchers conducted randomized, placebo-controlled trial with vitamin D3 as an adjunct to interferon beta-1b treatment in patients with multiple sclerosis. Patients taking vitamin D (20,000 IU per week) tended to have a smaller increase in disease burden on MRI compared to the placebo group, but the difference was not statistically significant. Changes in other MRI parameters were mixed, with a significant reduction in the number of T1 lesions in the vitamin D group [56].

In another study, in which patients took high doses of vitamin D (an average of 14,000 IU per day), there were no significant adverse effects.

The annual relapse rate was lower in the vitamin D-treated group, and patients in this group reported a persistent reduction in T-cell proliferation [56].

Another study showed that in white people, the risk of multiple sclerosis (MS) decreases by 41% for every 50 nmol/L increase in 25-hydroxyvitamin D levels. The risk analysis showed that those with the lowest vitamin D levels had the highest risk of MS, while those with the highest levels had the lowest risk. In addition, those who had 25-hydroxyvitamin D levels above 100 nmol/L had a 51% lower risk of MS compared to those with levels below 75 nmol/L [57].

An observational study was conducted to evaluate the impact of vitamin D levels on disease activity in patients with relapsing-remitting multiple sclerosis (MS). In a study from the Netherlands, serum 25(OH)D was measured every 8 weeks for an average of 1.7 years in a group of 73 patients with relapsing-remitting MS. During this period, 58 patients experienced a total of 139 relapses. The risk of relapse was significantly lower in individuals with moderate (50–100 nmol/L) and high (> 100 nmol/L) serum vitamin D levels compared to those with low levels. Each doubling of serum vitamin D concentration from baseline levels of 10, 20, or 30 nmol/L was associated with a 27% reduction in relapse risk [58]. Findings from various experimental and clinical studies indicate that vitamin D supplementation may help reduce inflammation during relapse phases and slow disease progression.

In conclusion, the growing body of evidence underscores the significant role of vitamin D in the context of multiple sclerosis. Higher serum levels of vitamin D are consistently linked to a reduced risk of developing MS and a decrease in disease activity for those already diagnosed. As such, monitoring and optimizing vitamin D levels should be integral to the management of MS. More research is needed to establish the recommended levels of vitamin D supplementation necessary to reduce the risk for MS and MS clinical activity. By enhancing our understanding of this relationship, we can improve the quality of care and outcomes for individuals affected by this complex condition.

Table 1. Effects observed in patients with selected autoimmune diseases after the administration of vitamin D

Autoimmune disease	**Noticeable improvement in the patient after using vitamin D**	**Type of observed improvement in the patient**
Rheumatoid Arthritis	Inconclusive results; in some studies, improvement is achieved, while in others, it is not	Reduces the severity of symptoms (the VAS and DAS28-CRP scores are significantly lower) and improving laboratory parameters in the patient's blood (CRP levels decreased)
Hashimoto's thyroiditis	Yes	Improving laboratory parameters in the patient's blood (TSH, anty-Tg Ab levels decreased)

Ulcerative colitis	Yes	Improvement in quality of life and laboratory parameters in the patient's blood (CRP levels decreased)
Psoriasis	No	-
Type 1 diabetes	Yes	Improving laboratory parameters in the patient's blood (slows down the decrease of C-peptide and C-peptide increased)
Multiple sclerosis	Inconclusive results; in some studies, improvement is achieved, while in others, it is not	Reduces the risk of disease relapse

Table 2. Doses of vitamin D at which a significant improvement was observed in selected autoimmune diseases

Autoimmune disease	**Dose of vitamin D**
Rheumatoid Arthritis	> 4 000 IU of vitamin D once a day
Hashimoto's thyroiditis	50 000 IU of vitamin D once a week for 12 weeks
Ulcerative colitis	2 000 IU of vitamin D3 once a day for 90 days
Type 1 diabetes	6 000 IU of vitamin 25D monthly for 6 months
Multiple sclerosis	10 000 IU of vitamin D3 once a day for 24 months

CONCLUSIONS

Although the understanding of the vital role that vitamin D plays in our body, especially regarding its regulatory, metabolic, and modulatory functions, is comprehensive and still growing, it is yet to be established whether the deficiency of this vitamin is a consequence or potentially a contributing factor in certain diseases [3, 4, 5, 22].

Deepening knowledge of the multifaceted functions of vitamin D in the body could help prevent many diseases, such as musculoskeletal disorders (e.g., osteomalacia, osteoporosis, and rickets), as well as immune system dysfunctions, which are strongly correlated with an increased risk of multiple autoimmune diseases (e.g., rheumatoid arthritis, Hashimoto's disease, ulcerative colitis, multiple sclerosis, and type 1 diabetes) [10, 11, 12, 13].

Awareness of the mechanisms of vitamin D's synthesis enables physicians to identify potential causes of its deficiency and consider its supplementation in therapeutic processes, or at least monitor its levels. This is particularly important when the supplementation therapy is low-cost, relatively safe, and has minimal side effects.

Various studies, which results are summarized in the Table 1, have proven that appropriate supplementation of vitamin D may help not only in reducing the risk of disease exacerbations but also in preventing further complications, including premature death. This suggests it is possible to improve the quality of patients' lives without resorting to costly or invasive measures [19, 20, 26, 37, 40, 41, 46, 53, 56].Since it is inexplicably difficult to obtain a sufficient level of vitamin D3 daily solely from dietary sources and sun exposure and vitamin D deficiency is not uncommon in the general population, it is crucial to develop guidelines to establish specific supplementation protocols and doses of vitamin D that are suitable for individuals. These should consider factors such as age, sex, race, weight, overall state of health, comorbidities, sun exposure, drug interactions, and season—all of which influence vitamin D levels in the human body [14, 15, 19, 48]. The Table 2 sums up doses of vitamin D at which beneficial effects were observed in few autoimmune diseases - RA, HT, ulcerative colitis DM 1 and MS, but it is unknown whether they are optimal doses. Therefore large, well-conducted studies with appropriate heterogeneity worldwide are still needed to comprehensively clarify and refine treatment options for these diseases [15, 19, 39, 40, 41, 43, 46, 48, 55].

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