KOWALCZYK, Agata, KIEŁBASA , Justyna, PRZESTRZELSKA, Magda, RYKUCKA, Aleksandra, WĄS, Marcin, ZOZULA, Natalia, TOMCZEWSKA, Zuzanna, BIL, Katarzyna, ŚLESICKA, Iga and LATAŁA, Aleksandra. The role of vitamin D in multiple sclerosis and its mechanisms of action. Quality in Sport. 2024;19:54188. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.54188
https://apcz.umk.pl/QS/article/view/54188

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 09.08.2024. Revised: 19.08.2024. Accepted: 29.08.2024. Published: 01.09.2024.

The role of vitamin D in multiple sclerosis and its mechanisms of action

Agata Kowalczyk, Justyna Kiełbasa, Magda Przestrzelska, Aleksandra Rykucka, Marcin Wąs, Natalia Zozula, Zuzanna Tomczewska, Katarzyna Bil, Iga Ślesicka, Aleksandra Latała,

Agata Kowalczyk [AK]
Mazovian Specialized Hospital in Ostrołęka of Józef Psarski, Jana Pawła II 120A, 07-410 Ostrołęka, Poland
https://orcid.org/0009-0007-9497-0970
agata.kowalczyk95@gmail.com

Justyna Kiełbasa [JK]
Independent Public Healthcare Complex in Pruszków 2/4 Armii Krajowej Avenue, 05-800 Pruszków, Poland
https://orcid.org/0009-0002-0616-7402
justynakielbasa1b@gmail.com

Magda Przestrzelska [MP]

Faculty of Medicine Collegium Medicum Uniwersytet Kardynała Stefana Wyszyńskiego w Warszawie
Wóycickiego 1/3, 01-938 Warszawa, Poland
https://orcid.org/0009-0009-8688-7047
magda.przestrzelska123@gmail.com

Aleksandra Rykucka [AR]
Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital with Outpatient Clinic named after in Gdańsk Polanki 117 street, 80-305 Gdańsk, Poland
https://orcid.org/0009-0003-0171-8647
aleksandra.rykucka@wp.pl

Marcin Wąs [MW]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec, Poland
https://orcid.org/0009-0004-8645-0121
mos1@vp.pl

Natalia Zozula [NZ]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec, Poland
https://orcid.org/0009-0009-9741-5061
nataliazozula0@gmail.com

Zuzanna Tomczewska [ZT]
Provincial Specialist Hospital named after Blessed Father Jerzy Popiełuszko in Włocławek, Wieniecka 49, 87-800 Włocławek, Poland
https://orcid.org/0000-0002-4327-3311
ztomczewska@gmail.com

Katarzyna Bil [KB]
Independent Public Specialist Western Hospital named after St John Paul II,
Daleka 11, 05-825 Grodzisk Mazowiecki, Poland
https://orcid.org/0009-0003-6518-1711
katarzynabil2503@gmail.com

Iga Ślesicka [IŚ]
Mazovian Specialized Hospital in Ostrołęka of Józef Psarski, Jana Pawła II 120A, 07-410 Ostrołęka, Poland
https://orcid.org/0000-0001-7282-4875
igaslesicka@gmail.com

Aleksandra Latała [AL]
District Medical Center in Grójec Piotra Skargi 10 street, 05-600 Grójec, Poland
https://orcid.org/0009-0007-1701-2728
aleksandra.latala10@gmail.com

ABSTRACT

Introduction and Purpose: Multiple sclerosis (MS) is a prevalent autoimmune disease affecting the central nervous system, particularly in young people. Characterized by neurodegenerative and demyelinating processes, MS is influenced by genetic and environmental factors. Research indicates that sufficient levels of vitamin D can reduce the risk of developing MS. Studies show that higher sun exposure and dietary vitamin D intake are associated with a lower incidence of MS. Moreover, vitamin D supplementation may benefit those already diagnosed by alleviating symptoms and improving their quality of life. This review explores the potential benefits of vitamin D and its neuroprotective mechanisms in MS.

State of Knowledge: MS research and treatments have focused on immunomodulation, with less emphasis on neuroprotection, including the role of vitamin D. It is well-established that vitamin D has anti-inflammatory effects on the immune system in MS. It influences the proliferation and differentiation of neural stem cells and oligodendrocytes, enhances neurotrophin expression, reduces reactive astrogliosis, decreases oxidative stress, and stabilizes the blood-brain barrier. Research suggests that adequate vitamin D levels and supplementation might improve MS outcomes.

Conclusion: New diagnostic tools and therapeutic strategies are urgently needed to address the complex nature of MS, which includes inflammation, neuronal death, demyelination, and oxidative stress. Promoting vitamin D sufficiency and supplementation, alongside developing new neuroprotective agents, remains a valuable approach in combating MS. Understanding

the mechanisms of MS and the effects of vitamin D could lead to better management strategies and enhanced quality of life for patients.

Keywords: vitamin D, multiple sclerosis, neuroprotection, neurodegeneration

1. Introduction and purpose:

Multiple sclerosis (MS) is a prevalent autoimmune disease affecting the central nervous system, commonly seen in young individuals. It is characterized by neurodegenerative and demyelinating processes that arise from a combination of genetic and environmental factors. Research indicates that maintaining adequate vitamin D levels can reduce the risk of developing MS. Studies have found that increased sun exposure and dietary intake of vitamin D correlate with a lower incidence of MS. Vitamin D supplementation is considered a crucial method for modifying disease risk. Additionally, some research suggests that vitamin D supplementation may benefit individuals already diagnosed with MS, potentially leading to milder symptoms and less frequent occurrences, thereby improving quality of life. This review aims to highlight the potential benefits of vitamin D on nerve cells and summarize the current evidence regarding the neuroprotective mechanisms of vitamin D in multiple sclerosis.

2. Description of the state of knowledge:

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system and probably the most common cause of neurological dysfunctions in group of young people. The disorder involves neurodegenerative and demyelinating components, which are results from an interplay of environmental and genetic factors [1]. MS is initiated by immune cells that cross the blood-brain barrier and cause abnormal immune responses leading to demyelination and neuroaxonal damage in the brain, spinal cord and retina [2, 3]. Adaptive immune cells play a significant role in the pathogenesis of the disease: cytotoxic T lymphocytes (CD8+), helper T lymphocytes (CD4+) and as the disease progresses plasma cells and B lymphocytes. Activation of immune system cells is associated with the secretion of proinflammatory cytokines and the recruitment of subsequent cells, which leads to the formation of perivascular cellular infiltration. The progression of the inflammatory process leads to the destruction of the blood-brain barrier and allows T lymphocytes to enter the central nervous system (CNS). The consequence of this process is the formation of demyelinating foci, where activated microglia and macrophages absorb myelin debris, leading to neurodegeneration and damage to axons deprived of the myelin sheath. In the course of MS, secondary hypertrophy of astroglial also occurs. The development of lymphatic tissue takes

place in the connective tissue compartments of the brain, which is responsible for the ongoing inflammation and consequently, further progression of the disease [4]. The clinical symptoms of the disease observed in patients, depend on the location of the lesions in the central nervous system. Most patients, approximately 80%, present symptoms that are non-specific, including: fatigue, spasticity, depression, euphoria, sexual dysfunction, and slight cognitive impairment [5, 6]. More common symptoms of multiple sclerosis are neurological disorders such as sensory and gait disorders, limb weakness, vision problems, urination disorders, and constipation [7]. Other symptoms noticeable during the examination include: the Unthoff's phenomenon, characterized by a transient intensification or fluctuation of MS symptoms with a rise in body temperature and the Lhermitte's phenomenon, which is an abnormal sensation of electric shock down the spine or limbs, caused by bending the head forward [8]. It should be noted that the sudden appearance of focal neurological signs or symptoms, e.g. numbness, aphasia, visual disturbances, paresthesia, are the main reason for hospitalization of patients [5, 6].

The diagnosis of multiple sclerosis is based on McDonald criteria. The diagnostic criteria have undergone numerous changes in the past, but the original ones were published in 1965 as the Schumacher criteria, based on temporal and spatial dissemination focal neurological deficits [9]. Currently, the 2017 McDonald criteria facilitate the diagnosis of MS. They are based on clinical grounds, but when clinical evidence is lacking, it is possible to use other diagnostic methods like magnetic resonance imaging and try to prove the presence of demyelinating lesions. This means that, the sensitivity of diagnosis is significantly increased in patients with the first episode of the disease without compromising the specificity [10]. To standardize terminology and enhance consistency in clinical trials, a 1996 study defined four distinct MS phenotypes: relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and progressive-relapsing (PRMS) MS. In 2013, this classification was revised to include the concepts of disease activity characterized by relapses and/or lesion formation on MRI and disease progression. This updated framework categorizes patients as either active or nonactive and progressing or nonprogressing, thus aiding in the identification of patients who might benefit from disease-modifying treatments [11].

Multiple sclerosis (MS) manifests in various phenotypes, with 80% of cases initially presenting as clinically isolated syndrome (CIS). CIS entails an acute attack on one or more CNS sites and may transition to relapsing-remitting MS (RRMS); this occurs at a rate of 21%

with normal baseline MRI versus 82% with silent white matter lesions. Early-stage RRMS shows good relapse recovery, driven by inflammatory processes involving autoreactive lymphocytes crossing the blood-brain barrier. Over 10-15 years, 80% of RRMS patients progress to secondary progressive MS (SPMS), marked by axonal injury, grey and white matter atrophy, and reduced inflammation. Around 10-15% of MS patients display primary progressive MS (PPMS) from the onset, typically starting around age 40 and associated with progressive spinal cord-related symptoms [8, 12].

Regrettably, there is no cure for MS, and the available therapies offer only partial effectiveness, mainly delaying the disease's progression and they are mainly aimed at treating the relapsing-remitting phases, not the progressive phase. At present, the primary focus of MS treatments is on targeting the inflammatory phase of the disease, which, while significant, is not the only critical aspect. Therefore, therapeutic strategies must address not only inflammatory mechanisms but also other critical processes such as neuronal death, demyelination, and oxidative stress. As the disease progresses, nerve dysfunction and demyelination become more critical than inflammation. Approved medications do not alter the disease's trajectory, highlighting the urgent need for new therapeutic strategies. Developing novel diagnostic tools and treatments is essential to effectively combat MS and reduce the severe side effects of existing treatments, such as cancer and liver damage, ultimately improving patients' quality of life and reducing long-term consequences [13]. Treatments for multiple sclerosis encompass a variety of drugs, including interferon (IFN) beta-1a and beta-1b, fingolimod, ozanimod, and siponimod (sphingosine-1-phosphate receptor modulators), natalizumab (a monoclonal antibody targeting alpha4-integrin), dimethyl fumarate, glatiramer acetate, teriflunomide, cladribine (2-chlorodeoxyadenosine), rituximab (a chimeric anti-CD20 monoclonal antibody), ocrelizumab, ofatumumab (a humanized anti-CD20 monoclonal antibodies), alemtuzumab (a humanized anti-CD52 monoclonal antibody) and mitoxantrone (an inhibitor of the proliferation of B cells, T cells, and macrophages). These medications aim to accelerate recovery from relapses, decelerate disease progression, and manage symptoms. However, side effects often necessitate discontinuation of treatment due to intolerance, and in rare instances, more severe adverse events may occur [9, 14, 15].

The etiology of multiple sclerosis (MS) is widely recognized as multifactorial, involving a complex interaction between genetic predisposition and environmental influences like: infectious agents, obesity, vitamin D deficiency and smoking that contribute to immune system dysregulation and central nervous system (CNS) inflammation. Although the precise

cause of MS remains elusive, an individual's genetic profile is thought to significantly impact their risk of developing the disease. Historically, the primary genetic risk factors identified were the human leukocyte antigen (HLA) genes [16, 17]. The HLA genes significantly influence T cell immune reactivity. HLA molecules present antigens to T cells, and certain haplotypes increase disease susceptibility by potentially initiating or perpetuating autoimmune responses against CNS components. Molecular mimicry, where pathogens resemble self-antigens, can trigger cross-reactive immune responses. This can enhance autoimmune cascades in MS, as specific HLA haplotypes might present both pathogen-derived and self-antigens, leading to an attack on CNS tissues [16]. Genome-wide association studies (GWAS) have identified over 200 genetic variants associated with MS risk [18], many in the MHC region on chromosome 6, which is crucial for antigen presentation and T-cell activation. Variants in genes related to immune regulation, like the interleukin 7 receptor (IL7R), also increase MS risk by affecting T-cell function [19]. Despite identifying many variants, the genetic complexity of MS suggests there are still numerous undiscovered factors contributing to the disease's heritability [16]. Genetic studies have identified variants in immune function that contribute to MS risk, offering insights into the disease's biology. However, genetic factors alone are insufficient to cause MS; environmental factors like viral infections, smoking, and vitamin D deficiency are also crucial. These factors interact with genetic predisposition to influence disease susceptibility [17, 20-22]. For instance, variants in genes involved in vitamin D metabolism are linked to an increased risk of MS, indicating that vitamin D deficiency may play a role. Research shows low vitamin D levels are associated with a higher MS risk and that supplementation might reduce disease activity [16, 23]. MS prevalence is higher among individuals of Northern European descent, partly due to their skin's efficiency in synthesizing vitamin D from sunlight [24]. Additionally, living far from the equator during early childhood, which often correlates with lower levels of vitamin D, is also considered a contributing factor [25]. A significant association exists between genetically reduced 25-hydroxyvitamin D (25(OH)D) levels and an increased risk of developing multiple sclerosis. Further long-term randomized controlled trials are needed to investigate whether maintaining sufficient vitamin D levels can delay or prevent the onset of MS [26]. For nearly a century, researchers have explored the link between viruses and the development of multiple sclerosis. Jean-Martin Charcot and Pierre Marie, in the late 19th century, suggested an infectious basis for MS. Initial evidence showed increased titers of rubella and measles in the cerebrospinal fluid of MS patients. The viral hypothesis was further supported in the 1980s

when studies revealed higher antibody levels against Epstein-Barr virus (EBV) and herpes simplex virus 2 in MS patients compared to healthy controls. Other viruses such as varicella-zoster, herpes simplex 1 and 2, HHV-6, and cytomegalovirus (CMV) have also been implicated. These viruses can infiltrate the brain, establish chronic latent infections, and potentially induce an autoimmune response against the myelin sheath, causing demyelination and neurodegeneration. Moreover, viruses may modify host gene expression, leading to tissue damage. While the infectious origin of MS remains debated, viruses are acknowledged as potential risk factors in individuals with a genetic predisposition [16, 17]. Smoking is another factor that increases MS risk and can lead to more severe disease progression. Cigarette smoke impacts the immune system at the cellular level by promoting the production of proinflammatory cytokines. Smokers exhibit elevated levels of these cytokines, such as IL-6, along with increased concentrations of C-reactive protein, fibrinogen, and other inflammatory markers. Chronic exposure to high levels of proinflammatory cytokines may lead to ongoing autoimmune responses [21, 27]. Additionally, diet impacts MS risk; high saturated fat intake and low consumption of fruits and vegetables are linked to higher risk, while diets rich in omega-3 fatty acids and antioxidants may reduce disease activity [28].
The risk of developing multiple sclerosis tends to rise as one moves farther from the equator. Populations in Northern Europe exhibit a higher prevalence of the disease. However, if people relocate from high-risk regions to areas with a lower risk of developing multiple sclerosis during their early childhood, their likelihood of developing the disease diminishes [22].

Multiple sclerosis is a condition predominantly affecting young adults, typically starting between the ages of 20 and 40, with a higher incidence in women. It is estimated that around 2.3 million individuals globally have MS, but this number may be underestimated due to incomplete data from some regions of the world [8, 26, 29]. Research underscores the significant impact of MS on young adults. For instance, it is highlighted that MS is one of the primary causes of neurological disability in this demographic, contributing to substantial personal and societal burdens due to long-term disability [30] .

Increasing evidence suggests that lifestyle modification, which involves changing long-term habits such as diet and physical activity, as well as adopting behaviours to reduce recognized risk factors, effectively manages disease progression and symptom severity in multiple sclerosis. Avoiding smoking, maintaining a healthy diet, engaging in physical activity, ensuring adequate vitamin D levels, supplementing with omega-3 fatty acids are all associated

with reducing the chronic inflammatory state of MS. These modifications lead to improved health outcomes, including better mental and physical quality of life, a reduced relapse rate, lower depression risk, and decreased clinically significant fatigue, thereby lessening the overall burden of disability and symptoms [31].

Vitamin D

Vitamin D, a hormone with ancient evolutionary roots, plays essential roles in various human physiological processes. It helps maintain calcium and phosphate balance, supports bone growth, and regulates cardiometabolic and immune functions [32, 33]. Recent studies highlight its significant impact on the composition and activity of the gut microbiota. Despite its crucial role, vitamin D deficiency is prevalent worldwide, contributing to numerous health issues, including chronic and autoimmune diseases. This deficiency is exacerbated by factors such as decreased sun exposure due to lifestyle changes and migration to less sunny regions. To combat this, vitamin D supplementation is widely recommended, usually in daily or weekly/monthly bolus doses. However, the optimal supplementation regimen remains a subject of ongoing research and debate [32]. Regions between latitudes 40° North and 40° South receive sufficient UVB radiation throughout the year to enable the production of vitamin D in the skin. In contrast, areas outside these latitudes lack available UVB radiation during winter, requiring individuals in these regions to depend on dietary sources and supplements to maintain adequate serum vitamin D levels [34]. Vitamin D can be sourced from natural foods like fatty fish and egg yolks, and also from fortified items such as UV-irradiated mushrooms and supplements including fish oil. In the dietary context, enzymes like trypsin and pepsin are involved in vitamin D absorption by releasing it from binding proteins found in food. Furthermore, in the duodenum, enzymes such as amylase, lipase, and protease facilitate the release of vitamin D from the food matrix, improving its absorption in the small intestine [33]. As a fat-soluble hormone, the absorption of dietary vitamin D depends on the amount of fat consumed [35].

Vitamin D exists in two primary forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2 is produced by plants, specifically through the ultraviolet irradiation of ergosterol in certain mushrooms and yeasts. In contrast, vitamin D_3 is synthesized in the skin's epidermis through a series of chemical reactions. These reactions start when 7-dehydrocholesterol, a cholesterol type found in the skin, is exposed to UVB radiation (in the spectral range of 290–320 nm) from sunlight [36]. This UVB radiation converts 7-dehydrocholesterol into pre-vitamin D_3, which then undergoes thermal

isomerization to become cholecalciferol [23, 32, 37]. Vitamin D must undergo activation through two sequential hydroxylation steps. The initial hydroxylation occurs in the liver, where cholecalciferol is rapidly converted into 25-hydroxyvitamin D (25(OH)D) by the enzyme 25-hydroxylase, also known as CYP2R1, which is CYP450-dependent. This process is not regulated. The second hydroxylation happens mainly in the kidneys, but also in other tissues, further activating the vitamin D [38]. Low plasma calcium or phosphate levels regulate parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) levels, which in turn stimulate the 1α-hydroxylation of 25(OH)D in the kidneys. This process primarily occurs in the mitochondria of proximal convoluted tubule cells and is facilitated by the enzyme 1α-hydroxylase (CYP27B1), resulting in the production of active forms of vitamin D ($1,25(OH)_2D_2$ - 1,25-dihydroxyvitamin D_2 and $1,25(OH)_2D_3$ - 1,25-dihydroxyvitamin D_3) [39]. The process of 1α-hydroxylation can also take place in several extrarenal tissues, such as epithelial tissues, placenta, bone, brain, endocrine glands, endothelium, liver [40, 41] and notably in immune cells [40-44]. In target cells, both $1,25(OH)_2D_2$ and $1,25(OH)_2D_3$ bind to the VDR (vitamin D receptor), forming a complex with the retinoid X receptor γ (RXR-γ). This complex then binds to vitamin D response elements in DNA, modifying the transcription rates of genes involved in numerous functions, including immune regulation and cellular proliferation and differentiation [45]. However, because vitamin D_3 is primarily synthesized in the skin, $1,25(OH)_2D_3$ is more commonly recognized as the active form of vitamin D in the human body [42-44].

Mechanisms of vitamin D action

The vitamin D receptor (VDR) is a nuclear receptor for steroid hormones that acts as a ligand-activated transcription factor, regulating gene expression. It is crucial for the genomic actions of vitamin D and one of the most potent regulators of the vitamin D receptor's function is 1,25(OH)D [36]. The inner surface of the vitamin D receptor (VDR) has a ligand-binding pocket that encloses and binds 1,25(OH)D with an exceptionally high affinity of 0.1 nM, which is much higher compared to other nuclear receptors. When 1,25(OH)D activates the VDR, it directly affects the epigenome and regulates the expression of over 1,000 genes in various human tissues and cell types, leading to significant changes in both the transcriptome and proteome. Remarkably, 1,25(OH)D uniquely targets the VDR within the cell nucleus [36, 46]. Vitamin D deficiency is associated not only with MS but also with several other autoimmune disorders [45]. Studies conducted both in vitro and in vivo have demonstrated

that $1,25(OH)_2D_3$ exhibits anti-inflammatory effects by suppressing both the innate and adaptive immune systems [47].

Oligodendrocyte proliferation and differentiation promotion

Key pathological features in MS demyelination include oligodendrocyte dystrophy and apoptosis. Oligodendrocytes, which support neurons by producing myelin in the CNS, are capable of remyelinating neuronal axons during tissue injury to ensure proper brain function. This remyelination process is robust in early MS but declines during later stages. Oligodendrocyte regeneration depends on the availability of neural stem cells (NSCs) and oligodendrocyte progenitor cells (OPCs). In progressive MS, the capacity of NSCs and OPCs to regenerate oligodendrocytes diminishes, leading to neuronal degeneration and impaired axonal conduction [48]. Both OPCs and oligodendrocytes express the vitamin D receptor (VDR) [49], which is essential for OPC differentiation through VDR-RXR signalling [48, 50]. Blocking VDR reduces the neuroprotective effects of $1,25(OH)_2D_3$ on these cells [51]. Studies indicate that VDR is constitutively expressed in NSCs and that increasing vitamin D levels upregulates VDR expression, enhancing NSC proliferation and their differentiation into oligodendrocytes. In a lysolecithin-induced model in rats, treatment with $1,25(OH)_2D_3$ resulted in a higher concentration of OPCs at lesion sites compared to controls, suggesting a potential therapeutic effect of vitamin D in promoting remyelination and repair in MS [48]. In a murine experimental autoimmune encephalomyelitis (EAE) model, administering $1,25(OH)_2D_3$ led to increased concentrations of NSCs, OPCs, and oligodendrocytes. EAE models, which display both immune-mediated inflammation and demyelination, are often considered more representative of MS pathogenesis compared to demyelination-only models. Furthermore, the administration of $1,25(OH)_2D_3$ upregulated the expression of myelin basic protein and proteolipid protein, both markers of myelin content. This upregulation indicates that $1,25(OH)_2D_3$ may reduce demyelination and/or enhance remyelination [52].

Neurotrophin expression enhancement

Inadequate neuroprotection in neurodegenerative disorders like MS is partly due to reduced neurotrophin secretion. Neurotrophins, a family of proteins, stimulate the proliferation and differentiation of neural stem cells (NSCs) and support the growth, survival, and function of neuronal and glial cells. Various cell types, including NSCs, neurons, oligodendrocytes, astrocytes, and M2 microglia, secrete neurotrophins. Key neurotrophins such as NT-3, BDNF, CNTF, GDNF, and NGF play protective and regenerative roles. Vitamin D can increase

neurotrophin secretion, potentially creating a less neurotoxic environment that promotes the repair and regeneration of CNS cells [48, 53].

Mitigating reactive astrogliosis

Astrocytes make up a significant portion of glial cells in the CNS. They perform crucial roles such as supporting neuronal growth metabolically, signaling immune cell entry into the CNS, and being a key component of the blood-brain barrier (BBB). When the CNS is injured, astrocytes become reactive and rapidly divide, a process known as astrogliosis, which has both beneficial and detrimental effects [54]. Reactive astrocytes help recovery by forming a glial scar at the site of demyelination, preventing the injury from spreading [55]. However, an excessive increase in reactive astrocytes can contribute to the development of MS lesions [48] by releasing pro-inflammatory cytokines and reactive oxygen species (ROS), which are neurotoxic to OPCs, oligodendrocytes, and neurons [56]. Reducing astrocyte activation and abundance could create a more favorable environment for neurodegeneration repair processes. MS plaques with fewer reactive astrocytes show increased OPC content and enhanced remyelination. In LPS-stimulated rats (rats that have been exposed to lipopolysaccharide), astrocytes upregulated VDR and CYP27B1 expression, suggesting a potential vitamin D response. Studies in rodent models of cuprizone-induced demyelination and LPS injection demonstrated that intraperitoneal injections of $25(OH)D_3$ and $1,25(OH)_2D_3$ reduced astrocyte concentration and activation [48].

Reducing the activation of pro-inflammatory and neurodegenerative microglia

Microglia are essential for normal CNS development and maintenance. In multiple sclerosis, activated microglia are prevalent in demyelination plaques and contribute to disease progression. These activated microglia are polarized into two phenotypes: M1, which are pro-inflammatory and neurotoxic, and M2, which are anti-inflammatory and neuroregenerative, existing likely on a continuum [57, 58]. Evidence suggests that increased vitamin D exposure can reduce the M1 phenotype. In cultured microglia exposed to $1,25(OH)_2D_3$ and in vitamin D-supplemented mouse models, there is a reduction in pro-inflammatory cytokines IL-12, IL-6, IL-1β and TNF-α. This reduction supports the survival of oligodendrocytes and neurons [48]. Additionally, vitamin D promotes a shift towards the neuroprotective M2 phenotype [59]. Studies indicate that vitamin D is associated with increased levels of M2-associated cytokines, including IL-4, IL-10, and TGF-β1. These cytokines are involved in regenerative CNS functions such as oligodendrogenesis and neurogenesis [48, 60] .

Mitigating oxidative stress

Oxidative stress is another crucial factor in the pathogenesis of MS. Normally, reactive oxygen species (ROS) like nitric oxide, hydrogen peroxide and superoxide are produced during cellular respiration when electrons escape the electron transport chain and react with oxygen. Under normal conditions, low levels of ROS are neutralized by antioxidant enzymes in cells [48]. However, in MS, the inflammatory environment continuously activates various cells, including peripheral immune cells, microglia, and astrocytes, which release ROS and pro-inflammatory cytokines, thereby amplifying inflammation through a positive feedback loop [61]. Microglia and peripheral macrophages are the primary ROS producers in MS. Despite the increased production of ROS in MS, their neutralization is hindered by decreased expression of antioxidant enzymes [48]. Vitamin D has been shown to reduce oxidative stress in the CNS tissue of EAE mice [62]. Treatment with $1,25(OH)_2D_3$ lowered oxidative stress biomarkers (lipid hydroxides and protein carbonyls) and restored the expression of antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase) to normal levels [63]. Additionally, vitamin D sufficiency and supplementation are associated with reduced oxidative stress and elevated antioxidant biomarkers [48].

Stabilization of the blood-brain barrier

The blood-brain barrier (BBB) constitute a complex network that creates a continuous cellular barrier between the CNS and systemic circulation [48, 64]. The BBB controls the entry of molecules, ions, and cells from the blood into the CNS, thereby stabilizing and protecting the neuronal environment [64, 65]. In MS, the BBB breakdown and increased permeability occur early in the disease process [48]. Pro-inflammatory cytokines from various immune cells stimulate endothelial cells of the BBB, leading to the downregulation of tight junctions and upregulation of cell adhesion molecules [66]. This destabilizes the BBB, enhancing leukocyte recruitment into the CNS, allowing CD4+ Th1 and Th17 cells to enter and release cytokines that cause oligodendrocyte and myelinated axon degeneration [67]. Vitamin D is believed to mitigate BBB hyperpermeability through several mechanisms. It has been shown that $1,25(OH)_2D_3$ can directly act on endothelial cells to upregulate tight junction proteins and downregulate cell adhesion molecules, both of which contribute to BBB stabilization [48]. Additionally, vitamin D may reduce matrix metalloproteinase-9 (MMP-9) expression, further promoting BBB stabilization. $1,25(OH)_2D_3$ has been found to lower MMP-9 expression in mouse brain endothelial cells and in a rat model of ischemic stroke. MMPs degrade extracellular matrix components, which contributes to BBB instability [59].

3. Conclusions:

Multiple sclerosis is an autoimmune disease that affects the central nervous system, characterized by neurodegenerative and demyelinating processes and continues to be serious problem worldwide. These processes are influenced by both genetic and environmental factors [1]. There is no cure for MS, current treatments focus on managing symptoms and delaying disease progression, especially during the relapsing-remitting phases [13]. These treatments include various drugs such as interferons, monoclonal antibodies, and immunomodulators. However, these treatments have limitations and side effects, highlighting the need for new therapeutic strategies that address not only inflammation but also neuroprotection and remyelination [9, 14, 15]. Vitamin D plays a significant role in modulating immune responses is considered potential neuroprotective agent in MS and may help reduce MS progression [16, 23, 26]. Recent studies have shown positive results regarding its neuroprotective effects. Vitamin D supports neurons by promoting neurotrophin expression, which stimulate neurogenesis and protect against degeneration and apoptosis. It also shifts microglia towards the M2 phenotype, reducing inflammation, and suppresses M1 microglia and reactive astrocytes, decreasing pro-inflammatory cytokines and ROS. Additionally, vitamin D helps stabilize the blood-brain barrier, reducing the entry of autoreactive T-cells. These effects collectively create a stable environment for CNS glial cells to aid in neuronal repair and recovery [48, 52-56, 58, 64, 65]. Studies suggest that adequate vitamin D levels and supplementation may improve MS outcomes [32]. MS is a multifactorial disease involving genetic predisposition, environmental factors (e.g., smoking, obesity, vitamin D deficiency), and infections. Genetic studies have identified multiple variants associated with MS risk, and environmental factors interact with these genetic predispositions to influence disease susceptibility [16, 17, 20-22]. There is an urgent need for new diagnostic tools and therapeutic approaches that address the complex nature of MS, including inflammation, neuronal death, demyelination, and oxidative stress. Enhancing our understanding of MS mechanisms and the role of vitamin D could lead to better management strategies and improved quality of life for patients [13, 26].

DISCLOSURES

Author's contribution:

Conceptualization: Agata Kowalczyk, Justyna Kiełbasa, Katarzyna Bil

Methodology: Zuzanna Tomczewska

Software: Marcin Wąs

Check: Agata Kowalczyk, Iga Ślesicka

Formal analysis: Justyna Kiełbasa, Katarzyna Bil

Investigation: Magda Przestrzelska, Iga Ślesicka

Resources: Aleksandra Rykucka, Zuzanna Tomczewska

Data curation: Natalia Zozula, Aleksandra Rykucka

Writing–rough preparation: Aleksandra Latała, Justyna Kiełbasa, Katarzyna Bil

Writing–review and editing: Natalia Zozula, Magda Przestrzelska

Visualization: Agata Kowalczyk, Marcin Wąs

Supervision: Aleksandra Latała, Natalia Zozula

Project administration: Marcin Wąs

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interests: The authors declare no conflict of interest.

References:

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359(9313):1221-1231. doi:10.1016/s0140-6736(02)08220-x

2. Wang W, Li Y, Meng X. Vitamin D and neurodegenerative diseases. Heliyon. 2023:e12877. doi:10.1016/j.heliyon.2023.e12877

3. Koduah P, Paul F, Dörr JM. Vitamin D in the prevention, prediction and treatment of neurodegenerative and neuroinflammatory diseases. EPMA J. 2017;8(4):313-325. Published 2017 Nov 15. doi:10.1007/s13167-017-0120-8

4. Lassmann H, Brück W, Lucchinetti CF. The Immunopathology of Multiple Sclerosis: An Overview. Brain Pathol. 2007;17(2):210-218. doi:10.1111/j.1750-3639.2007.00064.x

5. Kamińska J, Koper O, Piechal K, Kemona H. Multiple sclerosis - etiology and diagnostic potential. Advances in Hygiene and Experimental Medicine. (2017);71(null):551-563. doi:10.5604/01.3001.0010.3836. Polish.

6. Rodzajewska A, Kuryło W. The efficacy of vitamin D in multiple sclerosis: a review. J Educ Health Sport. 2023;32(1):156-171. doi:10.12775/jehs.2023.32.01.012. Polish.

7. Institute of Medicine (US) Committee on Multiple Sclerosis: Current Status and Strategies for the Future. Multiple Sclerosis: Current Status and Strategies for the Future. (Joy JE,

Johnston RB, eds.). National Academies Press (US); 2001. Accessed May 2, 2024. http://www.ncbi.nlm.nih.gov/books/NBK222399/

8. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med. 2016;16(Suppl 6):s53-s59. doi:10.7861/clinmedicine.16-6-s53

9. Baskaran AB, Grebenciucova E, Shoemaker T, Graham EL. Current Updates on the Diagnosis and Management of Multiple Sclerosis for the General Neurologist. J Clin Neurol. 2023;19(3):217-229. doi:10.3988/jcn.2022.0208

10. Ntranos A, Lublin F. Diagnostic Criteria, Classification and Treatment Goals in Multiple Sclerosis: The Chronicles of Time and Space. Curr Neurol Neurosci Rep. 2016;16(10). doi:10.1007/s11910-016-0688-8

11. Pitt D, Lo CH, Gauthier SA i in. Toward Precision Phenotyping of Multiple Sclerosis. Neurol Neuroimmunol Neuroinflammation. 2022;9(6):e200025. doi:10.1212/nxi.0000000000200025

12. Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. New Engl J Med. 2018;378(2):169-180. doi:10.1056/nejmra1401483

13. Coveñas R, Marcos P, Mangas A. Editorial: New drugs, approaches and strategies for multiple sclerosis treatment. Front Neurosci. 2024;18. doi:10.3389/fnins.2024.1372140

14. Apostolopoulos V, Matsoukas J. Advances in Multiple Sclerosis Research–Series I. Brain Sci. 2020;10(11):795. doi:10.3390/brainsci10110795

15. Yang JH, Rempe T, Whitmire N, Dunn-Pirio A, Graves JS. Therapeutic Advances in Multiple Sclerosis. Front Neurol. 2022;13. doi:10.3389/fneur.2022.824926

16. Landry RL, Embers ME. The Probable Infectious Origin of Multiple Sclerosis. NeuroSci. 2023;4(3):211-234. doi:10.3390/neurosci4030019

17. Waubant E, Lucas R, Mowry E i in. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol. 2019;6(9):1905-1922. doi:10.1002/acn3.50862

18. Cotsapas C, Mitrovic M. Genome-wide association studies of multiple sclerosis. Clin Amp Transl Immunol. 2018;7(6):e1018. doi:10.1002/cti2.1018

19. Galarza-Muñoz G, Briggs FB, Evsyukova I i in. Human Epistatic Interaction Controls IL7R Splicing and Increases Multiple Sclerosis Risk. Cell. 2017;169(1):72-84.e13. doi:10.1016/j.cell.2017.03.007

20. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. Mult Scler Relat Disord. 2017;14:35-45. doi:10.1016/j.msard.2017.03.014

21. Putscher E, Hecker M, Fitzner B i in. Genetic risk variants for multiple sclerosis are linked to differences in alternative pre-mRNA splicing. Front Immunol. 2022;13. doi:10.3389/fimmu.2022.931831
22. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018;391(10130):1622-1636. doi:10.1016/s0140-6736(18)30481-1
23. Sintzel MB, Rametta M, Reder AT. Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol Ther. 2017;7(1):59-85. doi:10.1007/s40120-017-0086-4
24. Kingwell E, Marriott JJ, Jetté N i in. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC Neurol. 2013;13(1). doi:10.1186/1471-2377-13-128
25. Simpson S, Blizzard L, Otahal P, Van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Amp Psychiatry. 2011;82(10):1132-1141. doi:10.1136/jnnp.2011.240432
26. Mokry LE, Ross S, Ahmad OS i in. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. PLOS Med. 2015;12(8):e1001866. doi:10.1371/journal.pmed.1001866
27. Nishanth K, Tariq E, Nzvere FP, Miqdad M, Cancarevic I. Role of Smoking in the Pathogenesis of Multiple Sclerosis: A Review Article. Cureus. 2020;12(8):e9564. Published 2020 Aug 5. doi:10.7759/cureus.9564
28. Stoiloudis P, Kesidou E, Bakirtzis C i in. The Role of Diet and Interventions on Multiple Sclerosis: A Review. Nutrients. 2022;14(6):1150. doi:10.3390/nu14061150
29. Gandhi F, Jhaveri S, Avanthika C, et al. Impact of Vitamin D Supplementation on Multiple Sclerosis. Cureus. 2021;13(10):e18487. Published 2021 Oct 5. doi:10.7759/cureus.18487
30. Ismail II, Saqr M. A Quantitative Synthesis of Eight Decades of Global Multiple Sclerosis Research Using Bibliometrics. Front Neurol. 2022;13. doi:10.3389/fneur.2022.845539
31. Neate SL, Donald A, Jelinek GA, Nag N. Experiences of and attitudes to lifestyle modification for the management of multiple sclerosis: A qualitative analysis of free-text survey data. Health Expect. 2022;25(1):214-222. doi:10.1111/hex.13364
32. Sorrenti V, Buriani A, Davinelli S, Scapagnini G, Fortinguerra S. Vitamin D Physiology, Deficiency, Genetic Influence, and the Effects of Daily vs. Bolus Doses of Vitamin D on Overall Health: A Clinical Approach. Nutraceuticals. 2023;3(3):403-420. doi:10.3390/nutraceuticals3030030

33. Maurya VK, Aggarwal M. Factors influencing the absorption of vitamin D in GIT: an overview. J Food Sci Technol. 2017;54(12):3753-3765. doi:10.1007/s13197-017-2840-0
34. Mendes MM, Hart KH, Botelho PB, Lanham-New SA. Vitamin D status in the tropics: Is sunlight exposure the main determinant? Nutr Bull. 2018;43(4):428-434. doi:10.1111/nbu.12349
35. Dawson-Hughes B, Harris SS, Lichtenstein AH, Dolnikowski G, Palermo NJ, Rasmussen H. Dietary Fat Increases Vitamin D-3 Absorption. J Acad Nutr Diet. 2015;115(2):225-230. doi:10.1016/j.jand.2014.09.014
36. Voltan G, Cannito M, Ferrarese M, Ceccato F, Camozzi V. Vitamin D: An Overview of Gene Regulation, Ranging from Metabolism to Genomic Effects. Genes. 2023;14(9):1691. doi:10.3390/genes14091691
37. Rebelos E, Tentolouris N, Jude E. The Role of Vitamin D in Health and Disease: A Narrative Review on the Mechanisms Linking Vitamin D with Disease and the Effects of Supplementation. Drugs. 2023;83:665-685. doi:10.1007/s40265-023-01875-8
38. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008;88(2):582S—586S. doi:10.1093/ajcn/88.2.582s
39. Tanaka Y, DeLuca HF. Stimulation of 1,25-dihydroxyvitamin D3 production by 1,25-dihydroxyvitamin D3 in the hypocalcaemic rat. Biochem J. 1983;214(3):893-897. doi:10.1042/bj2140893
40. Saponaro F, Saba A, Zucchi R. An Update on Vitamin D Metabolism. Int J Mol Sci. 2020;21(18):6573. doi:10.3390/ijms21186573
41. Bikle DD, Patzek S, Wang Y. Physiologic and pathophysiologic roles of extra renal CYP27b1: Case report and review. Bone Rep. 2018;8:255-267. doi:10.1016/j.bonr.2018.02.004
42. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. J Clin Virol. 2011;50(3):194-200. doi:10.1016/j.jcv.2010.12.006
43. Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc National Acad Sci. 2004;101(20):7711-7715. doi:10.1073/pnas.0402490101
44. Prietl B, Treiber G, Pieber T, Amrein K. Vitamin D and Immune Function. Nutrients. 2013;5(7):2502-2521. doi:10.3390/nu5072502
45. Miclea A, Bagnoud M, Chan A, Hoepner R. A Brief Review of the Effects of Vitamin D on Multiple Sclerosis. Front Immunol. 2020;11. doi:10.3389/fimmu.2020.00781

46. Molnár F, Peräkylä M, Carlberg C. Vitamin D Receptor Agonists Specifically Modulate the Volume of the Ligand-binding Pocket. J Biol Chem. 2006;281(15):10516-10526. doi:10.1074/jbc.m513609200

47. Colotta F, Jansson B, Bonelli F. Modulation of inflammatory and immune responses by vitamin D. J Autoimmun. 2017;85:78-97. doi:10.1016/j.jaut.2017.07.007

48. Sangha A, Quon M, Pfeffer G, Orton SM. The Role of Vitamin D in Neuroprotection in Multiple Sclerosis: An Update. Nutrients. 2023;15(13):2978. doi:10.3390/nu15132978

49. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. J Chem Neuroanat. 2005;29(1):21-30. doi:10.1016/j.jchemneu.2004.08.006

50. Huang JK, Jarjour AA, Nait Oumesmar B i in. Retinoid X receptor gamma signaling accelerates CNS remyelination. Nat Neurosci. 2010;14(1):45-53. doi:10.1038/nn.2702

51. de la Fuente AG, Errea O, van Wijngaarden P i in. Vitamin D receptor–retinoid X receptor heterodimer signaling regulates oligodendrocyte progenitor cell differentiation. J Cell Biol. 2015;211(5):975-985. doi:10.1083/jcb.201505119

52. Gomez-Pinedo U, Cuevas JA, Benito-Martín MS, et al. Vitamin D increases remyelination by promoting oligodendrocyte lineage differentiation. Brain Behav. 2020;10(1):e01498. doi:10.1002/brb3.1498

53. Zou Y, Mu M, Zhang S i in. Vitamin D3 suppresses astrocyte activation and ameliorates coal dust-induced mood disorders in mice. J Affect Disord. 2022;303:138-147. doi:10.1016/j.jad.2022.02.026

54. Chiareli RA, Carvalho GA, Marques BL, et al. The Role of Astrocytes in the Neurorepair Process. Front Cell Dev Biol. 2021;9. doi:10.3389/fcell.2021.665795

55. Correale J, Farez MF. The Role of Astrocytes in Multiple Sclerosis Progression. Front Neurol. 2015;6. doi:10.3389/fneur.2015.00180

56. Yan YQ, Ma CG, Ding ZB, Song LJ, Wang Q, Kumar G. Astrocytes: a double-edged sword in neurodegenerative diseases. Neural Regen Res. 2021;16(9):1702. doi:10.4103/1673-5374.306064

57. Zrzavy T, Hametner S, Wimmer I, Butovsky O, Weiner HL, Lassmann H. Loss of 'homeostatic' microglia and patterns of their activation in active multiple sclerosis. Brain. 2017;140(7):1900-1913. doi:10.1093/brain/awx113

58. O'Loughlin E, Madore C, Lassmann H, Butovsky O. Microglial Phenotypes and Functions in Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018;8(2):a028993. doi:10.1101/cshperspect.a028993
59. Galoppin M, Kari S, Soldati S, et al. Full spectrum of vitamin D immunomodulation in multiple sclerosis: mechanisms and therapeutic implications. Brain Commun. 2022;4(4):fcac171. Published 2022 Jun 30. doi:10.1093/braincomms/fcac171
60. Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-beta 1 and IL-4. J Immunol. 1998;160(11):5314-5319.
61. Ohl K, Tenbrock K, Kipp M. Oxidative stress in multiple sclerosis: Central and peripheral mode of action. Exp Neurol. 2016;277:58-67. doi:10.1016/j.expneurol.2015.11.010
62. de Oliveira LR, Mimura LA, Fraga-Silva TF, et al. Calcitriol Prevents Neuroinflammation and Reduces Blood-Brain Barrier Disruption and Local Macrophage/Microglia Activation. Front Pharmacol. 2020;11. doi:10.3389/fphar.2020.00161
63. Haider L, Fischer MT, Frischer JM, et al. Oxidative damage in multiple sclerosis lesions. Brain. 2011;134(7):1914-1924. doi:10.1093/brain/awr128
64. Luissint AC, Artus C, Glacial F, Ganeshamoorthy K, Couraud PO. Tight junctions at the blood brain barrier: physiological architecture and disease-associated dysregulation. Fluids Barriers CNS. 2012;9(1):23. doi:10.1186/2045-8118-9-23
65. Larochelle C, Alvarez JI, Prat A. How do immune cells overcome the blood-brain barrier in multiple sclerosis? FEBS Lett. 2011;585(23):3770-3780. doi:10.1016/j.febslet.2011.04.066
66. Elahy M, Jackaman C, Mamo J, et al. Blood–brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment. Immun Amp Ageing. 2015;12(1):2. doi:10.1186/s12979-015-0029-9
67. Lutz SE, Smith JR, Kim DH, et al. Caveolin1 Is Required for Th1 Cell Infiltration, but Not Tight Junction Remodeling, at the Blood-Brain Barrier in Autoimmune Neuroinflammation. Cell Rep. 2017;21(8):2104-2117. doi:10.1016/j.celrep.2017.10.094