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REVIEW

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What is known about the effects of vitamin D in neuropsychiatric lupus?

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect several organs and systems. The central and/or peripheral nervous system can suffer from complications known as neuropsychiatric lupus (NPSLE). Studies have associated the manifestations of SLE or NPSLE with vitamin D deficiency. It has been shown that hypovitaminosis D can lead to cognition deficits and cerebral hypoperfusion in patients with NPSLE. In this review article, we will address the main features related to vitamin D supplementation or serum vitamin D levels with neuropsychiatric manifestations, either in patients or in animal models of NPSLE.

Keywords Systemic lupus erythematosus, Neuropsychiatric lupus, Vitamin D, Hypovitaminosis D, Vitamin D supplementation

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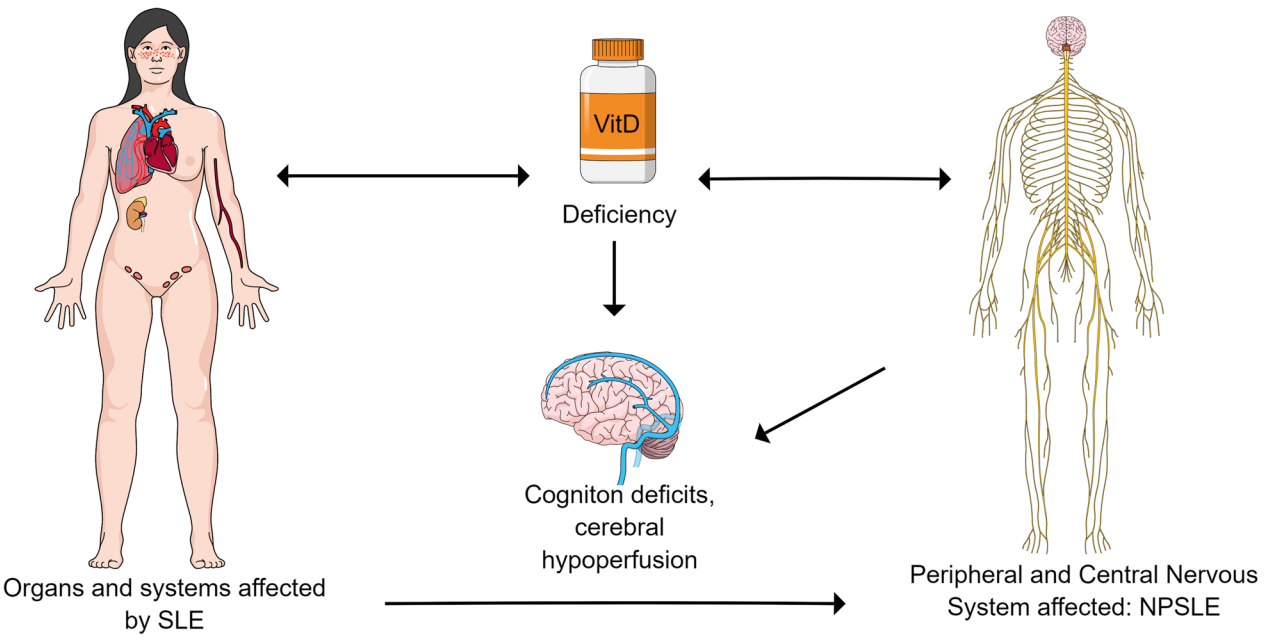
Graphical abstract



Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies and chronic inflammation. It can affect various organs and systems, such as the central nervous system (CNS) and/or the peripheral nervous system (PNS). When these are compromised, the consequent syndrome is known as neuropsychiatric lupus (NPSLE) [1, 2]. NPSLE is the second leading cause of morbidity and mortality in SLE patients [7]. Some of the observed clinical features are headache, mood disorder, seizures and psychosis [3].

Vitamin D (vit-D) low levels are frequently identified in autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes mellitus and SLE [4–6]. In animal models of SLE, some studies have demonstrated that vit-D supplementation improves important outcomes like proteinuria, arthritis, skin lesions and survival [7, 8].

Vit-D, which acts in the immunomodulation of the innate and adaptive immune response, has also been investigated as an alternative therapy to control or minimize the clinical manifestations of SLE. Studies published in recent years demonstrated the importance of vit-D, not only in bone and calcium metabolism, but also in the regulation of the immune system, and in other tissues, such as the brain [9–11]. Furthermore, the deficiency of vit-D has been associated with the severity of clinical manifestations in patients with SLE [10, 11].

In this review, we examined studies related to hypovitaminosis D in patients with SLE and neuropsychiatric manifestations, as well as data regarding to vitamin D supplementation in animal models of NPSLE.

Materials and methods

PubMed, SciELO, and Embase databases were searched for articles published from 1984 to 2022, using the following terms and combinations: "systemic lupus erythematosus", "neuropsychiatric systemic lupus erythematosus", "vitamin D and systemic lupus erythematosus", "vitamin D and neuropsychiatric systemic lupus erythematosus". The article inclusion criteria were: complete articles on the pathophysiology of SLE and NPSLE, as well as original articles that evaluated vitamin D supplementation or vitamin D levels in animal models or patients with NPSLE. The exclusion criteria for articles were: themes unrelated to the research objectives, articles whose full versions were unavailable, articles with repeat information and articles not published in English and/or Portuguese (Fig. 1).

Neuropsychiatric lupus

Neuropsychiatric symptoms can range from relatively mild or non-specific manifestations to more severe complications. The heterogeneity and non-specificity of

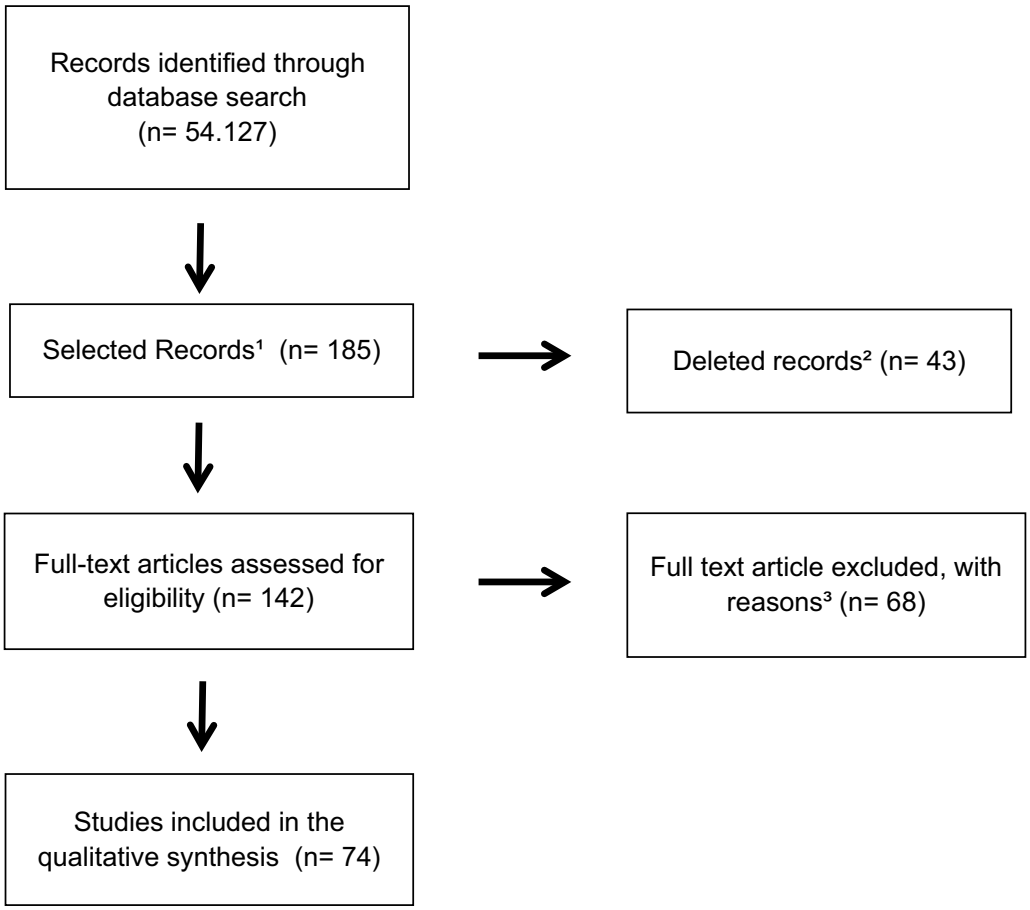


Fig. 1 Schematic model of the information search strategy. [1,2,3] Full articles excluded for not being related to the topic of this article, articles with repeated information or articles not published in English and/or Portuguese

clinical symptoms tend to make the diagnosis difficult [3, 12, 13]. Different mechanisms have been associated with NPSLE, like blood–brain barrier (BBB) disruption, autoantibody production, proinflammatory cytokines and premature atherosclerosis. Throughout the disease course, both CNS and PNS can be affected; symptomatology in the CNS generally is divided into focal and diffuse manifestations. Focal manifestations can be partially characterized by the presence of autoantibodies targeting membrane phospholipids on the blood vessels endothelial cells in the CNS. While diffuse symptoms appear to be related to the inflammation triggered by different mediators, some of them are associated with the leakage of the BBB [3, 12].

Cohen and colleagues [14] performed a brain histopathology post-mortem study in NPSLE patients, with the majority of the lesions found in the cerebral cortex. In their study, micro and macroinfarction, microthrombi and vasculitis were more frequently found in NPSLE individuals; with microthrombi being exclusively found in NPSLE. It was noticed that in NPSLE and individuals with SLE vasculitis was found alongside diffuse vasculopathy, but focal vasculopathy was present in SLE and also in control patients. Deposits of complement components C1q and C4d, and the terminal complement complex C5B-9, were present in the cerebral blood vessels of both NPSLE and SLE patients. The accumulation of antibodies in small vessels could be what leads to the activation of the complement pathway, followed by endothelial injury and formation of microthrombi [14]. Leukocyte agglutination and accelerated atherosclerosis contribute to the thrombosis process in patients with NPSLE, and this process is involved in the pathophysiology of the disease [15]. Thrombosis can cause several complications to the patient, including focal cerebral ischemia and intracranial vascular embolism [16]. Animal models of NPSLE also demonstrate signs of depression, anxiety, cognitive deficits and brain IgG deposits [3, 17–20].

Table 1 Neuropsychiatric syndromes observed in patients with Systemic Lupus Erythematosus

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy
Cerebrovascular disease	(Guillain–Barre syndrome)
Demyelinating syndrome	Autonomic disorder
Headache (including migraine and benign intracranial hypertension)	Myasthenia gravis
Movement disorder (chorea)	Cranial neuropathy
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

Adapted from LIANG et al. [21]

The American College of Rheumatology (ACR) classified 19 neuropsychiatric manifestations (Table 1) and recommended diagnostic methods, such as laboratory and image tests, aiming to simplify clinical cases identification and scientific research [21, 22]. NPSLE shows a higher prevalence of 91% when non-specific symptoms are included in the diagnosis, such as anxiety and headache, compared to the 46% prevalence described without them [23]. This wide variation would be associated with several factors such as population type and characteristics, the patient symptoms severity, study model, etc. [2]. Cognitive impairment, acute confused state and peripheral neuropathy would be symptoms manifested in a few SLE patients, 1 to 5%. Myelitis, aseptic meningitis and face or members involuntary movements are extremely rare to occur [1]. The difficulty presented in the identification and diagnosis remains an obstacle to establishing a clinical pattern, despite the NPSLE guidelines. It is still a major challenge without robust diagnostic tests.

Cognitive disorder (CD) is defined as a significant deficit in any of the cognitive domains of simple and complex attention, reasoning, executive function, memory, visual-spatial processing, language, and psychomotor speed. Other factors which have been associated with CD in SLE include depression status, longer disease duration, regular glucocorticoid use and the presence of anti-neuronal and anti-phospholipid antibodies (aPLs), neuronal loss or dysfunction, and vit-D deficiency [24].

Depression and cognitive dysfunction are the most common psychiatric manifestations in SLE and were found to be present and associated in newly diagnosed SLE patients. Whether they are associated with lupus activity or medications, or are a consequence of the stress of living with a chronic disease remains debatable [25]. The signs of CD are often subtle and screening tools have been validated for the diagnosis. To date, there are no consensus guidelines for the treatment of CD in SLE [24].

PNS involvement in patients with SLE is the biggest cause of morbidity. Despite its substantial potential to impact a patient's condition, PNS involvement in SLE has not been comprehensively characterized in terms of severity, clinical associations, and electrophysiological findings. Prevalence of PNS in SLE occurs more frequently in SLE patients with high disease activity and CNS involvement, reaching approximately 8% of SLE patients [26–28].

Common PNS manifestations are chronic inflammatory demyelinating polyneuropathy, Guillain–Barré, peripheral neuropathy associated with vasculitis. There is a predilection for asymmetric and lower extremities involvement, especially peroneal, medium and sural nerves. The pathogenesis is still poorly understood. However, several factors have been identified, including vasculitis affecting small blood vessels, the presence of immune complex deposits, and lesions caused by the overproduction of antibodies or hyperactivity of B-lymphocytes [26, 29, 30].

Despite this standardized nomenclature by the ACR, the attribution of neuropsychiatric events to SLE is challenging. For correct diagnostic characterization, attribution algorithms were created, which contribute to a better characterization of the disease. Such algorithms can be translated into a probability score to determine the strength of the relationship (i.e., attribution) between a given neuropsychiatric event occurring and the underlying SLE [31–33].

The algorithm proposed by Hanly is based on three simple rules, which take into account the temporal relationship between the neuropsychiatric event and the SLE diagnosis, the type of neuropsychiatric event and a comprehensive list of exclusions/associations according to ACR nomenclature. Bortoluzzi et al. [34] added a new item to the algorithm and proposed assigning a numerical score to each selected item and its corresponding subtitle, generating a global score that varies from 0 to 10, where the higher the global score, the greater the probability whether the neuropsychiatric event can be attributed to SLE [34].

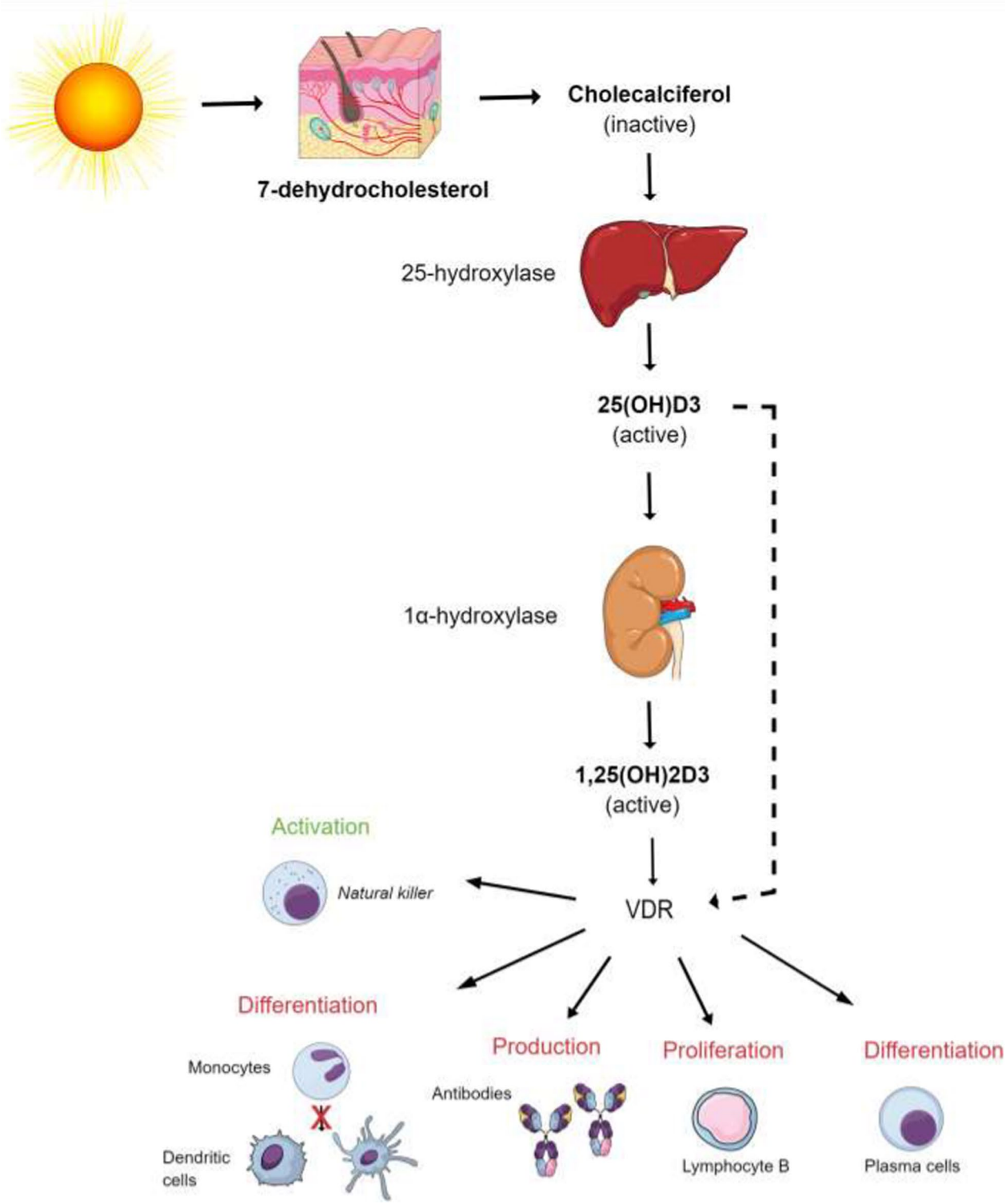


Fig. 2 Vitamin D metabolism, activation and immunomodulatory effects. Vitamin D3 (cholecalciferol) can be obtained from food intake or by synthesis in the skin of 7-dehydroxycholesterol in response to ultraviolet (UV) light also emitted by sunlight. In the liver, hydroxylation occurs by 25-hydroxylase, forming 25-hydroxyvitamin D3 (25(OH)D3). In the kidneys, 1α-hydroxylase acts in the hydroxylation of 25(OH)D3 to the most biologically active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3). Both 1,25(OH)2D3 and 25(OH)D3 are immunomodulators by binding to a vitamin D receptor (VDR) present in the nucleus of almost all immune cells. Its immunomodulatory effects include inhibition of monocyte differentiation into dendritic cells, B cell proliferation, plasma cell differentiation and antibody production. The vitamin also induces the activation of natural killer (NK) cells

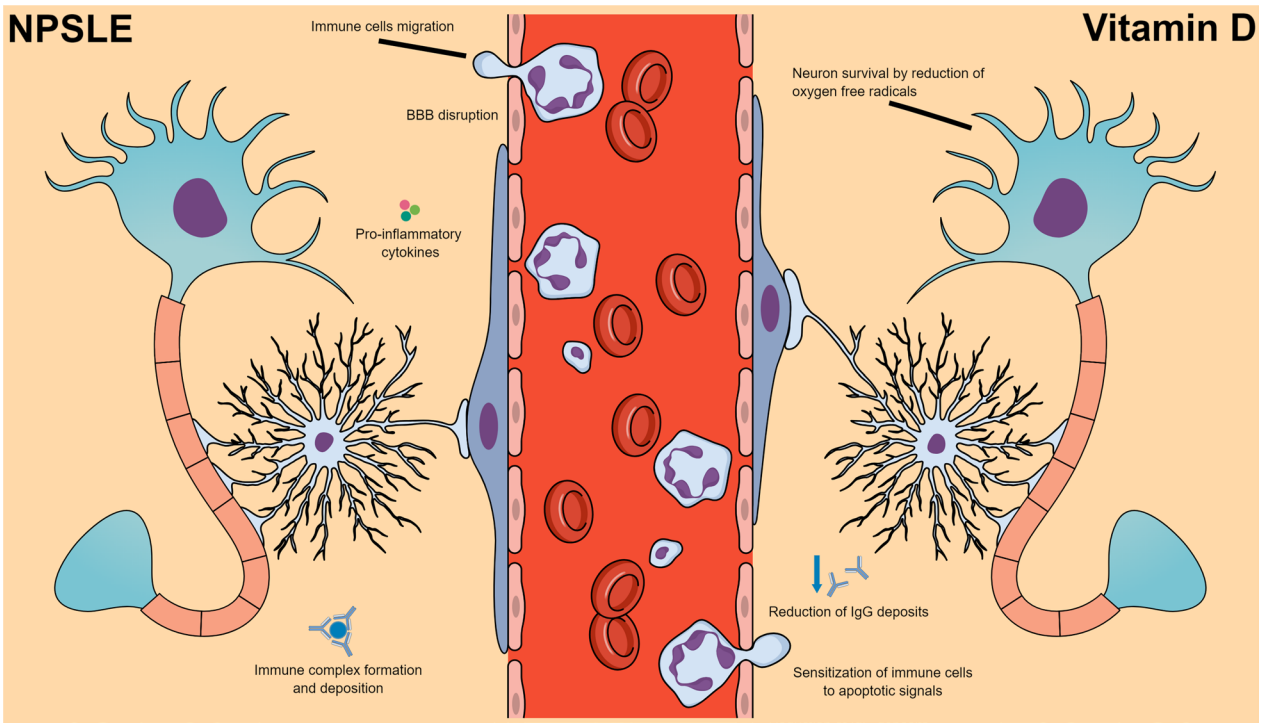


Fig. 3 In NPSLE, the disruption of the blood–brain barrier allows the passage of cells from the immune system and molecules to the brain. Vitamin D is able to reduce free radicals in the brain environment providing neuronal survival. It is also able to reduce IgG deposits and ensure apoptotic signaling by immune system cells

Vitamin D

Vitamin D is a steroid hormone that can be found in several forms, being vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) the main types found. Cholecalciferol is formed in the skin through exposure to sunlight or ultraviolet light (Fig. 3), as well as nutrient sources such as fatty fish. Ergocalciferol is obtained from the ingestion of plant-based food. There are some known limitations for the synthesis of this vitamin, such as age, skin pigmentation, use of sunscreen and clothing [35, 36].

This steroid is widely known for its participation in the calcium metabolism [10]. In recent years, some non-classical functions of vit-D have been reported, such as effects on cell proliferation and differentiation, as well as immunoregulatory actions, resulting in the ability to maintain tolerance and promote protective immunity. Both antigen-presenting cells (macrophages and dendritic cells) and T and B cells have the necessary machinery to synthesize and respond to 1,25(OH)2D [37].

Evidence suggests that vit-D has a regulatory role in the innate and adaptive immune systems. This molecule can contribute to hematopoiesis, assist in the antimicrobial response or even decrease the antigen presentation by monocytes, the latter probably having a role in maintaining immune tolerance [38, 39]. It also aids in inhibiting the differentiation and maturation of dendritic cells (DC). When mature, DCs present the antigen to T cells, facilitating an immune response against that antigen. When immature, antigen presentation facilitates self-tolerance [10]. In addition to inducing the activation of Treg cells and natural killer cells (NK), it increases apoptosis induced by dendritic cells and T lymphocytes (Fig. 2) [40]. In addition, vit-D inhibits proliferation and blocks B cell differentiation and immunoglobulin secretion [41, 42]. It also suppresses T cell proliferation and assists in inhibiting the production of inflammatory cytokines such as IL-1, IL-6, IL-17 and IL-21 and TNFα, increasing the production of anti-inflammatory cytokines such as IL-10 [10, 43, 44].

The main source of vit-D biosynthesis is exposure to sunlight. Vit-D deficiency is a consequence of low exposure to sunlight and has been associated with several physiological complications [4]. Due to the photosensitivity caused by SLE, sunlight becomes a trigger for patients with this disease [45]. Vit-D deficiency is common in SLE patients [4]. In addition, researchers have found an association between low levels of vitamin D and cognitive dysfunction in diseases such as multiple sclerosis, Alzheimer's and SLE [9, 46–48].

Vitamin D and central or peripheral nervous system

Vitamin D expresses metabolites that are able to cross the BBB. In the human brain and in murines, vitamin D receptor (VDR) proteins are also expressed in different regions such as the cerebellum, thalamus, hypothalamus, basal ganglia, hippocampus, olfactory system and the temporal, orbital and cingulate cortices [49–51]. In some brain cells, VDR is co-localized with 1α-hydroxylase enzymes. With this, there is a local conversion of vit-D to its active form (1,25 (OH)2D3 [50, 52]. Also, VDR expression in the cortex and hippocampus suggests a potential involvement of vit-D in cognition [53].

Vit-D supports brain function by contributing to the physiology of transmission and connectivity of neural circuits that are involved in reward-dependent locomotor and emotional behavior and cognition [54]. Evidence indicates an association between low serum levels of vit-D and different autoimmune and neurological diseases, as well as neuromuscular disorders and increased sensitivity to pain [55–58]. Researchers suggest the participation of vit-D in the regulatory mechanisms of the sleep–wake cycle, demonstrating that the reduction of this vitamin may be associated with sleep disorders [59, 60], as well as the perception of painful stimuli [61, 62].

This vitamin plays an important role in promoting neuron survival. It may suppress oxidative pathways in the brain by decreasing the formation of oxygen free radicals [63]. Studies show the immunomodulatory effects of vit-D in the brain (Fig. 3). Such effects can be observed on neurotrophic function, neuroprotection and neuroimmunomodulation in vitro, positive regulation of the synthesis of nerve growth factor and neurotropin 3. Furthermore, it inhibits the expression of class II proteins of the major histocompatibility complex (MHC II) and sensitizes inflammatory cells to apoptotic signals [64, 65]. In addition to these properties, 1,25(OH)2D3 is capable of regulating intraneuronal calcium homeostasis through voltage-gated calcium channels, in addition to obtaining antioxidant effects with neuroprotective properties against glutamate toxicity [64, 66].

Vit-D has also been shown to be involved in remyelination in immune-mediated diseases of the central nervous system (CNS), such as multiple sclerosis (MS). The metabolism of vit-D present in the CNS participates in myelination and can be influenced by external factors such as diet, sun exposure or vit-D supplementation [67].

Vitamin D and NPSLE

Vit-D deficiency has been linked to cognitive dysfunction in lupus patients [68], as well as being associated with the neuropsychiatric manifestations of lupus [69] (Table 2). Studies on the effects of vit-D on NPSLE are scarce. A study carried out with MRL/lpr mice supplemented with 2 μg/kg/day once a day for four weeks demonstrated beneficial effects of supplementation. The findings revealed an improvement in the animals' cognition, as well as an increase in VDR expression in the hippocampus [70]. Our group also carried out a study to verify the effects of vitamin D supplementation (2 μg/kg once a day on alternate days for 180 days) in the hippocampus of BALB/c mice with pristane-induced lupus. Our findings revealed a positive correlation between levels of IgG deposits and VDR expression in the hippocampus [18]. Also, there is evidence in the literature that vit-D can delay cell infiltration in the choroid plexus and decrease markers suggestive of cognitive decline in MRL/lpr mice [71].

Similar to those findings in animal models, a worsening of cognitive function was identified in humans with NPSLE and 25(OH)D3 deficiency [48, 68]. Sultana and colleagues [69] suggest, from their findings in patients, that NPSLE is associated with reduced vit-D binding protein expression in patients' serum. Furthermore, the authors suggest that hypovitaminosis D precedes the progression of cerebral hypoperfusion in NPSLE patients and that vit-D may have prophylactic implications [69].

Hypovitaminosis D is common in patients with SLE and NPSLE, dosage adjustment must be made for each patient taking into account their clinical history and metabolism capacity. Although vit-D supplementation brings numerous benefits to the body and brain, including neuroprotection and neuroimmunomodulation, as well as improving cognition, high doses can be harmful, becoming toxic. The most common symptoms of vit-D toxicity are gastrointestinal disorders like anorexia, diarrhea, constipation, nausea, and vomiting. After a few days or weeks, other symptoms may appear, such as bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle and joint pain, frequent urination, especially at night, excessive thirst, weakness, nervousness and itching, and kidney stones [72].

Jones, in his review of vit-D doses and toxicity, concluded that plasma vit-D concentration is a good biomarker of toxicity. The author indicates that the threshold for toxic symptoms is approximately 750 nmol/L [73]. Although there are no reports on the effects of high doses in patients with NPSLE, a study carried out with patients with multiple sclerosis reveals that high doses of vit-D can be harmful to the CNS, promoting the worsening of demyelination [74].

Table 2 Published articles relating vitamin D and neuropsychiatric manifestations in SLE

Author	Animal models			Humans		
	Yan et al. (70)	**Karnopp et al. (18)**	**Li et al. [71]**	**Tay et al. [68]**	**Hussein et al. [48]**	**Sultana et al. (69)**
Origin	China	Brazil	China	Singapore	Egypt	Bangladesh
Mouse model	MRL/lpr	Pristane-induced lupus	MRL/lpr	N/A	N/A	N/A
Summary	Twenty male MRL/lpr mice (aged 2 months) were divided into two groups: SLE and SLE + VD; ten male C57BL/6 J mice were used as the control group	Twenty-three female BALB/c mice (aged 2 months) were divided into three groups: control (CO), pristane-induced lupus (PIL) and PIL mice supplemented with VD (VD)	Forty-eight female MRL/lpr mice (aged 2 months) were divided into two groups: VitD3-treated group and control group. Mice were euthanized at 0 weeks (T1), 2 weeks (T2), 4 weeks (T3) and 6 weeks (T4)	Cross-sectional study in which SLE patients and healthy controls were administered Automated Neuropsychological Assessment Metrics, evaluating total throughput score (TTS) and the Hospital Anxiety and Depression Scale (HADS). Levels of 25(OH)D3 and 25(OH)D were measured	Cross-sectional, case–control study for which thirty patients diagnosed with SLE were recruited along with twenty control individuals with no history of neurologic or psychiatric conditions. All subjects were submitted to a battery of neuropsychological tests. Blood samples were collected to assess serum molecules, including vitamin D	Cross-sectional study in which 19 patients undergoing brain perfusion SPECT were retrospectively studied. All individuals had vitamin D serum level determined
Treatment	SLE-VD group was treated with *Aerococcus* and one daily intraperitoneal injection of Vitamin D (2 ug/kg/day) for 4 weeks	VD mice were supplemented with subcutaneous injections of Calcijex (2 µg/kg) every two days for 6 months	Mice in the VitD3-treated group received a 4 µg/kg 1,25-dihydroxivitamin D3 intraperitoneal injection twice a week for 3 weeks	N/A	N/A	N/A
Main outcomes	SLE + VD group presented: better performance on Morris maze test; less degeneration in the hippocampus; increased expression of VDR and Bcl-2 and decreased expression of Aβ and cleaved caspase-3 in the hippocampus	Positive correlation between VDR and IgG levels in the hippocampus of PIL and VD groups	VitD3-treated group presented: inhibited expression of genes related to cognitive dysfunction; decrease of pathological findings in brain tissues; decreased anti-dsDNA and increased C3 serum levels; increased expression of occludin and claudin-2 in the brain; increased PPAR-γ, BDNF, TGF-β1, TβR-I, Smad2/3 and P-Smad2/3 expression; decreased NF-κB and TNF-α expression	SLE patients presented more 25(OH)D_3 deficiency than healthy controls; this deficiency predicted worse TTS; age was the only predictor of TTS	SLE patients presented significantly lower levels of serum Vit-D compared with controls; there was a negative correlation between vitamin D serum levels and performance in executive function tests in the SLE group	Positive correlation between vitamin D serum level and brain perfusion

Conclusion

There is a growing scientific interest about the immunomodulatory properties of vit-D in the brain, with new articles being published in recent years in the field of NPSLE. With this review, we concatenated those studies to show that vit-D seems to have a positive association with cognitive function and beneficial effects on neuropsychiatric manifestations. Nonetheless, we believe that more studies are needed to dig deep into the questions that remain unanswered, specially about the effects of vit-D on both the central and the peripheral nervous system, either in human patients or animal models.

Abbreviations

1,25(OH)2D3	1,25-Dihydroxyvitamin D3
25(OH)D3	25-Hydroxyvitamin D3
ACR	American College of Rheumatology
CD	Cognitive disorder
CIDP	Chronic inflammatory demyelinating polyneuropathy
CNS	Central nervous system
DC	Dendritic cells
ECs	Endothelial cells
MS	Multiple sclerosis
NK	Natural killer cells
NMO	Neuromyelitis optica
NPSLE	Neuropsychiatric lupus
MHC	Major histocompatibility complex
PNS	Peripheral nervous system
PRES	Posterior reversible encephalopathy syndrome
SFN	Small fiber neuropathy
SLE	Systemic lupus erythematosus
VDR	Vitamin D receptor
Vit-D	Vitamin D

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Author contributions

The first draft of the manuscript was written by TEK, ALDD and VSF. Figures in the article were made by TEK, VSF and GFC. The tables were prepared by TEK and GFC. Text review and corrections were performed by NGS, ECF, AAG and OAM. All other authors commented on the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

None.

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