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THE ROLE OF VITAMIN D IN THE PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS: SUPPLEMENTATION AND PREVENTIVE AND THERAPEUTIC POTENTIAL

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Abstract: Introduction: Multiple sclerosis is a neuroinflammatory disease that can manifest itself in different stages and clinical patterns. There is a growing prevalence worldwide, which is the subject of numerous health studies, and the incidence has been associated with low levels of vitamin D, an important metabolite due to its anti-inflammatory and antioxidant role, which can contribute to the management and prevention of MS. Objective: To analyze the effects of vitamin D on the pathogenesis of multiple sclerosis due to its immunomodulatory potential. Methodology: A bibliographic search was carried out on the PubMed and Virtual Health Library platforms and, using the inclusion and exclusion criteria, 18 articles were selected to support this systematic literature review. Results: This study highlighted the strong association between multiple sclerosis recurrence and decreased serum vitamin D levels, linking the pathophysiology of the disease to the effects of this vitamin on the immune system. These factors suggest that supplementation can be seen as a viable strategy for the prevention and treatment of the disease. Final considerations: The review described associates vitamin D hypovitaminosis with a greater susceptibility to MS, but it concludes that more studies and tests are needed to prove the effectiveness of supplementation.

Keywords: Vitamin D, Multiple Sclerosis, immunomodulation, autoimmunity.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and autoimmune neurological condition that results in demyelination and degeneration of the central nervous system (CNS) of affected individuals (SMOLDERS and DAMOISEAUX, 2011). It predominantly affects women (GALOPPIN et al., 2022) and populations living in high latitude areas (SIMPSON, S. et al., 2011), such as Caucasians, and presents a variety of symptoms, including ataxia, paresthesia, diplopia, amblyopia and sensory dysfunctions. The disease causes brain damage by promoting the entry of immune cells through disruption of the blood-brain barrier (BBB), causing perivascular inflammation, damage to axons and oligodendrocytes and destruction of the myelin sheath, which impairs neuronal communication (RICCIO, 2011; MAGHBOOLI et al., 2021).

MS can manifest itself in different clinical forms, the most common being relapsing--remitting multiple sclerosis (RRMS). There is also secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) (Lublin et al., 2020). Its etiology involves genetic factors - such as the variant of the HLA-DR (*Human Leukocyte Antigen*- DR) gene, especially the HLA--DRB1*15:01 allele, located in the class II MHC (Major Histocompatibility Complex) (Ramagopalan and Ebers, 2008) - as well as epigenetic and environmental factors.

Among the environmental factors, infection with the Epstein-Barr virus (EBV), smoking, obesity and vitamin D deficiency are particularly relevant to the development of the disease (KIM et al., 2022). Among these, vitamin D deficiency stands out, which is considered a crucial aspect for the prevention and prevalence of MS (FATIMA et al., 2022). This association is due to the greater recurrence of the disease in places with less sun exposure, where people tend to have lower serum vitamin D levels (OSTKAMP et al., 2021).

Vitamin D, a fat-soluble steroid hormone, has two forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), both of which are inactive, the latter being its main form. These different forms can be synthesized in two ways: through sunlight by exposure to B radiation (UVB) on the skin - the most effective method - and through food, such as eating fish, for example (ASCHERIO et al., 2010). This vitamin goes through a series of processes to be activated. The first stage takes place in the liver, where cholecalciferol is transformed into calcidiol, the main circulating form. Shortly after the first stage, in the kidneys, a hydroxyl is added to calcidiol and it is transformed into calcitriol, the active form of vitamin D. This is carried by the blood system. This is carried through the blood system by proteins, the DBPs, and fulfills its functions in the body after binding to cell receptors, the VDRs (GALOPPIN et al., 2022).

Calcitriol plays a crucial role in the genetic regulation of various tissues, including bone tissue, where it controls serum calcium levels, as well as influencing kidney function and immune system cells. The latter is particularly relevant in the context of the current study, due to its crucial implication in determining multiple sclerosis (KIM et al., 2022). In blood tests, the form assessed is 25-hydroxyvitamin D, known as calcidiol. It is recommended to keep its levels above 50 nmol/L to avoid deficiencies. However, recent studies suggest that maintaining calcidiol levels above 70 nmol/L, and even above 90 nmol/L, may be more beneficial for maintaining general health and preventing various conditions, including immune problems.

The regulation of the immune system by vitamin D explains why its hypovitaminosis is an environmental factor that, in addition to being associated with the onset of MS, is linked to the severity and course of the disease (PIERROT-DESEILLIGNY and SOUBERBIELLE, 2017). This vitamin modulates

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and positively adjusts anti-inflammatory cytokines, such as IL-10, reducing inflammation and promoting the homeostasis of T cells - mainly Th1 and Th17 phenotypes - and B cells, as well as acting in the regulation of the innate immune system, especially in dendritic cells and macrophages, which act in the body's first line of defense against infections, which explains the pathophysiology of multiple sclerosis (GALOPPIN et al., 2022). These actions are responsible for regulating the inflammatory mechanism, justifying considering vitamin D supplementation as a method of preventing and treating autoimmune diseases such as MS, but more studies are needed (GALOPPIN et al., 2022).

METHODOLOGY

This study is a systematic literature review with a qualitative and descriptive approach. The bibliographic search was conducted in July 2024, using the *National Library of Medicine* (PubMed) and Virtual Health Library (VHL) databases, using the descriptors "vitamin D" and "multiple sclerosis", found in the Health Science Descriptors (DeCS) and the Boolean operator "AND".

The literature review was carried out in the following stages: Delimitation of the topic; Definition of the eligibility criteria; Evaluation of the research found and elaboration of the results. The inclusion criteria were controlled clinical trials and observational studies published in the last 5 years (2019-2024). Articles that did not address the proposed theme, did not show an association between multiple sclerosis and vitamin D, duplicated research and were unavailable in the databases were excluded.

RESULTS

The search led to a total of 4152 papers. A total of 1774 articles were found in PubMed and 2378 articles in the Virtual Health Library (VHL). After restricting the publication period to the last 5 years (2019-2024), 490 remained in PubMed and 683 in the VHL. Of the remaining 1173, after filtering by type of research, 26 papers remained in PubMed and 221 in the VHL. After reviewing the titles, 10 articles remained in PubMed and 42 in the VHL. Of the remaining 52, 7 were duplicated on both platforms and were excluded from the VHL, resulting in 35 articles on the VHL and 10 on PubMed. Considering the availability of both platforms, a total of 38 articles were read, 30 in the VHL and 8 in PubMed. The results of this study showed that 18 articles clearly addressed the issue of the relationship between serum vitamin D levels and multiple sclerosis. These facts are shown in Table 1.

DISCUSSION

Multiple sclerosis is a complex condition whose cause is not yet fully understood, but it is known that genetic and environmental factors influence susceptibility to the disease (KARUSSIS, 2014). It is triggered by an inflammatory process mediated by an immunological cascade involving T cells and B cells, resulting in perivenular inflammatory lesions and demyelinating plaques (DOBSON and GIOVANNONI, 2019). As MS progresses, this inflammatory process gives way to a neurodegenerative process, in which axonal damage can lead to persistent neurological dysfunction (TRAPP et al., 1998).

With regard to the initial inflammatory process, it is necessary to highlight the importance of dendritic cells (DCs), which are essential components of the innate immune system and play a crucial role in the pathophysiology and development of multiple sclerosis by presenting antigens to virgin

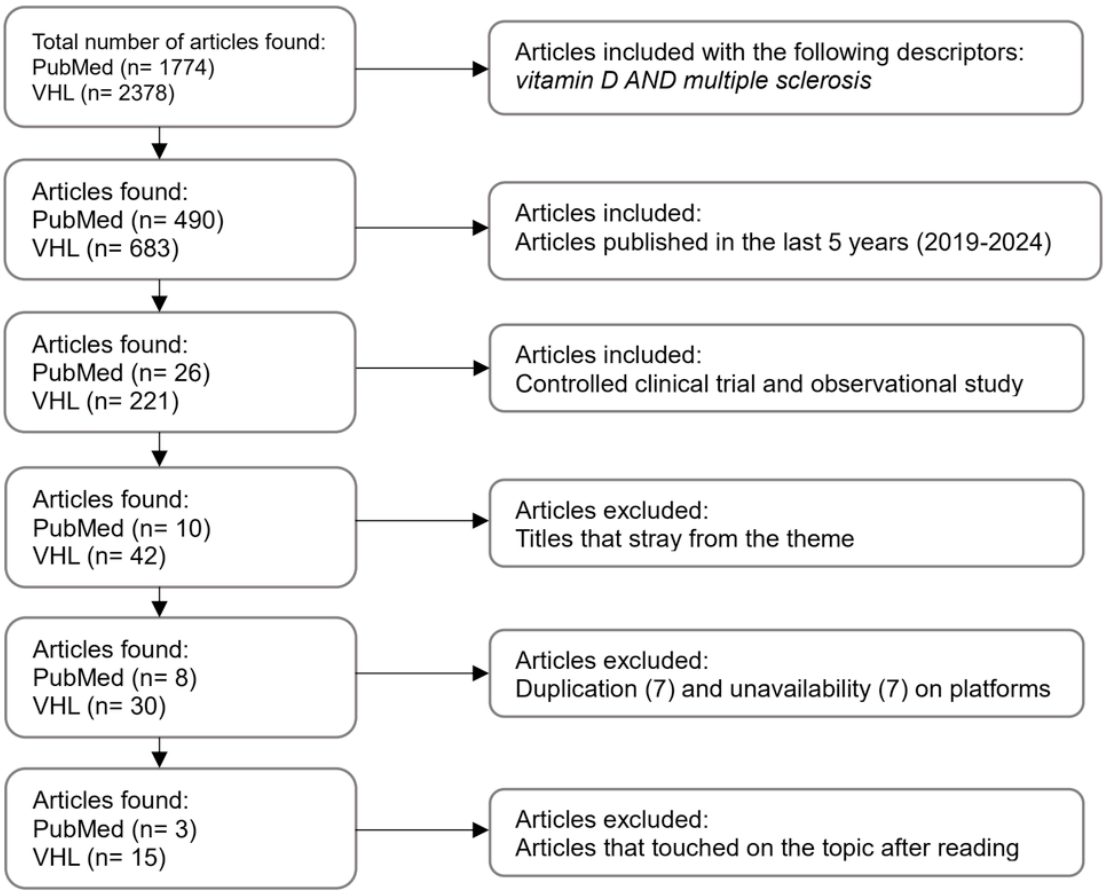

Table 1: Flowchart for identifying and selecting the articles selected from the PubMed and VHL databases.

TCD4 cells (GALOPPIN et al., 2022). DCs are initially activated by contact with antigens and, after this contact, migrate towards virgin TCD4 cells to initiate antigen presentation, which stimulates the differentiation of these cells into different phenotypes, such as Th1 and Th17, capable of producing pro-inflammatory cytokines, such as IFN-ɣ and IL-17, respectively, directly interfering in the disease mechanism (GRIGORIADIS and VAN PESCH, 2015; GALOPPIN et al., 2022).

After this differentiation, the resulting Th1 and Th17 cells cross the blood-brain barrier and infiltrate the central nervous system, contributing to the progression of MS and the intensification of the inflammatory response, which can contribute to the onset of autoimmunity (COLOMBO et al., 2000; GALOPPIN et al., 2022). In addition, the activity of these cells in the CNS provokes local immune responses that result in the destruction of the myelin sheath and neural damage, typical characteristics of the disease.

B lymphocytes are also highly relevant in the disease, as they play an indispensable role in initiating inflammatory lesions. This is corroborated by the presence of oligoclonal IgG bands in the cerebrospinal fluid (CSF) of MS patients, which are not usually identified in plasma (COLOMBO et al., 2000). In addition, studies have shown that B cells produce antibodies that recognize and attack components of the myelin sheath, such as myelin basic protein (MBP), thus contributing to the demyelination characteristic of multiple sclerosis (COLOMBO et al., 2000; CARVALHO et al., 2003).

In addition to the clinical and immunological manifestations already mentioned, oxidative stress is also a frequent factor in the

pathogenesis of multiple sclerosis (PĂDURE-ANU et al., 2020). It is characterized by the high generation of reactive oxygen species (ROS) accompanied by a decrease in the cells' ability to metabolize these species, resulting in the intensive oxidation of lipids, DNA and proteins. This process occurs as part of the inflammatory and immunological response of MS, where cells of the immune system, such as macrophages and microglia - cells of the CNS - produce excess ROS as an attempt to fight the disease (HONORAT et al., 2013). Furthermore, in the neurodegenerative stage of the disease, there is a mitochondrial dysfunction in the central nervous system (CNS), resulting in an exacerbated production of ROS, which directly contributes to the neurological symptoms of the disease, including neuronal dysfunctions and demyelination, characteristic of MS symptomatology (VAN HORSSEN et al., 2011).

In this context, hypovitaminosis D has been widely studied and associated with dysregulation of the immune system and severity and susceptibility to autoimmune diseases such as MS (DOBSON and GIOVANNONI, 2019; KIM, D. et al., 2022). Recognized for its anti-inflammatory and antioxidant properties, this vitamin plays a key role in combating the inflammatory and oxidative process present in the pathogenesis of MS (GALOPPIN et al., 2022). In view of this, vitamin D supplementation as a possible method of preventing and treating multiple sclerosis has been the subject of studies.

Vitamin D exerts its immunomodulatory action after interacting with its specific nuclear receptor, the VDR. The latter, when inactive, i.e. disassociated with vitamin D, remains in the cytoplasm (ADAMS et al., 2024). Calcitriol, the active form of this metabolite, binds to the VDR, activating it and inducing a conformational change that allows it to bind to the retinoid X receptor (RXR), present in the nucleus of various cells and tissues in the human body. Together, they form a heterodimeric complex (VDR-RXR) that translocates to the nucleus and binds to specific DNA sequences, known as Vitamin D Response Elements (VDREs) (KILLICK et al., 2020). This binding allows genes to be modulated and transcribed (PIKE and MEYER, 2010). The functional effects of VDR-RXR vary according to the cell type and the target genes involved, with an emphasis on immune system cells, which have their inflammatory response modulated through cell differentiation and cytokine production (EDWARDS et al., 2014). Macrophages, dendritic cells, T and B lymphocytes are examples of immune cells that possess the VDR receptor (SMOLDERS and DAMOISEAUX, 2011).

The interaction between activated vitamin D and the VDR has a positive impact on the cells of the innate immune system, especially macrophages and dendritic cells, when it comes to their homeostasis. DCs have their maturation reduced due to the suppression of MHC II, CD40, CD80 and CD86, which are proteins necessary for antigen presentation (FATIMA et al., 2022). In addition, there is a decrease in the production of the inflammatory cytokine IL-12 and an increase in IL-10, which has anti-inflammatory properties (FATIMA et al., 2022). Macrophages, on the other hand, are polarized towards the M2 phenotype (anti-inflammatory), reducing the production of pro-inflammatory cytokines such as IL-6 and TNF-alpha, which indirectly inhibits Th1 and Th17 differentiation (GALOPPIN et al., 2022), as well as increasing IL-10 production. Such modulations are important for maintaining a regulated inflammatory response (SINTZEL et al., 2017; GALOPPIN et al., 2022), thus preventing autoimmune-related pathologies such as multiple sclerosis.

1,25(OH)2VD acts on T cells by inhibiting the production of pro-inflammatory cytokines such as IL-2, IL-17 and INF-γ, thus suppressing cytotoxic activity and the proliferation of TCD4+ and CD8+ cells (SINTZEL et al., 2017; FATIMA et al., 2022). In addition, calcitriol induces the production and activation of regulatory T cells (Tregs), which have a tolerogenic character, preventing autoimmune diseases and regulating the inflammatory response so that there is no excessive tissue damage (GALOPPIN et al., 2022). In B cells, vitamin D immunomodulates the immune system by suppressing their proliferation, their differentiation into plasma cells and the production of immunoglobulins (antibodies) G and M (SINTZEL et al., 2017).

As vitamin D is structurally similar to steroids (anabolic steroids), it has the ability to increase the volume of erythrocyte mass and intensify erythropoietin, factors that lead to improved tissue perfusion (MÜLLER et al., 2019; 2021). With this, calcitriol reduces oxidative stress through mitochondrial homeostasis, for example (MÜLLER et al., 2019; 2021).

Although most of the studies referencing this article emphasize that the benefits of vitamin D supplementation in multiple sclerosis are not proven and that more studies are needed to confirm this hypothesis (FEIGE et al, 2020; BIVONA et al, 2022; FATIMA et al, 2022; GALOPPIN et al., 2022; GALUS et al., 2022), some studies claim that vitamin D replacement is beneficial, preventing and/or attenuating the manifestations of MS (DAMOISEAUX and SMOLDERS, 2018; VLOT et al., 2019; ALHUSSAIN et al., 2021). This favorable action is due to its role in T cells, controlling the inflammatory process (KILLICK et al., 2020).

The dosage and toxicity of vitamin D supplementation are other topics under discussion. Administration of doses between 2,000 IU and 4,000 IU/day, together with monitoring of blood levels, are proposed measures for maintaining adequate concentration of the metabolite in MS patients (GALUS et al., 2022). Calcidiol serum values above 150 ng/ml, achieved through the replacement of 50,000 IU/day or more, represent a toxic risk due to excess (FEIGE et al, 2020). Neuropsychic manifestations such as confusion, drowsiness, depression and psychosis (MARCINOWSKA-SUCHOWIERSKA et al., 2018), kidney problems such as hypercalciuria, polyuria and even kidney failure in more severe cases (ROLF et al., 2017), as well as gastrointestinal symptoms such as vomiting, abdominal pain, constipation and peptic ulcer, and cardiovascular symptoms such as hypertension and bradyarrhythmia (FEIGE et al, 2020), are some of the toxic effects of vitamin excess.

Other issues that make the benefit of vitamin D supplementation in multiple sclerosis uncertain are single nucleotide polymorphisms (SNPs), which are genetic variations in DNA (BIVONA et al., 2022; ADAMS et al., 2024). For example, the rs2881514 and rs2531804 variations (ASCHERIO et al., 2010) influence the interaction of the vitamin D receptor (VDR) with DNA, and can affect important genes in the regulation of the immune response, such as those related to the activation of B cells (ADAMS et al., 2024). The rs4588 and rs7041 polymorphisms, located in the gene encoding the vitamin D binding protein (VDBP), affect the plasma concentration and structure of this protein, which influences the availability of the vitamin in the body (AL--DAGHRI et al., 2019). These polymorphisms can result in the body not responding to supplementation, i.e. maintaining low serum levels of vitamin D, even at high doses (AL--DAGHRI et al., 2019; ADAMS et al., 2024). In this way, we emphasize the need for more research into the vitamin replacement under discussion, considering the particularities of the disease and the sufferer.

CONCLUSION

Multiple sclerosis is a chronic inflammatory condition characterized by an inflammatory process mediated by the innate immune system and T and B cells, resulting in inflammatory lesions and demyelination. Due to its anti-inflammatory and antioxidant potential, vitamin D has been the target of studies in the context of MS prevention and treatment when supplemented. Although several studies have concluded that vitamin D supplementation is beneficial for individuals, there are controversies in the scientific community - such as the ideal dosage and possible toxicity - about the benefits promoted by its administration before or during the course of the disease. In addition, the cause of MS is still not fully understood, making it even more challenging in the health field. In conclusion, more studies are needed to investigate the potential of vitamin D as an effective intervention in multiple sclerosis.

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