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IMPLICATIONS OF VITAMIN D INSUFFICIENCY/DEFICIENCY IN AUTOIMMUNE DISEASES: A REVIEW

IMPLICAÇÕES DA INSUFICIÊNCIA/DEFICIÊNCIA DA VITAMINA D NAS DOENÇAS AUTOIMUNES: UMA REVISÃO BIBLIOGRÁFICA

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ABSTRACT

Vitamin D is a fat-soluble steroid hormone with a wide range of biological effects that go beyond the regulation of calcium metabolism and bone health, reaching a preponderant role in maintaining systemic homeostasis, related to cell growth, differentiation and apoptosis, regulation of immune systems, cardiovascular and muscle and insulin metabolism; participating in the direct or indirect modulation of about 3% of the human genome. Considering the serious complications arising from vitamin D deficiency for health and life quality, a descriptive study was proposed in this work, which relates the insufficiency / deficiency of this vitamin to some autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease (Crohn's disease). This study was developed from 58 articles, among which include review articles, original articles from clinical and experimental research, published between 2008 to 2020, obtained from the research in the database Pubmed®, Google Scholar and Scientific Electronic Library Online (SCIELO). Based on studies related to autoimmune diseases, it can be concluded that vitamin D exhibits crucial immunomodulatory function, ensuring an efficient protection system. Studies that deal with vitamin D supplementation, both for the prevention and treatment of existing autoimmune diseases are necessary and of great value for understanding these implications.

Keywords: Diseases. Health. Vitamin D.

RESUMO

A vitamina D é um hormônio esteroide lipossolúvel com amplitude de efeitos biológicos que extrapolam a regulação do metabolismo do cálcio e da saúde óssea, que alcança preponderante papel na manutenção da homeostase sistêmica, relacionado ao crescimento, diferenciação e apoptose celular, regulação dos sistemas imunológico, cardiovascular e muscular e ao metabolismo da insulina; além de participar da modulação direta ou indireta de cerca de 3% do genoma humano. Frente o exposto, e considerando as graves complicações advindas da deficiência de vitamina D para a saúde e qualidade de vida, propôs-se neste trabalho um estudo descritivo, o qual relaciona a insuficiência/deficiência desta vitamina a algumas doenças autoimunes como o lúpus eritematoso sistêmico, o *diabetes mellitus*, a esclerose múltipla, a artrite reumatoide e a doença inflamatória intestinal (Doença de Crohn). Este estudo foi desenvolvido a partir de 58 artigos, dentre os quais incluem os de revisão, artigos originais de pesquisas clínicas e experimentais, publicados entre 2008 a 2020, obtidos a partir da pesquisa no banco de dados Pubmed®, *Google Acadêmico e Scientific Electronic Library Online (SCIELO)*. Com base nos estudos relacionados às doenças autoimunes, pode-se concluir que a vitamina D exibe função imunomoduladora crucial, garantindo eficiente sistema de proteção. Estudos que versam sobre a suplementação de vitamina D, tanto para a prevenção quanto para o tratamento das doenças autoimunes existentes são necessários e de grande valia para o entendimento dessas implicações.

Palavras-chave: Doenças. Saúde. Vitamina D.

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INTRODUCTION

Vitamin D or cholecalciferol is fat-soluble and has been considered a steroid hormone with a wide range of action in the human body; exhibiting as a basic function the increase of intestinal calcium absorption by enterocytes, as well as stimulating calcium homeostasis in the processes of bone formation and reabsorption, through its interaction with parathyroid glands, kidneys and intestines (MARQUES *et al.*, 2010).

Another relevant role of vitamin D includes its association with the immune system, considering that this substance has its receptor expressed in a wide variety of human tissues and organs. Through these widely distributed receptors, vitamin D regulates, directly or indirectly, the expression of more than 200 genes (WANG, 2014).

Vitamin D deficiency is widely reported worldwide, not only due to increased intake of foods with low levels of this vitamin, but also due to cultural factors related to the use of clothing that covers the entire body; age; sedentary lifestyle; the widespread use of sunscreens that reduce skin synthesis; or by the restriction imposed by the environmental conditions (seasonal variation and low latitude) to which they are subject (SANTOS JUNIOR *et al.*, 2011).

Vitamin D insufficiency/deficiency is considered a hidden epidemic, due to its implications for the development of several diseases (HOSSEIN-NEZHAD; HOLICK, 2013). The remarkable number of publications, which worldwide identify an inadequacy in the serum level of vitamin D, has aroused the interest of researchers, who frequently identify the relationship of this vitamin not only with osteometabolic disease, but also with the development of endocrine-metabolic diseases (SCHUCH; GARCIA; MARTINI, 2009), which affect the individual's quality of life and generate high costs for public health.

Considering that prolonged vitamin D deficiency in the body may be associated with an increased risk of colon and prostate cancer, cardiovascular disease, schizophrenia and infections, various diseases including autoimmune diseases (MARQUES *et al.*, 2010; SANTOS JUNIOR *et al.*, 2011; DINIZ *et al.*, 2012; ESERIAN; KALLEIAN, 2013; WANG, 2014; VAZ-CARNEIRO, 2017; JORGE *et al.*, 2018), and understanding that vitamin D plays a major role in human health, the goal of this study was to compile data regarding the implications of insufficiency/deficiency of this vitamin in autoimmune diseases, especially in systemic lupus erythematosus, diabetes mellitus, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease (Crohn's disease).

METHODOLOGY

Considering the planned objectives, a vast research of scientific articles was carried out centered on the proposed theme: "Implications of vitamin D insufficiency/deficiency in autoimmune diseases". Several search engines carrying scientific information in the health area were used in this study, such as Google Scholar and the Medical Publications database (PubMed) and Scientific Electronic Library Online (SCIELO).

For information collection, the descriptors used in this research were: vitamin D; vitamin D in preventing diseases; vitamin D and autoimmune diseases; vitamina D; doenças autoimunes (terms in Portuguese). From this methodology, it was possible to analyze a population of 58 articles that were selected for the study and constituted the sample used in this review. The inclusion criteria used in this study were publications of scientific articles available in full and with free electronic access, delimited between 2008 and 2020, and selected articles in Portuguese and English.

DEVELOPMENT

Vitamin D is a steroid hormone, whose active form is 1,25-dihydroxyvitamin D3 [1,25(OH)2D], with its inert intermediate form being 25-hydroxyvitamin D3 [25(OH)D], which is more stable, and therefore it is dosed to assess its organic reserve (MONTEIRO JÚNIOR *et al.*, 2014).

The ultraviolet B solar radiation (UV-B) in the skin converts the precursor molecule 7-dehydrocholesterol to cholecalciferol, which is transformed into 25(OH)D in the liver, however, its physiologically active form D3 [1,25(OH)2D], (or calcitriol) is activated in the kidney (DUTTA *et al.*, 2019). D3 [1,25(OH)2D], an essential agent in the maintenance of autoimmune tolerance, and which integrates a variety of cellular functions, including proliferation, differentiation and apoptosis (RAMOS-MARTÍNEZ *et al.*, 2013).

In addition to skin exposure to UV-B ultraviolet radiation (80 to 90% of the body's need), another alternative and less abundant source is in common foods. Egg yolk, milk and liver contain some amount of vitamin D, while some deep-water fish such as salmon, tuna and sardines contain a greater amount of this vitamin (SANTOS *et al.*, 2012; CHAROENNGAM; HOLICK, 2020).

Vitamin D synthesized in the skin or ingested is transported in the plasma by a specific protein (VDBP - vitamin D binding protein), primarily metabolized in the liver and subsequently in the kidney, where the first and second hydroxylations occur, respectively. This physiological process exhibits compensation mechanisms that prevent high levels of this vitamin that can generate toxicity (FERREIRA *et al.*, 2012).

One of the main functions of this vitamin is to maintain adequate concentrations of calcium and phosphorus, both serum and extracellular, in order to guarantee a variety of metabolic functions linked to the interaction of several organs, among them, adrenals, intestines, kidneys and parathyroids, which is also responsible for the intestinal absorption of phosphorus and calcium, from the bone, in the presence of parathyroid hormone (PTH), and for the increase in renal calcium absorption, thus regulating bone metabolism (GALVÃO *et al.*, 2013).

Another substantial role of vitamin D includes its interaction with the immune system, given that this substance has its receptor expressed in a wide variety of human tissues and organs. Through these receptors, vitamin D regulates, directly or indirectly, the expression of more than 200 genes (WANG, 2014). It performs biological functions through its connection to nuclear receptors; vitamin D receptors regulate the transcription of DNA and RNA that are expressed by various types of cells, including the small intestine and renal tubule epithelium, osteoblast, osteoclast, hematopoietic cells, lymphocytes, neurons, epidermal and pancreatic cells (SZODORAY *et al.*, 2008).

Vitamin D receptors are widely expressed in most immune cells, such as monocytes, macrophages, dendritic cells, NK cells, where they exhibit their regulatory and differentiating function of these cells, including interfering with the secretion of several cytokines in vivo and in vitro (MARQUES *et al.*, 2010).

Vitamin D and autoimmune diseases

Among the most common autoimmune diseases associated with vitamin D insufficiency/deficiency are: systemic lupus erythematosus, type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease (GRANT; TANGPRICHA, 2012).

Basically, vitamin D acts on the innate immune response, through the regulation and differentiation of cells of the immune system, such as lymphocytes; in the stimulation of natural killer cells (NK); as well as in the differentiation of monocytes into macrophages, amplifying their antimicrobial effects (PRIETL *et al.*, 2013). Vitamin D also acts on the acquired immune response, influencing the role of T cells, through four possible mechanisms: 1) direct endocrine effects mediated by this substance, systemically; 2) direct conversion of intracytoplasmic D3 [25(OH)D] in D3 [1,25(OH)2D] in T cells; 3) direct paracrine effects of 1,25(OH)2D by monocytes or dendritic cells; 4) indirect effects on the presentation of antigens to T cells, since D3 [1,25(OH)2D] affects the cells presenting localized antigens (LANG *et al.*, 2014).

At the genetic level, it is also found that hypovitaminosis D is associated with autoimmunity, due to mutations in genes involved in the transport, metabolism or transcriptional activity of the vitamin D receptor (VDR), increasing the incidence and severity in many of these diseases (CARVALHO *et al.*, 2015). Although there is a close and important correlation between

vitamin D and autoimmune diseases, rare clinical studies look at limited or no benefits via oral supplementation of this vitamin (JAMES *et al.*, 2013).

Chart 1 presents the synthesis of 14 original articles published between 2008 and 2020 that deal with the relationship of vitamin D with autoimmune diseases addressed in this literature review, among which are: Systemic Lupus Erythematosus (SLE), type I diabetes Mellitus (DM1), Multiple Sclerosis (MS), Rheumatoid Arthritis (RA) and Crohn's Disease (CD).

Chart 1 - Synthesis of the main studies presented in the literature review

Disease	Author	N	Sex	Age*	Objective of the study
Systemic Lupus Erythematosus (SLE)	Mandal *et al.* (2014)	129	125 women 4 men	28.14 ± 8.43	Assess vitamin D3 levels in Indian patients with SLE
	Zhao *et al.* (2017)	50	46 women 4 men	18 and 60	Investigate whether vitamin D levels affect the expression of genes related to autophagy and the counts of subsets of T cells in SLE, as well as to evaluate the association between autophagy and subsets of T cells.
	Hoffecker *et al.* (2013)	118	118 women	Over 2 years	Assess the relationship between vitamin D status, cell aging (telomere length) and anti-telomere antibodies among African-American women with SLE.
Type 1 Diabetes Mellitus	Chakhtoura e Azar (2013)	21.813	Not described	Not described	Review the different mechanisms of the protective effect of vitamin D against insulitis and present the available data on the role of vitamin D deficiency in the control, progression and complications of DM1.
	Grammatiki, Karras e Kotsa (2019)	Not described	Not described	Not described	Summarize current knowledge about the effect of vitamin D on pathogenesis, prevention and treatment of DM1 and DM2, as well as in micro- and macrovascular complications of the disease.
	Schuch, Garcia e Martini (2009)	Not described	Not described	Not described	Review the evidence on the participation of vitamin D in these diseases, as well as to elucidate the probable mechanisms of action.
Multiple Sclerosis (MS)	Sassi, Tamone e D'amelio (2018)	Not described	Not described	Not described	Summarize experimental data and clinical observations on the potential immunomodulatory properties of vitamin D.
	Berezowska *et al.* (2019)	627	463 women 164 men	Not described	Evaluate the evidence from randomized controlled trials for the effectiveness of vitamin D supplementation compared to placebo supplementation on disease and symptom management in people with MS.
	Smolders *et al.* (2011)	Not described	Not described	Not described	Review whether the substrate, transport mechanisms and enzymatic machinery necessary to obtain sufficient amounts of 1.25 (OH) 2D are present in the CNS, and to discuss their possible implications for Multiple Sclerosis (MS).
Rheumatoid arthritis	Rosa *et al.* (2011)	Not described	Not described	Not described	Report new developments with specific reference to metabolism and signaling mechanisms associated with the complex immunoregulatory effects of vitamin D on immune cells.
	Gatenby *et al.* (2017)	Not described	Not described	Not described	Review the role of vitamin D in relation to immunological rheumatic diseases.
Crohn's disease (CD)	Basson (2014)	Not described	Not described	Not described	Review the molecular evidence that points to the immunoregulatory role of vitamin D and its supplementation in patients with CD, based on existing literature.
	Suibhne *et al.* (2012)	151	91 women 60 men	≥18 years	Determine the prevalence and risk factors for vitamin D deficiency.
	Raftery e O'sullivan (2015)	Not described	Not described	Not described	Discuss the potential roles of vitamin D and possible levels required.

Notes: *(mean ± sd)
Source: the authors.

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease of the connective tissue, which compromises the function of various organs and systems of the body, generating debilitating complications (DUTTA *et al.*, 2019).

Although the cause and epidemiology of SLE are not yet fully elucidated, it appears that factors such as ethnicity, sex and environmental aspects are involved. The disease most often affects young women of reproductive age (SOUSA *et al.*, 2017).

SLE patients show lower levels of vitamin D (TEIXEIRA; COSTA, 2012) due to photosensitivity, renal impairment, prolonged use of corticosteroids (SALMAN-MONTE *et al.*, 2016) and increasing recommendation for the use of sunscreen (SOUSA *et al.*, 2017). These factors interfere with the cutaneous synthesis of vitamin D stimulated by UV-B ultraviolet rays (MARQUES *et al.*, 2010; FRAGOSO *et al.*, 2012).

Clinical and experimental studies point to the close link between vitamin D and the progression of SLE that seems to be involved in cellular mechanisms, such as modulation of interferon levels (MANDAL *et al.*, 2014), maintenance of double positive peripheral $CD4^+/CD8^+$ T lymphocytes in adequate proportion (DING *et al.*, 2017), genetic polymorphism of the vitamin D receptor (VDR) (MAHTO *et al.*, 2018), control of the expression of genes linked to autophagy in peripheral blood cells and in T cell subtypes (ZHAO *et al.*, 2017) and intervention on leukocyte telomere length and cell aging (HOFFECKER *et al.*, 2013).

Sousa *et al.* (2017), in a systematic review with the objective of analyzing clinical trials conducted in the investigation of the effect of vitamin D supplementation on SLE, found the benefits of vitamin D supplementation on lupus in patients with insufficiency/deficiency of this vitamin. Despite the promising results of vitamin D supplementation, the authors warn of the need to clarify the action of its protective effects against this metabolic disorder; paying attention to issues such as standardization of type, dosage and supplementation time.

Diabetes Mellitus

Type 1 Diabetes Mellitus (DM1) is a pathology of multiple etiology and its main clinical manifestations are due to disturbances in the metabolism of carbohydrates, lipids and proteins due to hyperglycemia.

It is a pathology that can affect people of all ages, being more frequently diagnosed in children and adolescents. However, the main common late complications in patients with diabetes are micro- and macroangiopathy, atherosclerosis, nephropathy, retinopathy (SHULMAN; LUO; SHAH, 2018) and neuropathy (ASLAN *et al.*, 2019).

DM1 arises as a result of the autoimmune destruction of β cells in the pancreas, responsible for insulin production. In this case, the islets are infiltrated by macrophages, lymphocytes, dendritic cells and Natural Killer lymphocytes (NK); in addition to the high expression of several genes of the immune system (QIAN; SHI; DING, 2019).

The literature reports on the beneficial effects of vitamin D related to diabetic conditions; where there is evidence that this vitamin plays an immunomodulatory role in the prevention of DM1, via the vitamin D receptor (VDR), which is expressed in cells of the immune system and in the cells of the pancreatic islets (CHAKHTOURA; AZAR, 2013), in addition to providing insulin synthesis and secretion (GRAMMATIKI, KARRAS; KOTSA, 2019) and increase cellular sensitivity to insulin (SCHUCH, GARCIA; MARTINI, 2009).

Multiple sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative demyelinating disorder of the central nervous system (CNS), which is evidenced by extensive immune infiltration,

axonal injury and oligodendrocyte injury (BARTOSIK-PSUJEK; PSUJEK, 2019). MS is characterized by repeated episodes of neurological dysfunction with intermittent remission; being considered an autoimmune disease caused by environmental factors, such as exposure to infectious agents, smoking and a diet with low concentrations of vitamin D (MANDIA *et al.*, 2014) associated with genetic complexity (RAMAGOPALAN *et al.*, 2008). Although the etiology of MS is not completely elucidated; it is necessary to consider the notes of several studies strongly suggesting that the lack of exposure to the sun and/or vitamin D during the first phase of life constitutes a great risk for MS (MIRZAEI *et al.*, 2011; NIELSEN *et al.*, 2017; PIERROT-DESEILLIGNY; SOUBERBIELLE, 2017).

The relationship between the positive effects of the vitamin and the immune system is marked by the fact that the vitamin D receptor (VDR) has been found in antigen-presenting cells, macrophages and T lymphocytes. In addition, this vitamin inhibits proliferation and apoptosis of activated B lymphocytes and blocks the differentiation of these lymphocytes into plasma cells and memory cells (SASSI, TAMONE; D'AMELIO, 2018). Corroborating these findings, Berezowska *et al.* (2019) found in their systematic review that most studies revealed beneficial effects with vitamin D supplementation in patients with MS, since this substance plays a key immunomodulatory role, attenuating the production of pro-inflammatory cytokines and stimulating the production of anti-inflammatory cytokines.

Another crucial role of vitamin D is evidenced by its neuroprotective, neurotrophic and remyelination capacity, when bound to VDR receptors present in neurons, astrocytes, microglia and oligodendrocytes (SMOLDERS *et al.*, 2011).

Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a systemic autoimmune disease of the connective tissue, characterized by inflammation of the synovial joints; in which numerous cells and soluble inflammatory mediators stimulate these chronic inflammations and increase the severity of the disease (KHAJOEI *et al.*, 2019), causing significant morbidity and decreasing life expectancy. This disease affects 0.3 to 1.0% general population, being more prevalent among women and in developed countries (CHAUDHARI, RIZVI; SYED, 2016).

The initial trigger for RA is believed to be linked to antigen-dependent T cell activation, which triggers an essentially Th1-type immune response. There is evidence that RA patients have vitamin D deficiency and that D3 [1,25(OH)2D] and vitamin D receptor (VDR) are present on the surface of macrophages, chondrocytes and synoviocytes in the joints of these patients (MARQUES *et al.*, 2010). Polasik *et al.* (2017) found a positive correlation between vitamin D and IL-6 levels in Polish patients with rheumatoid arthritis. Based on the data obtained, the authors inferred that high levels of pro-inflammatory IL-6 in these patients may stimulate the synthesis of D3 [25(OH)D] as a compensation mechanism for the inflammatory portion and this assumption is supported by the fact that UVB radiation, being the key factor for the synthesis of cholecalciferol (vitamin D3) in the skin, can also trigger cutaneous inflammatory response mediated by induction of IL-6 expression in an IL-1α dependent way.

Beneficial effects of vitamin D in individuals with RA consist of: 1) inhibiting the differentiation of monocytes into macrophages, subsequently reducing the number of antigen-presenting cells available to stimulate T lymphocytes, which are believed to contribute an essential role in RA (WEN; BAKER, 2011); 2) inhibiting the proliferation of B lymphocytes before their differentiation into plasma cells, consequently, reduces the production of antibodies (ROSA *et al.*, 2011); 3) contribute to immune tolerance by affecting both innate and adaptive immune responses (GATENBY, LUCAS; SWAMINATHAN, 2013).

Crohn's disease

Crohn's disease is considered to be a subcategory of inflammatory bowel diseases (IBD), of a chronic and autoimmune nature, which can compromise any part of the digestive tract, especially

the small intestine and the colon (GUIMARÃES; YOSHIDA, 2008; BASSON, 2013). However, in more than 50% patients there are perianal manifestations, as well as extraintestinal manifestations that appear alone or in combination, affecting skin, liver, eyes, joints and urinary tract more continuously. These disorders are notorious in individuals of any age, but the diagnosis is most often ascertained in the second or third decade of life (LESKOVAR *et al.*, 2018).

Vitamin D deficiency is a frequent finding in patients with inflammatory bowel disease, and is linked to increased disease activity in patients with Crohn's disease (KO *et al.*, 2019). According to Scolaro *et al.*, (2018), the mechanism by which vitamin D deficiency occurs more frequently in this disease is due to a set of factors, which are listed as intestinal malabsorption due to functional impairment in the ileum; reduced enterohepatic circulation of this vitamin and low intake of foods rich in vitamin D.

Vitamin D supplementation has been shown to be efficient in this pathological condition, when its role is demonstrated in innate immunity, through the activation of macrophage receptors by intestinal bacteria that culminate in the conversion and bioavailability of active vitamin D; in addition to increasing the expression of antimicrobial peptides, such as cathelicidins and β-defensins that prevent infections by acting as local barriers on mucous membranes and epithelial surfaces (BASSON, 2014). In animal models, vitamin D has been found to act against the growth of intestinal inflammation by partially attenuating the effects of tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)10 (SUIBHNE *et al.*, 2012).

Another essential aspect of vitamin D, for the maintenance of homeostasis of the gastrointestinal tract, is that it acts on the epithelial barrier that strengthens the proteins of the adherent and occlusive cell junctions, in addition to improving the healing of the post-injury intestinal mucosa (RAFTERY; O'SULLIVAN, 2015).

CONCLUSION

The literature points to several studies showing the importance of vitamin D for the body and alert to the increasing prevalence of its deficiency in the world population, due to the lack of consumption of nutrients that contains the vitamin and due to little exposure to the sun, due to cultural factors related to the use of clothing that covers the entire body; age; institutionalized people; sedentary lifestyle; widespread use of sunscreens that reduce skin synthesis; or environmental conditions in temperate countries. Knowing the beneficial biological properties such as regulating the differentiation and activation of CD4 lymphocytes, increasing the number and function of regulatory T cells, differentiating monocytes into dendritic cells, decreasing the production of interferon-γ cytokines, among others linked to the maintenance of body health, it is extremely important to consider the benefits of replacing this vitamin (either by increasing sun exposure or oral supplementation), as a preventive measure for various diseases, especially autoimmune diseases.

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