VITAMIN D, IN THE BEST CLINIC IN AUTOIMMUNE, INFLAMMATORY INFECTIOUS AND DEMELINIZING DISEASES: A CRITICAL ANALYSIS

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Abstarct

The term demyelination is used to characterize any inflammatory changes that occur in the medullary or cephalic region. Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and in general, besides being inflammatory [08, 25], demyelinating and with significant neuronal degeneration, it is considered an important cause of permanent disability in young adults [02-05]. The inflammatory process occurs by an irregular immune response usually mediated by T cells and acts as autoantigens and leads to destruction of the myelin sheath with genetic predispositions [21]. Thus, these chronic and disabling characteristics place a high cost on public health coffers by temporarily or permanently restricting the economic and social activities of their holders and also impacting the lives of their families in a financial and emotional way [15-18]. Still regarding the high cost treatment to inflammatory-infectious processes, primary and autoimmune demyelinating agents, such as sepsis in the adult and child population is considered a critical disease as the main cause of death in children intensive care in Brazil. In recent years in Brazil [24], the high rate of death from sepsis in Brazilian intensive care units has surpassed deaths from stroke and infarction and approximately 230.000 adult patients undergoing intensive care unit treatment have sepsis and estimated 55.7% of hospitalized patients with sepsis died [24]. It is recognized that Vitamin D deficiency is common in both children and adults hospitalized in severe clinical conditions in intensive care [06-12].

And high vitamin D exposure can protect against the development and progression of multiple sclerosis and sepsis and autoimmune diseases [04-10], such as lupus, possibly through of the immunomodulatory properties of its biologically active metabolite is [1,25-dihydroxyvitamin D] [10-13]. And the improved survival of children and adults infected with viruses or bacteria in the immune system during hospitalization has focused attention on the benefit of adjunctive therapies such as Vitamin D [15-17].

Thus, Vitamin D is a potent immune system activator [07-11], being an absolute and protective component of the natural defense mechanisms against microbial invasion and the neural demyelination process [18-21]. Vitamin D is a fat-soluble steroidal hormone with endocrine, paracrine and autocrine functions [24-25].

For humans, the main source of Vitamin D is exposure of the skin to sunlight, which can produce around 10,000 IU (250 μg) of Vitamin D3 per day [24].

Vitamin D biogenesis occurs in the skin [12], specifically in Malpighi cells [03-05], through a chemical reaction known as photolysis [20-25], where Ultraviolet rays mainly B induces breakage of B nucleus of precursor steroids [02-04] and the individual receiving solar ultraviolet rays [21-22], specifically, ultraviolet B radiation with The presence of [7-DHC] absorbs the UVB photon which results in the carbon bond breakage and as a response occurs the disruption of ring B with the pre-formation of Vitamin D [22-25]. And through heat, an isomerization reaction gives rise to Vitamin D [13]. The genetic predisposition in the pathogenesis of autoimmune diseases is constructed as a mosaic, aggregated to hormonal and environmental factors [18].

Vitamin D blood level and VDR polymorphism have highlighted an important environmental risk factor in the development of autoimmune diseases [24].

Scientific evidence links VDR polymorphism [24], specifically linked to Bsml, Apal, Taql, and Fokl polymorphism genotypes to the increased frequency of autoimmune diseases, and has highlighted that the interaction between VDR and their biomolecular bonds produce an anti-inflammatory effect on innate cells of the immune system and also [20-24], performs a regulatory and immunosuppressive action on adaptive immunity [21-25].

Decreased blood levels of Vitamin D are usually defined in autoimmune diseases [21], such as Diabetes Melittus, SLE, rheumatoid arthritis, inflammatory bowel disease, thyroiditis, and autoimmune gastritis [21-24]. In the last ten years in northern Europe the prevalence of Multiple Sclerosis has been strongly correlated with Vitamin D deficiency and risk of disease development [24]. It is noteworthy that Vitamin D has immunomodulatory and suppressive functions in Multiple Sclerosis [19-24].

Vitamin D may interfere with the pathophysiology of Multiple Sclerosis [18] by altering inflamed tissues [22].

This interference is due to Vitamin D binding protein (DBP) and Vitamin D receptor (VDR) protein [19-21], as well as the presence of metabolite enzymes (CYP27B1) [19] which is present in the central nervous system [24] and VDR, CYP27B1 are expressed in a cell variety that includes invasive neurons, glial cells and lymphocytes [21-24], as Vitamin D plays a modulating action in various pathophysiological processes of the disease. Multiple Sclerosis [24] and includes the inflammatory, demyelinating process, axon damage repair and remyelination [25].

Vitamin D has the function of regulating the system in innate and adaptive immunity [24], because the innate immune response is characterized by activation of monocytes and macrophages capable of recognizing molecular patterns. pathogen-associated pathogens and [19-21] thus provide a first line of defense against external agents and increase the antimicrobial activity of macrophages and the enhancement of phagocytic chemotactic and capacity [22-24]. Conversely, Vitamin D deficiency impairs the ability of macrophages to mature [24-25] to produce specific surface antigens and macrophages and

acid lysosomal phosphatase enzymes and to secretion of hydrogen peroxide which is essential for their function antimicrobial [25].

Also, in the process of up-regulation of VDR in the Toll-like receptor activation of monocytes and macrophages leads to induction of catelicidins; a family of polypeptides found in macrophage lysosomes and polymorph-nuclear leukocytes that have a critical function in innate immune defense [23-25].

Catelicidin production is increased after bacterial and macrophage infection by recognizing bacterial invasion regulates VDR expression by activating the catelicidine gene, thereby destroying the bacterial invader [21-24] Monocytes are activated in the presence of [1,25 (OH) 2 D] by showing decreased TNF-α, IL-1α and IL-6 production and an increase in IL-10 production [24]. Thus, Vitamin D can modulate the immune response in a more anti-inflammatory way and exert a regulatory function [19-24]. Active immunity is also influenced by Vitamin D in many ways [24]. Vitamin D acts on monocyte-macrophage cells by developing a cell line capable of preventing differentiation into dendritic cells and reduces the expression of CD80 and CD86 surface co-stimulatory molecules [25], thus affecting T-cell stimulating capacity [21].

In addition, [1,25 (OH) 2D] can supply maturing dendritic cells by decreasing T and B antigen presentation and cellular activity [24]. Following vitamin D stimulation [20-24], dendritic cells have the ability to reduce and trigger T cell proliferation [17-19]. Also, in [1.25 (OH) 2D] dendritic cells has a direct action on T lymphocytes and alters the cytokine profile of T cells by inhibiting pro-inflammatory action in the production of cytokines such as IL-2, INF-γ, IL-17 and IL-21 [19-22]. Vitamin D also influences B cell population production (RAMOS et al., 2019), because exposure of B cells to [1,25 (OH) 2D] inhibits their proliferation (LEE, 2011), cell differentiation. Plasma and immunoglobulin secretion (IgG and IgM) and memory B cell generation also induce cellular apoptosis [06-10].

Currently there has been strict control by health professionals in requesting serum vitamin D dosing related to the steady increase in vitamin D deficiency in Brazil and some countries around the world [02] and to perform the determination of Vitamin D metabolites there is a difficulty because they are lipophilic molecules that circulate in reduced concentrations [25 (OH) D equivalent to 8 - 60 ng / ML-1] and [1,25 (OH) 2D [02-04] equivalent at 20 - 60 pg / ML-1] and are strongly adherent to proteins (DBP and Albumin) [02,24]. Generally Vitamin D deficiency is a result of PTH secretion which induces production [1,25 (OH) 2D] (BIKLE, 2011), high levels of [1,25 (OH) 2D] or normal may be presented in patients with Vitamin D deficiency [02].

In Brazil the "Endocrine Society" (2011) and the "Brazilian Society of Endocrinology and Neurology" (2017) defined Vitamin D deficiency below 20 ng / ML-1 [24], insufficiency with [25 (OH) D] of 21 - 29 ng / ML-1 and [25 (OH) D] sufficiency greater than or equal to 30 ng / ML-1 [02, 24]. These cohort patterns are the most commonly used today to define blood Vitamin D level [25].

There is a consensus that daily intake of 50.000 IU/day (100 ng/ml in the blood) of Vitamin D by patients has no toxic effects on the body [17] which would not cause adverse health effects [14].

Based on immunological health [24], bone and neurological recommendations of the "Brazilian Society of Endocrinology and Neurology" (2017) for adequate daily intake of Vitamin D in patients without pre-existing diseases are: 400 IU/day for infants up to one year old, 600 IU/day for children, adolescents

and the elderly up to 70 years old and 800 IU/day for elderly over 70 which should correspond to the ideal blood dose level of 20 ng/day. ML^{-1} [24].

For patients at risk and with pre-existing autoimmune, inflammatory, infectious and demyelinating diseases, the recommended guideline is (B: 400 - 1000 IU/day for infants up to one year of age, 600 - 1000 IU/day for infants up to 18 years and 2000 IU/day for persons over 18 years of age and should have a blood level of at least 30 ng / ML^{-1} of at least [25 (OH) D] [02,24].

In addition, the result reinforces that the problematization of sepsis in critically ill patients with vitamin D deficiency [24] occurs according to changes in glucose metabolism and especially calcium or immune and endothelial cell related disorders Vitamin D deficiency [03].

However, the points of this study are related to serum vitamin D (VENKATRAM et al., 2011), which proposes a relationship between infection rate and vitamin D deficiency [04], a trend reinforced by the increase in hospital intensive care infection people with hypovitaminosis D [16]. This study confirms that the high prevalence of low Vitamin D levels in critically ill patients triggers immune system changes that may result in sepsis [17-19]. Therefore, there is a need for blood serum analysis at the beginning of the hospitalization period for Vitamin D dosing [14], since there is an easy probability of avoiding complications during hospitalization [17]. Vitamin D deficiency can lead to imbalance of the immune system [13], Vitamin D has a primary role in defense against bacterial and viral agents and this defense occurs by stimulation of antimicrobial peptides which [12] can intensify the reduction of catelicidine and therefore the Vitamin D concentration level get a better significance (NAIR et al., 2015), for example, in the samples of intensive care patients with sepsis in reference to non-sepsis patients [17]. In this context, it is emphasized that the role of Vitamin D is to function as an immunomodulators [02-04], as Vitamin D identifies and nullifies the action of inflammatory cytokines mainly interleukins 6 (IL-6) which induces the systemic inflammatory response syndromes [20-24].

When comparing the serum vitamin D level during the intensive care admission process of the sepsis patient, there is an increased likelihood of developing organic disease when the patient has a vitamin D deficit [14].

In view of the above evidence, the protective role of vitamin D is biologically plausible [24], since [1,25 dihydroxyvitamin-D] is present in various immune cells [21] such as macrophages, activated T cells and B, IL-04, IL-06, IL-08, IL-10 and myelin specific [22]. Thus, this study highlighted that the increase in immune system cells occurs by stimulating receptors in the production of inflammatory cytokines [22-24].

This study highlights that Vitamin D supplementation above 50.000 IU/week is safe and protective against acute respiratory tract infections. It is emphasized that Vitamin D has several immunomodulatory functions including the regulation of antiviral peptides that are part of human innate immunity and may, for example, inactivate influenza virus [18-24].

The synthesis of the evidence showed that Vitamin D deficiency is high in patients with sepsis. There is a direct relationship with clinical improvement in patients with sepsis supplemented with Vitamin D [24], which shows a greater reduction in the indicators of the intensity of organic dysfunction and Vitamin D is increasingly recognized as an important agent with immune function and may be a preventive factor in the development of sepsis in intensive care patients [19-24].

Vitamin D supplementation (equal to or greater than 50 IU/week) has been shown to be more effective compared to lower supplementation doses [24]. These findings highlight the urgent need for further research and guidance for health professionals regarding the dose and duration of the intervention to be administered in the treatment associated with autoimmune, inflammatory-infectious and demyelinating diseases [18-21].

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