

## THE ROLE OF VITAMIN D IN THE DEVELOPMENT/ WORSEAGE OF MOOD DISORDERS, WITH A FOCUS ON BIPOLAR AFFECTIVE DISORDER AND DEPRESSION

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**Abstract:** Purpose: examine the literature on the role of vitamin D in the evolution and exacerbation of mood disorders, with a focus on bipolar and depressive disorders. Methodology: Literature review in the PubMed database. Through the following search strategy: vitamin D AND (bipolar disorder OR mood disorders). After applying the inclusion and exclusion criteria, 15 articles were selected to compose the collection of this study. Results: Vitamin D plays two main roles in the body. The first is related to the regulation of the immune system, where it suppresses the production of pro-inflammatory cytokines and increases levels of anti-inflammatory ones. This role is relevant in the context of bipolar disorder, which is associated with increased pro-inflammatory cytokines. The second paper focuses on the mechanisms linked to depression, specifically in the hypothalamic-pituitary-adrenal axis. In this context, vitamin D acts as an antagonist of glucocorticoids, which are excessively active in these disorders. Furthermore, there is evidence that vitamin D can also regulate the formation of new neurons in the hippocampus. Final considerations: Vitamin D plays a significant role in the evolution and exacerbation of disorders, being essential for the proper functioning of the central nervous system and for the regulation of the immune system.

**Keywords:** Vitamin D; Bipolar disorder; Mood Disorders; Depression.

## INTRODUCTION

Mood disorders, including bipolar affective disorders, constitute significant challenges in public health, being correlated with comorbidities, low quality of life, various diseases and suicide cases. These disorders pose difficulties to treat, and a new line of investigation has linked low vitamin D levels to bipolar disorder. Vitamin D, especially D3,

can cross the blood-brain barrier, binding to receptors in brain areas that are intrinsically linked to depression, such as the hypothalamus, prefrontal cortex and substantia nigra, influencing the neuroendocrinological mechanisms responsible for depression. mood regulation (MARSH WK et al., 2020).

Vitamin D is known for its multifaceted actions in human physiology, including in the brain, where it performs essential functions such as brain regulation, development and differentiation. This vitamin plays a neuroprotective and regulatory role in human behavior (CEREDA G. et al., 2021). Studies suggest that there may be an important interaction between genetic factors and vitamin D, which could play a role in modulating the severity of mental illness. This relationship could be partially mediated by the ability of vitamin D to activate genes that modulate serotonin synthesis (PATRICK R.; MENON V., 2015).

Vitamin D levels also seem to correlate with episodes of bipolar disorder (BD), whether in depressive or manic phases. During active phases of the disease, the immune system of TB patients leans more toward an inflammatory response, usually with increased levels of pro-inflammatory cytokines and concomitant decreases in brain-derived neurotrophic (BDNF) levels. In view of these observations, recent studies have focused on investigating the role of vitamin D in psychiatric disorders, including mood disorders, seeking to establish a link between the immunomodulatory activity of vitamin D and the neuroinflammatory hypothesis of mood disorders (PATRICK R.; MENON V., 2015; CEREDA G. et al., 2021).

The purpose of this literature review is to examine the literature on the role of vitamin D in the evolution and exacerbation of mood disorders, with a focus on bipolar and depressive disorders. Recent clinical,

epidemiological and experimental studies that investigate the relationship between vitamin D levels and the incidence, prevalence and progression of mood disorders, as well as the biological mechanisms underlying this association will be explored. In addition, we intend to identify risk factors and individual vulnerabilities, discuss the therapeutic and preventive implications of this association, in addition to highlighting areas for future research and development in psychiatry to improve the understanding and management of mood disorders related to levels of vitamin D.

## METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used for the elaboration of the research through its guiding question: “What is the role of vitamin D in the development and worsening of mood disorders, with a focus on bipolar affective disorder and depressive disorders, and what are the underlying biological mechanisms, risk factors and therapeutic implications of this association, based on the literature?” In this sense, according to the parameters mentioned above, the population of this research refers to adult patients with bipolar disorder, the variable would be the levels of vitamin D and its possible adjuvant supplementation to traditional treatments, and the outcome would be the therapeutic implications of such a variable. The searches were carried out through searches in the PubMed Central (PMC) databases. The descriptors used were: vitamin, bipolar disorder and mood disorders; combined through the Boolean operator “AND”, with the following search strategy: vitamin D AND (bipolar disorder OR mood disorders). From this search, 147 articles were found, subsequently submitted

to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish, published from 2015 to 2023 and that addressed the themes proposed for this research, studies of the type systematic reviews, clinical trials, cohort studies and case-controls made available in full. Exclusion criteria were: duplicate articles, available in abstract form, that did not directly address the studied proposal and did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 147 articles were found. Of which, they belonged to the PubMed database. No articles relevant to the topic were found in the Scielo database. After applying the inclusion and exclusion criteria, 15 articles were selected from the PubMed database to compose the collection of this study.

## **RESULTS**

### **VITAMIN D: PROPERTIES AND ACTIONS ON THE CENTRAL NERVOUS SYSTEM AND ITS IMMUNOLOGICAL PERFORMANCE**

Vitamin D's main function is to regulate osteomineral physiology. Its levels are dependent on sun exposure, absorption from food sources and supplements. Studies indicate the presence of the enzyme 1,25-dihydroxycholecalciferol (1,25(OH)<sub>2</sub>D<sub>3</sub>), responsible for the active metabolic synthesis of vitamin D, and of the vitamin D receptor (VDR) in the brain, thus highlighting the role of vitamin D in maintenance and functioning of the central nervous system. These factors play an important role in all organs, especially in the brain (CUI X.; EYLES DW, 2022).

Vitamin D<sub>3</sub> is produced in the skin from 7-dehydrocholesterol, through the action of ultraviolet radiation from sunlight. It is also

synthesized by animals such as fish and birds. On the other hand, vitamin D<sub>2</sub> is derived from the sterol ergosterol and can be found in yeast, mushrooms and vegetables. Both forms are converted to their active form through hydroxylation reactions. Initially, vitamin D is converted to 25-hydroxyvitamin D (25OHD), and later it is transformed into 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). This active form acts as a ligand for the vitamin D receptor (VDR), present in various parts of the body, including the central nervous system.

Therefore, low serum levels of vitamin D can impair brain functions and consequently lead to significant neurological and psychiatric disorders (CUI X. ; EYLES DW, 2022).

Ultimately, the effects of 1,25-(OH)<sub>2</sub>D<sub>3</sub> on the central nervous system involve neurotrophic factors and neurotransmitters. Brain disorders are associated with deficiency or absence of vitamin D receptors, resulting in changes in the central nervous system. In neurons, 1,25(OH)<sub>2</sub>D<sub>3</sub> acts to reduce inflammation, combat oxidative stress, neuroprotection and inhibit several inflammatory mediators. Therefore, the low concentration of vitamin D could facilitate the development of several psychiatric diseases, such as depression, schizophrenia and bipolar affective disorder (LANGA F. et al., 2019).

Vitamin D acts as a modulator in the immune systems, being able to modulate inflammation, reducing the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines, with immunomodulatory effects on the cells of the immune system and on the production and action of pro-inflammatory and anti-inflammatory cytokines. Both the vitamin D receptor and the enzymes involved in its metabolism are expressed by cells of the immune system. Studies have shown that immune system cells such as macrophages, lymphocytes and dendritic cells, which play

an important role in regulating the immune system, express the vitamin D receptor (TOMOKA A. et al., 2021).

Vitamin D is able to suppress the production of cytokines by dendritic cells, in particular the interleukin IL-12, and promote the expression of the anti-inflammatory cytokine IL-10, favoring the control of immune responses (TOMOKA A. et al., 2021). In addition, vitamin D is able to differentiate monocytes into macrophages, further enhancing their immune role in the body. It plays an important role in regulating the differentiation and activation of CD4 T lymphocytes, inhibiting the differentiation of monocytes into dendritic cells and reducing the production of cytokines such as interferon- $\gamma$ , IL-2 and TNF- $\alpha$ .

In the active form, 1,25(OH) $_2$ D, vitamin D modulates and differentiates antigen-presenting cells, thereby reducing the production of inflammatory interleukins such as IL-12. Thus, vitamin D performs several actions in the innate and acquired immune systems, and its deficiency is directly related to the emergence of some inflammatory, autoimmune, neurological and psychiatric diseases.

## **VITAMIN D MOOD DISORDERS - DEPRESSION**

At first, it is important to understand that depression is the main cause of disability in the world, making it relevant to understand the role of vitamin D in the brain and its relationship with this disease. Simply put, individuals with depression have hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal cortex to release the glucocorticoid cortisol. In contrast, the active form of vitamin D acts

precisely as a glucocorticoid antagonist, acting as a neuroactive steroid. Accordingly, vitamin D, its receptors and enzymes that activate and metabolize it are present in neurons, glial cells and brain macrophages, mainly in the hippocampus. Added to this, studies in patients with major depressive disorder have shown low serum concentrations of 25-(OH) - MIKOLA T. et al., 2022).

Furthermore, vitamin D can regulate the formation and maturation of new neurons in the hippocampus, stimulating neurotrophic factors that are essential for the survival, maintenance and development of cells in the nervous system. This fact reinforces and validates the indication to patients with depressive disorder for a higher consumption of foods rich in vitamin D, such as olive oil, fish, fruits and vegetables, which have been widely studied in relation to their benefits for mental health (GUZEK D. et al., 2023).

According to Guzek D. et al. (2023), vitamin D is a beneficial nutrient in the treatment of depression. Vitamin D supplementation is already recommended in some countries for specific population groups, such as the elderly, since low concentrations are associated with a reduction in the volume of brain tissue and hippocampus, as observed in magnetic resonance imaging (MOREIRA RT et al., 2021).

Hypovitaminosis D is related to mood disorders due to the biological mechanisms underlying this condition. Several studies have pointed to the relationship between vitamin D and the risk of developing and severity of depression. For example, the Third National Health and Nutrition Survey found that serum 25-OH VitD levels  $\leq 50$  nmol/L are associated with an increased risk of developing depression compared with levels  $\geq 75$  nmol/L. Furthermore, a randomized, double-blind study demonstrated that administration of vitamin D3 resulted in clear improvement

in positive affect and reduction in negative affect. However, there are still aspects that have not been fully clarified, such as whether vitamin D deficiency is a cause or a result of depression (GIORDANO N. et al., 2017).

According to Van Der Burg KP et al. (2021), nutraceuticals can be used as adjuvant agents or even as monotherapy in psychiatric treatments, especially in mood and psychotic disorders. They can potentiate the activity of certain drugs and add different effects to the nervous system, which can result in clinical improvements for patients, with the advantage of reducing side effects. Vitamin D is included in nutraceutical therapies, and biomarker analyzes have been performed to confirm the efficacy of treatment effects. Although some studies have shown a significant increase in vitamin D concentrations, the markers found were not considered useful, limiting effective evidence of treatment effects.

## **VITAMIN D BIPOLAR AFFECTIVE DISORDERS**

Vitamin D deficiency is related to the development of mood disorders due to multiple pathophysiological mechanisms. It is believed that the immune system of patients with bipolar disorder is associated with increased levels of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-2, IL-6, IL-8 and IFN- $\gamma$ , in addition to decreased levels of cerebral neurotrophic factor. Vitamin D has immunomodulatory activity, inhibiting the production of pro-inflammatory cytokines, therefore, its deficiency can aggravate acute episodes of depression or mania in bipolar disorder (CEREDA G. et al., 2021). In addition, vitamin D has antioxidant effects that may contribute to the reduction of systemic inflammatory markers, which is related to the neuroinflammation theory found in individuals with mood disorders such as depression (VELLEKKATT F.; MENON, V.,

2019).

One study reports that vitamin D deficiency is associated with the incidence of bipolar disorder or schizophrenia in outpatients, as well as the severity of negative symptoms and cognitive deterioration in young adults. On the other hand, studies show that vitamin D can protect against psychotic outcomes in children and that its supplementation has a positive effect on the severity of depression, since low levels of vitamin D are associated with depression. It is also noted that its insufficiency is significantly lower in depressed adults compared to non-depressed adults (BOERMAN R. et al., 2016). Vitamin D deficiency during early fetal development could also be related to social cognition problems, decision-making and brain morphology, which are associated with brain disorders (PATRICK R.; MENON V., 2015).

Vitamin D3 acts on several mechanisms that can affect the improvement or worsening of mood disorders. Its active form is able to cross the blood-brain barrier and bind to vitamin D receptors (VDR) present in brain areas such as the prefrontal cortex, hypothalamus and substantia nigra, which are involved in depression. Vitamin D3 acts as a neuroactive steroid, regulating mood through modulation of gamma-aminobutyric acid (GABA) and exerting neuroprotective effects, including calcium-mediated antioxidant defense in the brain (MARSH WK et al., 2020). Regarding vitamin D supplementation, studies have shown that eight-week supplementation with cholecalciferol 50,000 IU in individuals with vitamin D deficiency brought about improvements in manic episodes, showed a significant reduction in the severity of depressive symptoms and consequently improved the patients' quality of life (MARAZZITI D. et al., 2023).

It is also noted that acute manic episodes may be related to low levels of vitamin D due

to dysregulation of the glutamatergic system. Vitamin D deficiency can lead to increased calcium, which can damage the GABAergic system and result in manic symptoms. A study carried out in young patients with bipolar affective disorder, in an episode of mania, showed that vitamin D3 supplementation improved symptomatology due to the improvement in brain neurochemistry. The binding of vitamin D to the VDR affects the metabolism of monoamines and influences the hypothalamic-pituitary-adrenal axis, in addition to modulating the levels of dopaminergic receptors. VDR is highly expressed in the central nervous system and can influence the behavior and emotions of patients (EGHTEDARIAN R. et al., 2022). However, further studies are needed for effective proof of the relationship between hypovitaminosis D and mood instability, as well as to highlight the positive effects after adequate supplementation for each level of insufficiency (MARAZZITI D. et al., 2023).

## **FINAL CONSIDERATIONS**

The literature shows that the development, exacerbation, and severity of psychiatric disorders such as depression and bipolar affective disorder are related to low serum vitamin D levels. Two main roles of this substance in the body have been listed. The first is related to modulation in the immune

system, being responsible for suppressing the production of pro-inflammatory cytokines and increasing the levels of anti-inflammatory ones, which is believed to be directly related to bipolar disorder since it is associated with increased levels of pro-inflammatory cytokines. The second action is focused on the mechanisms involving depression, related to the hypothalamic-pituitary-adrenal axis. In this context, vitamin D acts as an antagonist of glucocorticoids, which are hyperactive in such disorders. In addition, some studies indicate that it may also regulate the formation of new neurons in the hippocampus. In conclusion, vitamin D plays a significant role in the evolution and exacerbation of disorders, and is essential for the proper functioning of the central nervous system and the regulation of the immune system. Monitoring vitamin D levels and its possible supplementation as an adjunct to pharmacological treatment may be important, however, further experimental research is needed to substantiate its relevance and effective applicability in clinical practice. A better understanding of this relationship may pave the way for more effective therapeutic and preventive interventions, improving the quality of life and prognosis of affected individuals. the way for more effective therapeutic and preventive interventions, improving the quality of life and prognosis of affected individuals.

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