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VITAMIN D: AN ALLY IN THE MODULATION OF AUTOIMMUNE DISEASES OF THE THYROID GLAND

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Abstract: Introduction: Autoimmune thyroid diseases result from an immune imbalance in which the body attacks the cells of the thyroid gland itself, causing chronic inflammation and functional impairment. Evidence suggests a relationship between the incidence of these diseases and low serum levels of vitamin D, an immunoregulatory metabolite with the potential to act in the prevention and treatment of these conditions. Objective: To analyze the effects of vitamin D on the pathogenesis of autoimmune diseases of the thyroid gland. Methodology: A bibliographic search was carried out on the PubMed and Virtual Health Library platforms and, after applying the inclusion and exclusion criteria, 9 articles were selected to support this study. Results: The data obtained show an association between low levels of vitamin D and a higher incidence of thyroid autoimmune diseases, highlighting the role of this vitamin in modulating the immune system and its relationship with the pathophysiology of these autoimmune conditions. Final considerations: The review associated hypovitaminosis D with an increased susceptibility to autoimmune thyroid pathologies, however, it concludes that more studies and tests are needed to validate the effectiveness of therapeutic interventions based on vitamin D replacement, as well as to elucidate the mechanisms involved in this association.
Keywords: Autoimmunity; Calcitriol; Autoimmune Diseases; Thyroid Gland Diseases; Immunomodulation.

INTRODUCTION

Autoimmune diseases of the thyroid gland result from a failure in the self-regulation mechanisms, in which the immune system begins to identify components of the gland as threats, triggering persistent inflammatory processes (ANTONELLI et al., 2015). This mechanism results in aggressions to the gland, impairing its regular activity and culminating in conditions such as hypothyroidism or hyperthyroidism. Among the main autoimmune thyroid diseases are Graves' disease and Hashimoto's thyroiditis (ANTONELLI et al., 2015).

Hashimoto's thyroiditis is an autoimmune disease characterized by chronic inflammatory infiltration of the thyroid gland, predominantly involving TCD4+ lymphocytes, as well as B cells, dendritic cells and macrophages (ANTONELLI et al., 2015). This cell invasion compromises the integrity of the gland, reducing its ability to produce thyroid hormones at adequate levels, which results in the development of hypothyroidism. The main symptoms include weight gain, cold intolerance, fatigue and slowed metabolism (LUO et al., 2024).

Graves' disease, in turn, is also associated with lymphocyte infiltration - especially TCD4+ lymphocytes, B lymphocytes, macrophages and dendritic cells - however, it is recognized as the main cause of hyperthyroidism (ZHOU et al., 2021). In this condition, the thyroid begins to overproduce hormones, triggering symptoms such as weight loss, sweating, exophthalmos and goiter (MEI et al., 2021; ZHOU et al., 2021). Thus, both conditions reflect immune dysfunctions in which the immune system, instead of maintaining homeostasis, starts attacking the thyroid gland, impairing its proper performance.

Vitamin D has been widely studied due to its role in modulating immune responses and its potential to contribute to the prevention and management of autoimmune diseases, such as those affecting the thyroid gland. Its anti-inflammatory properties and ability to regulate immune processes make it a key element in these contexts. Classified as a fat-soluble steroid hormone, vitamin D is present in the body in two main forms: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Both vitamin variants depend on ultraviolet radiation (UVB) for their activation, completing the metabolic processes necessary for them to perform their biological functions (BIKLE, 2009).

After their synthesis, the D3 and D2 forms are transported in the bloodstream bound to the vitamin D binding protein (DBP) and distributed to different tissues. The action of vitamin D is mediated by binding to vitamin D receptors (VDRs), which are widely distributed throughout the body, including cells of the immune system. This interaction with VDRs allows the metabolite in question to modulate inflammatory activity and immune balance, crucial factors in the pathophysiology of autoimmune thyroid diseases (BIKLE, 2009).

Vitamin D undergoes essential metabolic transformations for its activation in the body. The initial process takes place in the liver, where the enzyme CYP27A1, belonging to the cytochrome P450 system, hydroxylates cholecalciferol, giving rise to calcidiol [25(OH) D], the main circulating form of vitamin D in the blood and a marker of serum levels of this vitamin (KMIEC'P and SWORCZAK, 2015). Subsequently, in the kidney tissue, calcidiol undergoes a new hydroxylation catalyzed by the CYP27B1 enzyme, a mitochondrial P450 enzyme, and is converted into calcitriol [1,25$(OH)_2$D], the biologically active form of vitamin D (KMIEC'P and SWORCZAK, 2015).

Calcitriol plays a fundamental role in various physiological and metabolic activities in the human body. It stands out for its ability to modulate the immune system by binding to the vitamin D receptor (VDR). The active form of vitamin D regulates numerous signaling pa-

thways, such as cell proliferation and differentiation, apoptosis, inflammation, invasion and metastasis (BOZKURT et al., 2013). In addition, this metabolite influences the immunomodulation of the innate and adaptive immune systems, contributing to the maintenance of homeostasis. Due to these effects, vitamin D is considered an important immunomodulator, with suppressive, i.e. anti-inflammatory properties (BOZKURT et al., 2013).

The influence of calcitriol on the regulation of the immune system suggests an association between hypovitaminosis D and the development of autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroiditis (OJASWEE et al., 2022). From this perspective, maintaining adequate serum levels of vitamin D can be considered a potential therapeutic target, configuring a promising alternative for the prevention and treatment of these pathologies (ANTICO et al., 2012; BOZKURT et al., 2013).

METHODOLOGY

This systematic review of the literature, with a qualitative and descriptive approach, was drawn up through a bibliographic survey carried out in the *National Library of Medicine* (PubMed) and Virtual Health Library (VHL) databases. The search used the descriptors "vitamin D" and "thyroid diseases", extracted from the Health Sciences Descriptors (DeCS), combined with the Boolean operator "AND".

The review followed a systematic approach that included delimiting the topic, rigorously selecting the eligibility criteria, screening and evaluating the articles obtained and synthesizing the relevant information. Controlled clinical trials and observational studies published between 2019 and 2024 were included. Out-of-scope studies with no link to the association between thyroid diseases and vitamin D, as well as repeated or inaccessible studies, were excluded.

RESULTS

The bibliographic search identified 2,398 articles, of which 1,266 came from PubMed and 1,132 from the Virtual Health Library (VHL). After limiting the publication interval for the last 5 years (2019-2024), the numbers were reduced to 350 in PubMed and 293 in the VHL. Of the 643 articles, after selection by type of study, 25 remained in PubMed and 110 in the VHL, totaling 135. After analyzing the titles, 13 articles remained in PubMed and 16 in the VHL. Of the remaining 29, none were duplicated in the databases. Given their availability, 20 studies were selected for reading, 8 from PubMed and 12 from the VHL. After reading, it was observed that 9 studies presented an objective and detailed analysis of the relationship between blood levels of vitamin D and the recurrence of autoimmune diseases affecting the thyroid gland, as illustrated in Table 1.

DISCUSSION

Autoimmune diseases especially affect organs regulated by the presence of T cells, with the thyroid gland being one of the main targets (ANTONELLI et al., 2015). Typical examples of this T-lymphocyte-mediated autoimmunity include Hashimoto's thyroiditis and Graves' disease, in which the immune system targets and damages the thyroid gland itself. Although the exact mechanisms that trigger this immune response are not yet fully understood, there are strong indications that a complex interaction between genetic and environmental factors is at the root of this process (ANTONELLI et al., 2015). Among the environmental factors involved are exposure to radiation, inadequate iodine intake, smoking, high levels of stress and the use of certain drugs (ANTONELLI et al., 2015).

Initially, Th1 lymphocytes (T Helper 1) are directed towards the thyroid gland, which increases the secretion of pro-inflammatory cytokines such as IFN-γ and TNF-α

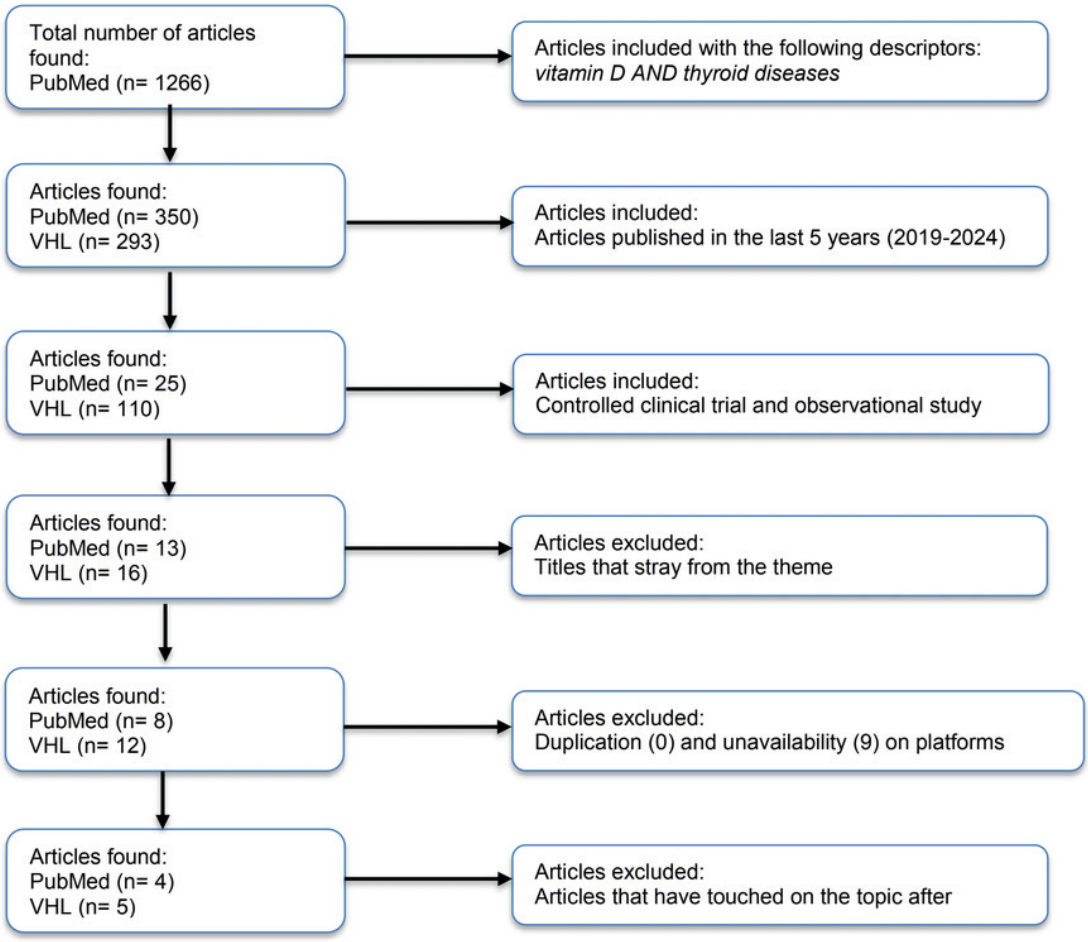

Table 1: Flowchart of the searches carried out on the PubMed and VHL research platforms.

(ANTONELLI et al., 2014). In response to the presence of these cytokines, thyroid cells produce and secrete the chemokine CXCL10, which is responsible for attracting other inflammatory cells to the thyroid tissue (LEE and SONG, 2009). The arrival of these additional cells contributes to the intensification of the autoimmune process, resulting in chronic inflammation that leads to the destruction of the gland and favors the development of autoimmune diseases such as Hashimoto's Thyroiditis and Graves' Disease (ANTONELLI et al., 2014).

Graves' disease (GD) is characterized by a chronic inflammatory cascade. In this condition, the immune system produces autoantibodies against the TSH receptor, a protein located on the surface of thyroid gland cells. TSH, or thyroid stimulating hormone, is produced by the pituitary gland, located in the brain, and its main function is to regulate the hormonal production of T3 (tri-iodothyronine) and T4 (tetra-iodothyronine) by the thyroid (WÉMEAU et al., 2018). The binding of autoantibodies to TSH receptors results in their excessive activation, leading to uncontrolled production of T3 and T4, which causes hyperthyroidism (WÉMEAU et al., 2018).

An important characteristic of hyperthyroidism is the low production of TSH by the pituitary gland. As T3 and T4 levels rise in the blood, the pituitary gland detects this rise and, through a negative feedback mechanism, reduces TSH secretion, understanding that it is no longer necessary to stimulate the thyroid gland to produce more hormones.

GD affects approximately six times more women than men, with most cases occurring between the ages of 30 and 50 (ZHOU et al., 2021). Treatment includes antithyroid drugs, which aim to reduce the exacerbated production of hormones. In addition, treatments with radioactive iodine - based on the emission of beta radiation, which destroys overactive thyroid tissue cells - or surgical removal of the gland can be considered (WÉMEAU et al., 2018).

On the other hand, Hashimoto's thyroiditis (HT) is also characterized by chronic inflammatory damage to the thyroid gland, but with different consequences. In HT, the immune system attacks the gland in such a way as to impair its ability to produce hormones. In this case, TSH receptors are blocked, preventing the thyroid from responding normally to hormonal stimulation. As a result, the pituitary gland increases the production of TSH in an attempt to stimulate the gland, but due to the blockage of the receptors, the production of T3 and T4 remains insufficient. Hashimoto's thyroiditis predominantly affects women and has a particularly high risk in middle-aged women (LUO et al., 2024). In addition, individuals with this condition have an increased risk of developing cardiovascular disorders (CHEN et al., 2015).

As a treatment, hormone replacement therapy fits in as one of the main approaches to HT (LUO et al., 2024). This therapy involves the administration of synthetic hormones to replace the thyroid hormones that the gland is not producing properly. In addition, studies suggest that selenium and vitamin D supplementation may also work as beneficial therapeutic modalities (BHAKAT et al., 2023; REZA CHAHARDOLI et al., 2024). People with HT have reduced serum vitamin D levels compared to healthy individuals, which reinforces the need for this supplementation (CVEK et al., 2021; LUO et al., 2024).

This metabolite plays a significant immunomodulatory role, influencing both innate and adaptive immune responses, which reinforces its importance in maintaining the homeostasis of the immune system and controlling inflammatory processes (BOZKURT et al., 2013). When vitamin D levels are low, immune self-tolerance may fail, favoring the development of autoimmune diseases (OJASWEE et al., 2022). In this context, inadequate vitamin D levels have been studied as a risk factor for these pathologies, such as Graves' disease and Hashimoto's thyroiditis (KOEHLER et al., 2019; CVEK et al., 2021; GALLO et al., 2022; OJASWEE et al., 2022). Thus, the supplementation of vitamin D emerges as a promising research strategy, both preventive and therapeutic, aimed at minimizing the impact of these autoimmune conditions (ANTICO et al., 2012; BOZKURT et al., 2013).

Vitamin D activates its immunomodulatory function by binding to its specific nuclear receptor, called the VDR (SHIN et al., 2014). This interaction induces conformational changes in the receptor, allowing it to connect with the retinoid X nuclear receptor (RXR), which is distributed in different cell types. This molecular partnership is essential for regulating gene expression, since RXR plays a central role in this process. The VDR-RXR complex formed travels to the cell nucleus, where it recognizes and interacts with specific DNA sequences called Vitamin D Response Elements (VDREs). This process modulates the transcription of target genes, promoting or suppressing their expression as necessary (SHIN et al., 2014; SZULC et al., 2023).

The VDR is present in various cells in the human body, especially in the cells of the immune system. This wide distribution allows vitamin D to act in fundamental processes such as proliferation, cell differentiation and regulation of the immune response, modulating immune activity in an integral

way (SZULC et al., 2023). Among the immune cells that express the VDR are activated T lymphocytes, B lymphocytes and antigen-presenting cells (APCs), including macrophages and dendritic cells, which are directly influenced by the action of this receptor and the immunomodulatory effects of vitamin D (KOEHLER et al., 2019; SZULC et al., 2023).

The binding of $1,25(OH)_2D$ to the VDR plays a crucial role in regulating immune activity, promoting anti-inflammatory effects that encompass cells of the innate and adaptive immune systems (SAFARI et al., 2023). In the innate system, macrophages and dendritic cells acquire a more tolerogenic profile (SHIN et al., 2014), characterized by a reduction in the expression of MHC II and co-stimulatory molecules such as CD40, CD80 and CD86. This modulation decreases the ability of these cells to present antigens to T cells, helping to attenuate autoreactive immune responses (KOEHLER et al., 2019; SZULC et al., 2023).

The macrophages, in turn, are directed towards the M2 phenotype, which is associated with anti-inflammatory properties. This phenomenon leads to a reduction in the production of pro-inflammatory cytokines, such as IL-6, IL-12 and TNF-α, and an increase in the production of IL-10, a cytokine with recognized anti-inflammatory properties. As a consequence of this increase, there is a modulation of the inflammatory profile of T helper cells, favouring an anti-inflammatory profile characterized by the induction of regulatory T cells (Tregs) (KOEHLER et al., 2019; SZULC et al., 2023).

In addition, vitamin D enhances the phagocytic power and microbicidal activity of macrophages, while suppressing the presentation of antigens, as also occurs in dendritic cells. This process leads to a decrease in the production of IL-1 and IFN-γ - pro-inflammatory cytokines - while increasing serum levels of transforming growth factor β (TGF-β), further reinforcing the anti-inflammatory effects and promoting the regulation of the immune system (SHIN et al., 2014). These changes are fundamental in immune regulation, contributing to the maintenance of immune tolerance and the prevention of autoimmune conditions, especially those involving the thyroid gland.

This vitamin plays an essential role in modulating TCD4 cells by suppressing their differentiation into the Th1 subtype, which is responsible for producing pro-inflammatory cytokines such as IL-2 and IFN-γ, which stimulate the activation of macrophages and other immune system cells to fight pathogens (SHIN et al., 2014). Simultaneously, calcitriol favors differentiation to the Th2 subtype, which secretes cytokines such as IL-4, IL-5 and Treg, which secretes IL-10 (KOEHLER et al., 2019). These cytokines attenuate inflammation mediated by Th1 cells, promoting a more anti-inflammatory immune environment and increasing immunotolerance, which is essential for preventing autoimmune responses (KOEHLER et al., 2019).

Vitamin D reduces the differentiation of TCD4 cells into Th17, a pro-inflammatory subtype, and favors differentiation into regulatory T cells (Tregs) (SHIN et al., 2014). Tregs produce IL-10, which helps maintain the balance of the immune response by controlling the activation and differentiation of other T cells. In this way, the effects of calcitriol help prevent the exacerbation of inflammatory responses, creating a more favorable environment for immunotolerance and hindering the development or progression of autoimmune conditions (SZULC et al., 2023).

The metabolite in question also exerts its homeostatic action on B cells, limiting their proliferation and inhibiting their differentiation into plasma cells, which results in lower antibody production (SZULC et al., 2023). This regulation is particularly beneficial in

controlling diseases autoimmune diseases, since excessive production of antibodies, such as IgG and IgM, can lead to attacks on the body's own tissues, aggravating autoimmunity. In addition, calcitriol promotes the apoptosis of activated B lymphocytes, contributing to the prevention of exacerbated immune responses and reducing the risk of developing autoimmune pathologies (SHIN et al., 2014; SZULC et al., 2023).

Given the immunomodulatory and anti-inflammatory potential of calcitriol, its supplementation has been widely investigated as a possible approach to the prevention and treatment of autoimmune thyroid diseases (GALLO et al., 2022; BHAKAT et al., 2023; REZA CHAHARDOLI et al., 2024). Studies suggest that vitamin D supplementation reduces autoantibody levels, however, the difficulty in adequate serum vitamin D replacement represents a significant barrier to advancing research into prevention and treatment, and more randomized studies are needed to confirm the efficacy of supplementation (KOEHLER et al., 2019).

Considering this event, one of the difficulties in administering vitamin D is the variation in recommended dosages. For example, studies show that a supplementation of 400 IU/day, considered the maximum in various studies, results in an increase of only 10 nmol/L in serum calcitriol levels. This modest increase may not be enough to achieve the expected beneficial effects, such as a reduction in autoantibodies in autoimmune thyroid diseases or significant improvements in general health (ANTICO et al., 201).

Furthermore, polymorphisms in the VDR gene represent another significant barrier to the efficacy of vitamin D supplementation. Genetic variants such as rs1544410, rs7975232, rs731236 and rs2228570 can alter the immune response and influence the onset of autoimmune thyroid diseases (ZHOU et al., 2021). These variants can alter the structure of the VDR, impacting the efficacy of supplementation and suggesting that vitamin D replacement may not have the same effects in all individuals (SHIN et al., 2014; GLONTI et al., 2023). These factors highlight the need for further randomized studies to ensure that serum replacement of this metabolite is effective in both the prevention and treatment of autoimmune thyroid diseases (KOEHLER et al., 2019).

CONCLUSION

Graves' disease (GD) and Hashimoto's thyroiditis (HT) are autoimmune disorders characterized by an unregulated immune response, in which the immune system attacks the cells of the thyroid gland. This process is triggered by chronic inflammation, mediated by both the innate and adaptive immune systems, resulting in thyroid dysfunction and hormonal changes, such as hyperthyroidism or hypothyroidism. Vitamin D, with its anti-inflammatory and immunomodulatory properties, has been studied as a possible preventative and therapeutic agent for these autoimmune conditions. However, although some studies indicate potential benefits, the efficacy of vitamin D supplementation is still a matter of debate, especially with regard to the ideal dosage and the most appropriate time for its administration - whether before or during the development of the disease. Further research is needed to clarify its role in the prevention and treatment of autoimmune diseases of the thyroid gland.

REFERENCES

ANTICO, A. *et al*. **Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature**. Autoimmunity Reviews, v. 12, n. 2, p. 127–136, 2012.

ANTONELLI, Alessandro *et al*. **Autoimmune thyroid disorders**. Autoimmunity Reviews, v. 14, n. 2, p. 174-180, 2015.

ANTONELLI, Alessandro *et al*. **Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases**. Autoimmunity Reviews, v. 13, n. 3, p. 272-280, 2014.

BHAKAT, Biva *et al*. **A Prospective Study to Evaluate the Possible Role of Cholecalciferol Supplementation on Autoimmunity in Hashimoto's Thyroiditis**. The Journal of the Association of Physicians of India, v. 71, n. 1, p. 1, 2023.

BIKLE, D. **Nonclassic Actions of Vitamin D**. The Journal of Clinical Endocrinology & Metabolism, v. 94, n. 1, p. 26–34, 2009.

BOZKURT, N. *et al*. **The Association Between Severity of Vitamin D Deficiency and Hashimoto's Thyroiditis**. Endocrine Practice, v. 19, n. 3, p. 479–484, 2013.

CHEN, Wei-Hung *et al*. **Hashimoto's Thyroiditis, Risk of Coronary Heart Disease, and l-Thyroxine Treatment: A Nationwide Cohort Study**. The Journal of Clinical Endocrinology & Metabolism, v. 100, n. 1, p. 109-114, 2015.

GALLO, Daniela *et al*. **Add-On Effect of Selenium and Vitamin D Combined Supplementation in Early Control of Graves' Disease Hyperthyroidism During Methimazole Treatment**. Frontiers in Endocrinology, v. 13, p. 886451–886459, 2022.

GLONTI, S. *et al*. **THE STUDY OF VDR FOKI RS2228570 SNP IN AUTOIMMUNE THYROIDITIS**. Georgian Medical News, v. 337, p. 99–103, 2023.

KMIEĆ, P.; SWORCZAK, K. **Vitamin D in Thyroid Disorders**. Experimental and Clinical Endocrinology & Diabetes, v. 123, n. 07, p. 386–393, 2015.

KOEHLER, V. F.; FILMANN, N.; MANN, W. A. **Vitamin D Status and Thyroid Autoantibodies in Autoimmune Thyroiditis**. Hormone and Metabolic Research, v. 51, n. 12, p. 792–797, 2019.

LEE, Eun Young; SONG, Yeong Wook. **CXCL10 and autoimmune diseases**. Autoimmunity Reviews, v. 8, n. 5, p. 379-383, 2009.

LUO, Jinli *et al*. **Clinical comparative efficacy and therapeutic strategies for the Hashimoto's thyroiditis: A systematic review and network meta-analysis**. Heliyon, v. 10, n. 16, p. e35114-e35137, 2024.

MEI, Xi *et al*. **Prevalence of hyperthyroidism with hypercalcemia in Xindu district and the efficacy of vitamin D3 treatment in these patients: a randomized trial.** ANNALS OF PALLIATIVE MEDICINE, v. 10, n. 9, p. 9640–9649, 2021.

OJASWEE SHERCHAND *et al*. **Autoimmune Thyroid Disease in Patients with Hypovitaminosis D in Department of Biochemistry of a Tertiary Care Centre: A Descriptive Cross-sectional Study**. Journal of Nepal Medical Association, v. 60, n. 251, p. 600–603, 2022.

REZA CHAHARDOLI *et al*. **Alterations in CD4+ T Cell Cytokines Profile in Female Patients with Hashimoto's Thyroiditis Following Vitamin D Supplementation: A Double-blind, Randomized Clinical Trial**. Endocrine Metabolic & Immune Disorders - Drug Targets, v. 24, n. 12, p. 1454–1463, 2024.

SAFARI, Sara *et al*. **Effects of vitamin D supplementation on metabolic parameters, serum irisin and obesity values in women with subclinical hypothyroidism: a double-blind randomized controlled trial**. Frontiers in Endocrinology, v. 14, p. 1306470–1306479, 2023.

SZULC, M. *et al*. **Vitamin D3 Metabolism and Its Role in Temporomandibular Joint Osteoarthritis and Autoimmune Thyroid Diseases**. International Journal of Molecular Sciences, v. 24, n. 4, p. 4080–4100, 2023.

WÉMEAU, Jean-Louis *et al*. **Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors**. Annales d'Endocrinologie, v. 79, n. 6, p. 599-607, 2018.

ZHOU, F. *et al*. **The VDR gene confers a genetic predisposition to Graves' disease and Graves' ophthalmopathy in the Southwest Chinese Han population**. Gene, v. 793-798, n. 15, p. 145750-145755, 2021.