



Immunopathological aspects of hashimoto's thyroiditis

Aspectos imunopatológicos da tireoidite de hashimoto

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ABSTRACT

Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is an autoimmune disease whose main characteristic is inflammation of the thyroid gland, and is the result of an error in the immune system. In this disease, the body produces antibodies against thyroid cells that cause the destruction or loss of function of the gland. This study aims to carry out an integrative review to describe the current state of knowledge about the immunopathological process involved in Hashimoto's Thyroiditis (HT), so that the research focused on understanding the immune response triggered in HT. It also aims to clarify its pathophysiology and its importance in understanding the body's exacerbated response to this autoimmune disease. This is a bibliographic review using indexed articles available in full for free, published between 2019 and 2023 in the U.S. National Library of Medicine (NLM), Google Scholar and the Scientific Electronic Library Online (SCIELO).

Keywords: Thyroid, Immune system, Autoimmune disease.



1 INTRODUCTION

The imbalance in the immune system resulting in an autoimmune attack on the thyroid gland is what we call autoimmune thyroid disease (AIDT), making it the most common group of autoimmune diseases (BOUTZIOS et al., 2022). Among this group, Hashimoto's thyroiditis stands out, which according to Ihnatowicz et al. (2021), consists of a lymphocytic infiltration with high levels of thyroid autoantibodies, such as thyroid peroxidase antibody (TPOAb), which is the enzyme responsible for catalyzing the production of thyroid hormone, and thyroglobulin antibody (TgAb), which is the protein that thyroid hormones are synthesized by iodination of their tyrosine residues. In this way, there is a reduction in the production of thyroid hormones, causing hypothyroidism, with clinical manifestations including fatigue, weight gain, constipation, dry skin, depression, muscle pain and increased sensitivity to cold (CHIOVATO et al., 2019).

Hashimoto's thyroiditis has an incidence of 0.3 to 1.5 cases per 1,000 people, with a higher risk of affecting women than men. The frequency among Caucasians is higher than among blacks, and its incidence increases with age (RAGUZA et al., 2019). In addition, according to the study by Qiu et al. (2021), the etiology of HT is multifactorial, being attributed to genetic, environmental and nutritional factors, but its pathogenesis is not fully understood.

In this context, due to its high incidence and the various theories and arguments that exist aimed at understanding the mechanism of origin and development of the destruction of the gland, more studies are needed to accurately understand the immunological mechanisms that trigger this condition, since despite the varied research carried out in recent years, the results are still questionable and remain incomplete. Therefore, the aim of this review is to describe the current state of knowledge about the immunopathological process involved in Hashimoto's thyroiditis and its perspectives, through scientific publications, as well as encouraging researchers to continue investigating and deepening their studies in order to accurately understand its role (BOGUSLAWKA et al., 2022).

2 METHODOLOGY

This study is a literature review using indexed articles published between 2019 and 2023 in the U.S. National Library of Medicine (NLM), Google Scholar and the Scientific Electronic Library Online (SCIELO). Articles with the full text available in English were included. To search the platforms, the descriptors used were: Hashimoto's Thyroiditis Autoimmunity; Hashimoto Thyroiditis Autoimmune Antibodies; Hashimoto Thyroiditis pd1 pdl1. In the BDTD, the "All Fields" option was selected among the descriptors in the "Advanced Search", with the "No



preference" illustration filter. In the Google Scholar search database, the "Advanced Search" option was selected, and the criterion was the presence of all the descriptors in the "Anywhere in the Article" field. In PUBMED, in advanced mode, the articles were selected using the "AND" filter between the descriptors. In SCIELO, the papers were also incorporated using the descriptors separated by the "AND" filter in the "Advanced Search" mode. After this first selection, a total of 3,796 academic papers were found, so a more specific assessment was carried out using the title of each bibliographic material as a parameter, selecting those that correlated with the keywords or with the theme of thyroiditis. This left 46 articles for analysis of the abstract, with 30 remaining for full reading. Finally, the selection criteria were scientific papers with content consistent with the aim of the research, of which 19 were included in this article.

3 RESULTS AND DISCUSSION

An analysis of the articles selected for this study revealed that the immune response triggered by Hashimoto's thyroiditis (HT) is still partially unclear. However, there is no doubt about its complexity and multifactoriality, in which genetic factors contribute around 70 to 80% of the pathogenicity and environmental factors around 20 to 30% (VILAR, 2021). Therefore, it is important to note that according to Dias et al. (2022) thyroid cells can be attacked by the mistaken cellular and humoral adaptive immune response.

In HT, exacerbated activation of CD4 T lymphocytes can trigger an exaggerated immune response inducing lymphocyte infiltration in the thyroid and increasing serum concentrations of anti-thyroperoxidase antibody (Anti-TPO) and anti-thyroglobulin antibody (RALLI et al., 2020). According to Zhang et al. (2022), three types of thyroid cells facilitate the passage of lymphocytes from the blood tissue to the thyroid: ACR1+ endothelial cells, CCL21+ myofibroblasts and CCL21+ fibroblasts. In addition, antigen-presenting cells, such as macrophages and dendritic cells, express high levels of IL-1 β in thyroid tissue, contributing to its destruction.

Regulatory T cells (Tregs) exert immunosuppressive capacity to excessive immune responses, and the study by HU et al. (2019) suggests that reduced effectiveness of Treg cells and overexpression of Helios and PD-1 may contribute to the pathogenesis of Hashimoto's thyroiditis. The study then suggests that regulating Treg cells *in vivo* may prevent the progression of the disease. To this end, selenium supplementation in patients with levels below 120 mg/L may increase the capacity of the antioxidant effect and increase the activation of regulatory T cells *in vivo*, as well as reducing anti-TPO and anti-thyroglobulin levels (HU et al., 2021).

In addition to Treg cells, the immune system relies on several checkpoints (molecules) to limit tissue damage and maintain body homeostasis during immune responses, one of these checkpoints being the PD-1/PD-L1 pathway. Treatment with immunobiologicals of the PD-1/PD-L1 pathway is already used in cancer treatment, and experimental models show that it is a promising approach in the treatment of autoimmune thyroid diseases (ÁLVAREZ et al., 2019) (ÁLVAREZ et al., 2023).

As soon as TCD4 lymphocytes are sensitized and receive protein fragments from thyroid tissue, the formation of serum antibodies characteristic for the diagnosis of HT begins, mainly anti-thyroglobulin (TGAb), anti-thyroperoxidase (TPOAb) and TSH receptor antibodies (TRAB) (WALISZEWSKA-PROSÓŁ and EJMA, 2022). Bogusławska (2022) states that anti-thyroglobulin is the largest and most abundant autoantigen of the thyroid gland, and that in contrast, TRAB (antibody against TSH) is widely expressed in extra-thyroidal tissues and cells.

However, Waliszewska-Prosól and Ejma (2022) mention other immunoglobulins that are also present in HT, acting against: apical pendrin anion exchanger (anti-PDS) and basolateral sodium-iodide symporter (Na-I symporter, or NIS). A clinical study carried out to verify the diagnostic usefulness of evaluating the autoantibodies of these transmembrane proteins found a similar prevalence of anti-PDS in the patients studied as in the control patients (7.7% vs. 5.0%), which shows that it is not yet of diagnostic value. However, anti-NIS was more prevalent in the patients studied than in the control patients (7.7% x 1.8%), showing the potential relevance of this immunoglobulin in autoimmune thyroid diseases such as HT (ELEFTHERIADOU et al., 2020).

Serum antibody levels correlate with disease activity, acting cytotoxically to destroy thyroid tissue, and also include increased production of cytokines such as IFN- γ and TNF- α , which increase the function of CD4+ and CD8+ T cells (KALANTAR et al., 2019).

The main findings of this analysis point out that too much immune response can compromise regulatory T cells (Tregs), which are important for body homeostasis, which is also maintained by proteins such as PD-1/PD-L1, and immunobiological therapy is already applicable against cancer, and experimental samples indicate that this is a hopeful approach to treating autoimmune thyroid diseases (ZAKE, et al., 2019). However, the impairment of regulatory T cells weakens the body's defenses.

Considering the implications of Hashimoto's thyroiditis, the limitations of this study correspond mainly to the few references available on the immunopathological mechanisms of this pathology, which corroborate the importance of encouraging these studies in view of the growing promise of treating autoimmune diseases and cancers with immunobiologicals.



4 CONCLUSION

This study reveals that the etiology of Hashimoto's thyroiditis is not fully understood, although there is interaction between genetic elements, environmental factors and epigenetic influences. It is therefore extremely important to address the activation of CD4 and CD8 T lymphocytes, regulatory T cells, serum anti-thyroglobulin (TGAb) / anti-thyroperoxidase (TPOAb) antibodies, TSH receptor antibodies (TRAB), the PD-1/PD-L1 pathway and cytokines such as IFN- γ and TNF- α , which reveal the complex network of mechanisms operating at cellular level to restrict autoimmunity. In addition, there are other immunoglobulins that are acting by reversing the apical pendrin anion exchanger (anti-PDS) and the basolateral sodium-iodide symporter, in particular anti-NIS, which is present in autoimmune thyroid diseases.

Thus, various immunopathological mechanisms are used in autoimmune diseases, but the scientific community still lacks enlightening studies to fully clarify the pathogenesis of Hashimoto's thyroiditis. As a consequence, this interferes with the development and protocol of treatment with immunobiologicals in HT. In view of the above, we stress the importance of researchers prioritizing this issue, making a significant contribution to the treatment of this disease and promoting a better quality of life for patients.



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