

Pathogenic Mechanisms of Autoimmune Thyroid Disease

Gulnara Dashdamirova, Rana Rahimova, Samira Baghirova, Ulviya Azizova

Biochemistry Department, Azerbaijan Medical University, Baku, Azerbaijan

doi: 10.51505/ijmshr.2022.6203

URL: <http://dx.doi.org/10.51505/ijmshr.2022.6203>

Abstract

Autoimmune thyroid illnesses are a category of disorders characterized by aberrant lymphocyte activity directed against self-tissues and are mostly represented by Hashimoto's thyroiditis and Graves' disease, which affect about 2% to 3% of the population, with a female predominance. Autoimmune thyroid disease is the most prevalent thyroid illness in children; the most typical age of onset is puberty, although the disease can strike at any age, including children as young as one-year-old. Autoantibodies to pendrin, an iodide transporter found at the apical pole of thyroid follicular cells, have recently been discovered in the majority of Hashimoto's thyroiditis and Graves' disease patients. Excessive iodine administration has been linked to an increased prevalence of thyroiditis in humans, according to recent epidemiologic research. People in North America consumed more than three times the recommended daily iodine intake. Anti-thyroglobulin antibody, anti-thyroperoxidase antibody, serum thyroid-stimulating hormone, and exacerbation of lymphocytic infiltration in the thyroid were all higher in these persons, indicating that iodine overconsumption could cause hypothyroidism and exacerbate the autoimmune response. However, the exact mechanism by which high iodine consumption causes autoimmune thyroid disease is yet unknown.

Keywords: autoimmune thyroid diseases, Hashimoto's thyroiditis, Graves' disease, thyroid-stimulating hormone, interleukin, cytokine

1. Introduction

Autoimmune thyroid disease (AITD) is a type of autoimmune illness that affects only one organ. AITD has a complex aetiology, with interactions between genetic and environmental predisposing stimuli leading to immunological tolerance dysregulation. Graves disease (GD) and Hashimoto's thyroiditis (HT), the two most common clinical manifestations of AITD, are estimated to affect 5% of the population [1]. Despite advances in effective diagnostic and therapeutic methods, there are still unresolved issues in the treatment of AITD, such as difficulties in making treatment decisions for patients who have subtle changes in thyroid function and limitations in treating hyperthyroidism definitively without destroying or removing the thyroid gland. To better select the best management technique, it is necessary to understand the etiological background of AITD and examine the existing clinical data. We focus on recent developments in understanding AITD and the contentious clinical issues in this review.

For quite some time, it has been recognized that polymorphisms exist in the AITD-related genes. Polymorphisms in the thyroid-stimulating hormone receptor (TSHR) gene are one of these genes that contribute to GD risk [2]. A single-nucleotide polymorphism (SNP) in the TSHR gene

linked to central tolerance was recently discovered. Homozygosity or heterozygosity for the receptor SNP rs179247 resulted in considerably lower extrathymic expression of TSHR mRNA transcripts, which could explain the lower central tolerance and increased risk of GD [3]. The discovery of the autoimmune regulator (AIRE) gene as a vulnerable locus for autoimmune Poly endocrinopathy-candidiasis-ectodermal dystrophy (APECED) in central tolerance opened up a new insight into how self-tolerance is maintained [2].

2. Autoimmune Thyroid disease

AIRE is a transcription factor that regulates the production of several proteins in medullary thymic cells; mutations in the AIRE gene cause central immunological tolerance dysregulation and multi-organ autoimmune disorders. Although a mutation in the APECED gene does not cause AITD, APECED patients in specific areas had a high rate of thyroglobulin antibodies, and a unique AIRE mutation (G228W) in a family with APECED was strongly associated with autoimmune thyroiditis. [2]. The progression of AITD is controlled by genes that regulate the immune response. The primary actors in AITD have been identified as cytotoxic T lymphocyte-associated factor 4 (CTLA4), CD40, CD25 (FoxP3), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), and cytokine regulating genes, in addition to MHC class I and II genes [4]. The non-human leukocyte antigen (NHLA) gene CTLA4 was the first to be linked to GD. An elevated risk of HT in East Asians and GD in the Chinese population was discovered in a recent meta-analysis of the A49G SNP in CTLA4 [5]. Although a meta-analysis of the C1858T polymorphism demonstrated a link with GD [6] previous studies on PTPN22 produced mixed results. CD40 is a tumor necrosis factor (TNF) superfamily immune regulatory gene that is expressed on thyroid follicular cells; the CD40 C/T1 polymorphism has been linked to GD [7]. In 202 HT patients, a recent large-scale study discovered an association with an interleukin 1 (IL-1) receptor antagonist variable number of tandem repeats IL-1 receptor antagonist gene (IL-1 RN) the variable number of tandem repeats (VNTR) polymorphism [8], and another study discovered an association between the rs763780 polymorphism in IL17F and HT in Chinese patients [9]. The signal transducer and activator of transcription (STAT) family protein, which is a transcription factor that regulates immune-regulatory pathways and cytokine signaling, has been linked to both HT and GD [10].

The pathogenesis of Autoimmune Thyroid disease is given as follows (Figure1).

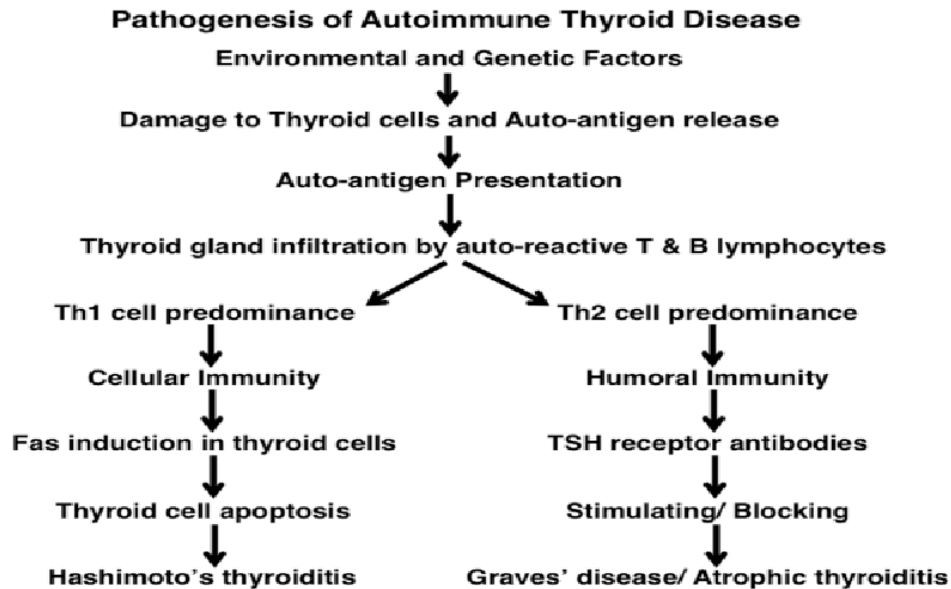


Figure 1. The pathogenesis of Autoimmune Thyroid disease

3. Selenoprotein

Selenoprotein (SEP) is involved in the deiodination of thyroid hormone, and a recent study identified a substantial relationship with an SNP in the promoter of the SEP S gene (SEPS1) in individuals with HT [11]. It's unclear whether dietary selenium plays a role in the development of AITD. Previous research suggested that a lack of selenium could worsen HT; however, a recent meta-analysis demonstrated that selenium supplementation had no beneficial effect on HT [2]. The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST), which is continuing, may shed more light on the function of selenium in AITD pathophysiology [12].

Although it is unclear how these genetic factors contribute to immunological dysregulation, we anticipate that this knowledge will be tremendously useful in the development of personalized and tailored AITD therapy methods. Selenium and vitamin D have been identified as the most important dietary components in recent investigations on the environmental causes of AITD. Low vitamin D levels are linked to the severity of AITD as well as being an etiological factor. Vitamin D deficiency was found to be more common in patients with GD in a recent meta-analysis [13]. Although the role of vitamin D in AITD is still being explored, it has not been determined whether vitamin D supplementation has any beneficial impact on the onset and pathogenesis of GD[14]. Several anticancer medications (cytokines, interferon, and tyrosine kinase inhibitors) have been shown to cause thyroid dysfunction [15]. After years of discussion, it has been demonstrated that moderate alcohol use protects against AITD, however, the particular mechanism is unknown [15], and the effect of smoking is still being explored. Rapid industrialization and environmental pollutants are also thought to be contributing contributors to

AITD. Individuals who live near petrochemical complexes have a higher risk of HT, according to one study [16].

Women in Siberia had a significant incidence of thyroid peroxidase (TPO) antibodies [2], indicating that climate has an impact on autoimmune. As a result, global warming and fast weather fluctuations may lead to an increase in the occurrence of autoimmune illnesses. Dysregulation of the immune system leads to an immunological attack on the thyroid, which is caused by genetic predisposition factors and environmental triggers. Intrathyroidal infiltration of T and B lymphocytes is a common observation in AITD, and these cells play an important role in the disease's pathophysiology. In the field of cellular immunity, regulatory T cells (Tregs) and follicular helper T (Tfh) cells have recently gained attention for their roles in the pathogenesis of AITD.

4. Regulatory T cells

Tregs make up 5% to 10% of CD4+ cells and express immunological responses either directly or indirectly through cytokines like transforming growth factor (TGF- α) and interleukin-10 (IL-10). Patients with AITD have been found to have altered Treg activity [17]. The cells produce IL-21, which acts as a promoter in antigen-specific B lymphocytes. Increased Tfh cell numbers in the peripheral blood have been linked to thyroid-specific antibody levels in HT patients [18]. The activation of Tfh cells and defects in Tregs is widely considered as the beginning events in AITD. A subset of Th3, which primarily synthesizes TGF- α , and Th17 cytokines such as IL-17 and IL-22 have been identified as additional participants in AITD in the case of cytokines. These cytokines have an important role in chronic inflammation, notably in HT [2]. Because IL-22 levels in HT correlate with TPO antibody levels, it has been postulated that IL-22 plays a role in antibody formation [19].

5. Graves' disease

Graves' disease (GD) and Hashimoto thyroiditis (HT) are autoimmune thyroid disorders (AITDs), which are defined by a breakdown of self-tolerance to thyroid antigens, resulting in antibody circulation and lymphocyte infiltration [20]. The prevalence of Hashimoto's illness is increasing, and it is now believed to be between 5 and 10% [20, 21]. It is diagnosed five to ten times more frequently in women than in men, and its incidence rises with age (the maximum number of cases are seen between 45 and 65) [21]. Although puberty is the most typical age of presentation in the pediatric population, HT can occur at any time, including in infants [20, 22]. In the case of GD, meta-analyses of various research have estimated that the disease affects roughly 1% of the population [20]. Graves' disease, on the other hand, is four to five times more common in women than it is in men [23].

HT is mostly caused by cell-mediated autoimmune disease, whereas GD is caused by humoral autoimmunity [24, 25]. In AITD, however, humoral and cellular immune processes are strongly coupled and crosslinked, as they are in other autoimmune illnesses [26]. Furthermore, the thyroid cell participates in the intrathyroidal immunological process in both disorders. HT was once thought to be a Th1-mediated illness, but this classification has changed as other Th cell subsets, such as Th17 cells, have been discovered [20]. Uncontrolled Th17 cell responses have been

implicated in several forms of autoimmune disorders, which were previously thought to be Th1-dependent diseases, according to recent research findings [27].

As a result of this, persistent inflammatory cells infiltrate the thyroid gland in HT, primarily thyroid-specific B and T lymphocytes. As a result, the goiter may be the original cause [20]. When sufficient numbers of follicular cells responsible for the generation and secretion of thyroid hormones thyroxine (T4) and triiodothyronine (T3) are killed, hypothyroidism, the hallmark of thyroiditis, can develop [28]. Thyroglobulin (Tg), thyroid peroxidase (TPO), sodium-iodide symporter (NIS), and the thyrotropin receptor (TSH-R) are known to be targets of GD, B, and T lymphocyte-mediated autoimmunity [20].

6. Thyroid-associated Ophthalmopathy

The TSH-R, on the other hand, is the primary autoantigen of GD [20]. Thyroid hormone synthesis and secretion are chronically stimulated by circulating agonist autoantibodies against the TSH-R (TRAb), which bind to and activate the receptor, resulting in hyperthyroidism, thyroid hyperplasia, and thyroid cancer (causing a diffuse goiter) [29]. Furthermore, TRAb stimulates thyroid function dramatically in children and has prognostic importance, most likely as costimulatory molecules [30, 31]. Thyroid-associated ophthalmopathy is the most prevalent extrathyroidal symptom of GD, occurring in around 25% of patients [32, 33]. In addition, both humoral and cellular immune responses appear to be involved in its pathogenesis [33]. The majority of researchers believe AITDs are multifactorial diseases caused by a complex interplay of genetic, hormonal, and environmental factors that cause the development of inappropriate immune responses against the thyroid on multiple levels, as well as the initiation of a long-term autoimmune reaction. [20, 34, 35].

7. Conclusion

AITD covers a wide range of thyroid dysfunctions, from minor abnormalities to life-threatening degeneration. Recent research has mostly focused on reaching an agreement on general AITD guidelines, as well as determining the best treatments for each unique AITD problem. The concerns that are still being debated are subgroup identification of Hashimoto's disease, reconsideration of long-term low-dose antithyroid medication therapy in patients with Graves disease, and LT4+LT3 combination therapy in hypothyroid individuals. Further research into the pathophysiologic mechanisms as well as the genetic origins of AITD will aid in the development of specific and tailored AITD therapy techniques.

References:

- Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. (2015) *Autoimmune thyroid disorders*, *Autoimmun Rev*;14:174-80.
- Won Sang Yoo, Hyun Kyung Chung (2016) Recent Advances in Autoimmune Thyroid Diseases, *Endocrinol Metab*;31:379-385 <http://dx.doi.org/10.3803/EnM.2016.31.3.379>
pISSN 2093-596X · eISSN 2093-5978

- Colobran R, Armengol Mdel P, Faner R, Gartner M, Tykocinski LO, Lucas A, et al. (2011) *Association of an SNP with intrathymic transcription of TSHR and Graves' disease: a role for defective thymic tolerance*, Hum Mol Genet;20: 3415-23.
- Hasham A, Tomer Y. (2012) *Genetic and epigenetic mechanisms in thyroid autoimmunity*, Immunol Res;54:204-13.
- Ji R, Feng Y, Zhan WW. (2013) *Updated analysis of studies on the cytotoxic T-lymphocyte-associated antigen-4 gene A49G polymorphism and Hashimoto's thyroiditis risk*, Genet Mol Res;12:1421-30.
- Luo L, Cai B, Liu F, Hu X, Wang L. (2012) *Association of protein tyrosine phosphatase nonreceptor 22 (PTPN22) C1858T gene polymorphism with susceptibility to autoimmune thyroid diseases: a meta-analysis*. Endocr J;59:439-45.
- Li M, Sun H, Liu S, Yu J, Li Q, Liu P, et al. (2012), *CD40 C/T-1 polymorphism plays different roles in Graves' disease and Hashimoto's thyroiditis: a meta-analysis*, Endocr J;59:1041-50.
- Zaaber I, Mestiri S, Marmouch H, Mahjoub S, Abid N, Hassine M, et al. (2014) *Polymorphisms in TSHR and IL1RN genes and the risk and prognosis of Hashimoto's thyroiditis*. Autoimmunity;47:113-8.
- Yan N, Yu YL, Yang J, Qin Q, Zhu YF, Wang X, et al. (2012) *Association of interleukin-17A and -17F gene single-nucleotide polymorphisms with autoimmune thyroid diseases*. Autoimmunity;45:533-9.
- Xiao L, Muhali FS, Cai TT, Song RH, Hu R, Shi XH, et al. (2013) *Association of single-nucleotide polymorphisms in the STAT3 gene with autoimmune thyroid disease in Chinese individuals*. Funct Integr Genomics;13:455-61.
- Santos LR, Duraes C, Mendes A, Prazeres H, Alvelos MI, Moreira CS, et al. (2014) *A polymorphism in the promoter region of the selenoprotein S gene (SEPS1) contributes to Hashimoto's thyroiditis susceptibility*. J Clin Endocrinol Metab;99:E719-23.
- Winther KH, Watt T, Bjorner JB, Cramon P, Feldt-Rasmussen U, Gluud C, et al. (2014) *The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST): study protocol for a randomized controlled trial*. Trials;15:115.
- Xu MY, Cao B, Yin J, Wang DF, Chen KL, Lu QB. (2015) *Vitamin D and Graves' disease: a meta-analysis update*. Nutrients;7:3813-27.
- D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. (2015) *Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases?* Autoimmun Rev;14:363-9.
- Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. (2012) *Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study*. Eur J Endocrinol;167:483-90.

- Arena S, Latina A, Baratta R, Burgio G, Gullo D, Benvenga S. (2015) *Chronic lymphocytic thyroiditis: could it be influenced by a petrochemical complex? Data from a cytological study in South-Eastern Sicily.* Eur J Endocrinol;172:383-9.
- Glick AB, Wodzinski A, Fu P, Levine AD, Wald DN. (2013) *Impairment of regulatory T-cell function in autoimmune thyroid disease.* Thyroid;23:871-8.
- Zhu C, Ma J, Liu Y, Tong J, Tian J, Chen J, et al. (2012) *Increased frequency of follicular helper T cells in patients with autoimmune thyroid disease.* J Clin Endocrinol Metab;7:943-50.
- Bai X, Sun J, Wang W, Shan Z, Zheng H, Li Y, et al. (2014) *Increased differentiation of Th22 cells in Hashimoto's thyroiditis.* Endocr J;61:1181-90.
- Marta Rydzewska, Michał Jaromin, Izabela Elżbieta Pasierowska, Karlina Stożek and Artur Bossowski (2018) *Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases,* Thyroid Research 11:2
- Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Rolinski J. (2015) *Immune disorders in Hashimoto's thyroiditis: what do we know so far?* J Immunol Res.; <https://doi.org/10.1155/2015/979167>.
- Brown RS. (2013) *Autoimmune thyroiditis in childhood.* J Clin Res Pediatr Endocrinol.;5 (Suppl 1):45–9.<https://doi.org/10.4274/jcrpe.855>.
- Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Laurberg P. (2011) *Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study.* Eur J Endocrinol.;164:801–9.
- Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. (2015) *Autoimmune thyroid disorders.* Autoimmun Rev.;14:174–80.
- Morshed SA, Latif R, Davies TF. (2012) *Delineating the autoimmune mechanisms in graves' disease.* Immunol Res;54:191–203.
- Ramos-Leví AM, Marazuela M. (2016) *Pathogenesis of thyroid auto-immune disease: the role of cellular mechanisms.* Endocrinol Nutr.;63:421–9.
- Bedoya SK, Lam B, Lau K, Larkin, J. (2013) *Th17 cells in immunity and autoimmunity.* Clin Dev Immunol., <https://doi.org/10.1155/2013/986789>.
- Caturegli P, De Remigis A, Rose NR. (2014) *Hashimoto thyroiditis: clinical and diagnostic criteria.* Autoimmun Rev.;13:391–7.
- Menconi F, Marcocci C, Marinò M. (2014) *Diagnosis and classification of graves' disease.* Autoimmun Rev.;13:398–402.
- Bossowski A, Stasiak-Barmuta A, Urban M. (2005) *Relationship between CTLA-4 and CD28 molecule expression on T lymphocytes and stimulating and blocking autoantibodies to the TSH-receptor in children with graves' disease.* Horm Res.;64:189–97. <https://doi.org/10.1159/000088875>.

- Bossowski A, Stasiak-Barmuta A, Urban M, Bossowska A. (2005) Analysis of costimulatory molecules OX40/4-1 BB (CD134/CD137) detection on chosen mononuclear cells in children and adolescents with graves' disease during methimazole therapy. *J Pediatr Endocrinol Metab.*;18:1365–72.
- Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. (2013) Prevalence and natural history of graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab.*;98:1443–9.
- Shan SJ, Douglas RS. (2014) The pathophysiology of thyroid eye disease. *J Neuroophthalmol.*;34:177–85.
- Duntas LH. (2008) Environmental factors and autoimmune thyroiditis. *Nat Clin Pract Endocrinol Metab.*;4:454–60.
- Marino M, Latrofa F, Menconi F, Chiovato L, Vitti P. (2015) Role of genetic and nongenetic factors in the etiology of graves' disease. *J Endocrinol Investig.*;38:283–94