

Modern View of Clinical and Immunological Aspects of Autoimmune Thyroiditis

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Received May 27, 2024; Revised September 10, 2024; Accepted October 12, 2024

Cite This Paper in the Following Citation Styles

(a): [1] Urunbaeva Muqaddas, "Modern View of Clinical and Immunological Aspects of Autoimmune Thyroiditis," *Universal Journal of Public Health*, Vol. 12, No. 6, pp. 1059 - 1069, 2024. DOI: 10.13189/ujph.2024.120604.

(b): Urunbaeva Muqaddas (2024). *Modern View of Clinical and Immunological Aspects of Autoimmune Thyroiditis*. *Universal Journal of Public Health*, 12(6), 1059 - 1069. DOI: 10.13189/ujph.2024.120604.

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Abstract The aim of this review is to examine the clinical and immunological aspects of AIT, emphasizing the need for further research to understand the specific clinical and immunological abnormalities in different forms of AIT. The paper covers studies from the last two decades, with a special focus on the clinical and immunological aspects of AIT. The review includes data from case-control studies, meta-analyses, and recent experimental studies, in particular those using advanced gene sequencing to identify susceptibility loci for GD and other forms of AIT. Inclusion criteria for the studies were based on their relevance to the clinical and immunological characteristics of AIT. Genetic studies have identified numerous susceptibility loci associated with GD, including genes involved in immune regulation and thyroid function, such as the HLA (Human Leukocyte Antigens) complex, CTLA-4 (англ. cytotoxic T-lymphocyte-associated protein 4; CD152), and PTPN22 (rs2476601 и rs2488457). Polymorphisms in the IL-2RA and FOXP3 (forkhead box P3 Homo sapiens (human)) genes, critical for T cell regulatory function, have been implicated in AIT. Epigenetic modifications and environmental factors, such as infections and stress, also contribute to the onset and progression of the disease. Despite significant advances, gaps remain in understanding the specific clinical and immunological abnormalities in the different forms of AIT. The mechanisms underlying the variability of autoantibody profiles and their impact on disease severity are not fully understood. The role of innate immune cells, such as mast cells and dendritic cells, in initiating and maintaining thyroid autoimmunity requires further investigation. These cells interact with adaptive immune cells to influence the immune response and clinical outcomes. The complexity

of the pathogenesis of AIT involves multifactorial interactions between genetic, environmental, and immunological factors. Identification of susceptibility loci has provided insights into the molecular mechanisms governing AIT. However, the clinical implications are still unclear. Understanding specific clinical and immunological abnormalities may lead to more precise diagnostic markers and targeted therapy.

Keywords Autoimmune Thyroiditis, Graves' Disease, Genetic Susceptibility, Immunopathogenesis, Autoantibodies, Clinical and Immunological Disorders

1. Introduction

Autoimmune diseases of the thyroid gland (AITD) occupy a leading place in the structure of endocrine pathology. The prevalence of autoimmune thyroiditis (AIT) and Graves' disease (GD) as the main AITDs reaches 2% of the total population, predominantly affecting women [1, 2]. That is why there remains constant interest in studying various aspects of the pathogenesis of this group of diseases.

Thyroid hyperfunction is detected in 2% of women; among men it occurs approximately 10 times less often. Hyperthyroidism in the age group 45–69 years was determined in 1.4%, without age differences [2]. The pathogenesis of AIT is based on the presence of genetic factors and exposure to environmental triggers, which leads to disruption of gene expression in specific immune cells [3]. A number of studies in recent years have revealed a relationship between TNF- α (Tumor necrosis factor alfa),

gene polymorphism and thyroid disease [4, 5]. Jung JH et al. [5] presented the results of a meta-analysis of 10 studies showing the relationship between IL-10 gene polymorphism and susceptibility to AIT.

The development of ideas about the pathogenesis of thyroid diseases in the 19th century and the first half of the 20th century was characterized by the emergence of theories, the significance of which still remains. In the “pre-immunological” period of studying AITH, a huge contribution to the understanding of the pathophysiological processes developing during thyrotoxicosis was made by the thyroid theory of K.A. Möbius, neurogenic theory of S.P. Botkin, later confirmed by I.P. Pavlov and his students, peripheral theories of G. Tsondek, I. Harvat, Blackburn and others [4].

In recent decades, more attention has been paid to theories about disturbances in the body’s regulation of the formation of a number of specific autoantibodies. These changes are considered as possible mechanisms for the development of HD [2-9]. It is assumed that these mutations give the lymphocyte clones autonomy, removing them from the control of the immunoregulatory system, and allow them to interact with organ-specific thyroid autoantigens.

Table 1 provides data on the prevalence of autoimmune thyroiditis (AIT) and Graves' disease (HD) in the population, and highlights gender differences and the influence of genetic predisposition.

Table 1. Prevalence of autoimmune thyroiditis and Graves' disease

Index	Meaning
AIT (all forms)	2-5% of the population
Women with AIT	2-5%
Men with AIT	0.2-0.5%
HD among patients with AIT	20-30%
Family predisposition	High

1. AIT (all forms) - 2-5% of the population

- **Explanation:** Autoimmune thyroiditis is a fairly common condition, affecting 2-5% of the population. This condition involves inflammation of the thyroid gland caused by the immune system and can lead to either hypothyroidism or hyperthyroidism.
- **Discussion:** This figure indicates that AIT is a relatively common disease among all forms of thyroid pathologies. Considering that this condition is associated with immune system disorders, it requires long-term monitoring and treatment.

2. Women with AIT - 2-5%

- **Explanation:** Women suffer from autoimmune thyroiditis with the same frequency as the general population - from 2 to 5%.
- **Discussion:** This confirms that women are much more likely to suffer from autoimmune diseases, including AIT, which is likely due to the hormonal and immunological characteristics of the female body. Gender differences in disease incidence may influence the choice of approaches to treatment and prevention.

3. Men with AIT - 0.2-0.5%

- **Explanation:** Men suffer from AIT much less frequently - only 0.2-0.5% of men are diagnosed with this disease.
- **Discussion:** This confirms that AIT is much less common in men than in women. The low incidence in men may lead to later diagnosis and treatment, as symptoms in men may be less frequent or less severe.

4. HD among patients with AIT - 20-30%

- **Explanation:** Graves' disease (HD), which causes hyperthyroidism, occurs in 20-30% of patients with autoimmune thyroiditis.
- **Discussion:** This high number indicates a link between the two diseases, as both are autoimmune disorders. It also highlights the importance of regular thyroid monitoring in patients with AIT, as they are at risk of developing HD.

5. Familial predisposition - High

- **Explanation:** Autoimmune diseases such as AIT and HD have a high familial predisposition, meaning that having one family member with these diseases increases the risk of other relatives developing them.
- **Discussion:** This suggests that genetics plays an important role in the development of autoimmune thyroid disease. Patients with a family history of AIT or HD should undergo regular screening for early diagnosis and treatment.

General conclusions

The data in the table show that autoimmune thyroid disease is a significant medical problem, especially for women. Family history plays an important role, so early diagnosis and genetic counseling can help in effective treatment.

Table 2 contains information on key genetic loci associated with autoimmune thyroiditis (AIT) and their role in the pathogenesis of the disease.

Table 2. Major genetic loci associated with autoimmune thyroiditis

Gene/Locus	Association with disease	Description
HLA complex	High	Regulation of the immune response
CTLA-4	Moderate	Inhibition of T cell activity
PTPN22	High	Regulation of T cell signaling
IL-2RA	High	Regulation of regulatory T cell activity
FOXP3	High	Regulation of regulatory T cell function

1. HLA complex (Major histocompatible antigen complex)

- **Relationship with disease:** High
- **Description:** The HLA complex plays a critical role in regulating the immune response. It includes various genes that encode proteins involved in the presentation of antigens to T cells. The presence of certain HLA alleles may increase the risk of developing autoimmune diseases, including AIT.
- **Discussion:** The high association with the disease suggests that genetic variations in the HLA complex play a key role in predisposing to autoimmune thyroiditis. This is because HLA molecules help the immune system recognize and respond to foreign antigens, and their abnormal functioning can contribute to the body mistakenly attacking its own tissues.

2. CTLA-4 (Cytotoxic T-lymphocyte antigen 4)

- **Relationship with disease:** Moderate
- **Description:** CTLA-4 is a molecule that inhibits the activity of T cells, regulating their function and preventing the immune system from becoming overactive. Mutations in this gene can disrupt this regulation, increasing the risk of autoimmune diseases.
- **Discussion:** Moderate association suggests that variations in CTLA-4 may contribute to the development of AIT, but not as critically as the HLA complex. Disruption of normal T-cell inhibition may lead to an uncontrolled immune response against thyroid tissue.

3. PTPN22 (Phosphatase and tyrosinase 22)

- **Relationship with disease:** High

- **Description:** PTPN22 encodes a phosphatase that is involved in the regulation of T-cell signaling pathways. Abnormalities in this gene may disrupt normal T-cell signaling behavior, which contributes to autoimmunity.
- **Discussion:** The high association indicates a significant impact of PTPN22 on the development of AIT. Alterations in this gene may lead to overactivation or underregulation of T cells, contributing to the development of the autoimmune process.

4. IL-2RA (Interleukin-2 receptor alpha)

- **Relationship with disease:** High
- **Description:** IL-2RA encodes one component of the interleukin-2 receptor, which is important for the activation and maintenance of regulatory T cells. Abnormalities in this gene can disrupt the normal functioning of regulatory T cells, leading to autoimmune reactions.
- **Discussion:** The high association with AIT highlights the importance of regulatory T cells in maintaining immune homeostasis. Defects in IL-2RA may contribute to underregulation of the immune response and promote autoimmune reactions.

5. FOXP3 (FORKHEAD BOX P3)

- **Relationship with disease:** High
- **Description:** FOXP3 is a transcription factor essential for the development and function of regulatory T cells. Its abnormalities may lead to dysregulation of the immune response, contributing to the development of autoimmune diseases.
- **Discussion:** The high association with the disease suggests that FOXP3 plays a critical role in maintaining immune tolerance. Mutations in this gene can impair the function of regulatory T cells, leading to the development of autoimmune thyroiditis.

General conclusions

Table 2 demonstrates that several key genetic loci play an important role in the development of autoimmune thyroiditis. These loci are associated with different aspects of immune response regulation, confirming the multifaceted genetic mechanisms that contribute to autoimmune diseases. Genetic factors such as variations in HLA, CTLA-4, PTPN22, IL-2RA, and FOXP3 may disrupt normal immune regulation and lead to autoimmune reactions against the thyroid gland.

Table 3. Clinical and immunological characteristics of various forms of autoimmune thyroiditis

Form of the disease	Basic antibodies	Clinical manifestations	Immunological features
Graves' disease (GD)	Antibodies to the TSH receptor	Hyperthyroidism, goiter, ophthalmopathy	Stimulation of thyrocyte growth and hormone synthesis
Hashimoto's thyroiditis (HT)	Antibodies to TPO and TG	Hypothyroidism, goiter	Cytotoxic effects on thyrocytes

Table 3 contains information on the clinical and immunological characteristics of various forms of autoimmune thyroiditis, such as Graves' disease and Hashimoto's thyroiditis.

1. Graves' disease (GD)

- **Main antibodies:** Antibodies to the TSH receptor (TSH antibodies receptor).
- **Clinical manifestations:**
 - **Hyperthyroidism:** Excess production of thyroid hormones leads to an accelerated metabolism and various symptoms such as weight loss, irritability and increased sweating.
 - **Goiter (goiter):** Enlargement of the thyroid gland.
 - **Ophthalmopathy:** Inflammation and swelling of the eye tissues, which can lead to exophthalmos (protruding eyeballs) and other ophthalmologic symptoms.
- **Immunological features:**
 - **Stimulation of thyrocyte growth and hormone synthesis:** Antibodies to the TSH receptor activate receptors on thyrocytes (thyroid cells), causing the thyroid gland to overproduce thyroid hormones and enlarge. This leads to hyperthyroidism and its associated symptoms.

2. Hashimoto's Thyroiditis (HT)

- **Main antibodies:** Antibodies to thyroid peroxidase (TPO) and thyroglobulin (TG).
- **Clinical manifestations:**
 - **Hypothyroidism:** Underproduction of thyroid hormones, resulting in symptoms such as fatigue, depression, weight gain and cold intolerance.
 - **Goiter (goiter):** An enlargement of the thyroid gland that may be caused by the

body's attempts to compensate for a lack of hormones by increasing the size of the gland.

- **Immunological features:**

- **Cytotoxic effect on thyrocytes:** Antibodies to TPO and TG attack thyroid cells, causing them to be destroyed and hormone production to decrease. This process causes inflammation and damage to the gland, which in turn leads to hypothyroidism.

Discussion

The table illustrates the key differences between Graves' disease and Hashimoto's thyroiditis in the context of their pathogenesis and clinical manifestations:

- **Graves' disease** is characterized by excessive production of thyroid hormones and immune stimulation of thyroid cell growth. This leads to hyperthyroidism and specific symptoms such as ophthalmopathy. TSH receptor antibodies play a central role in this process by activating receptors on thyrocytes.
- **Hashimoto's thyroiditis** is characterized by insufficient production of thyroid hormones due to the destruction of thyrocytes. Antibodies to TPO and TG lead to cytotoxic effects on the cells of the gland, which causes inflammation and decreased functionality of the thyroid gland, leading to hypothyroidism.

Conclusion

These differences in clinical manifestations and immunological characteristics help physicians to correctly diagnose and effectively treat various forms of autoimmune thyroiditis. Understanding the mechanisms of action of antibodies and their impact on thyroid function is key to choosing the appropriate therapeutic approach.

Table 4. The role of various cells and cytokines in the pathogenesis of autoimmune thyroiditis

Cell type/Cytokine	Role in pathogenesis	Notes
T helper cells (CD4+)	Initiation of an autoimmune response	Includes Th1, Th2, Th17 and Tfh subtypes
Regulatory T cells (Tregs)	Maintaining immunological tolerance	Defect in Tregs function is associated with AIT
Mast cells	Inflammatory activity	Have receptors for T3 and TSH
Cytokines (IL-2, IL-10)	Regulation of the immune response	Polymorphisms of these genes are associated with AIT

Table 4 describes the role of various cells and cytokines in the pathogenesis of autoimmune thyroiditis (AIT). It highlights how various elements of the immune system contribute to the development of this disease.

1. T-helper cells (CD4+)

- **Role in pathogenesis:** Initiation of an autoimmune response.
- **Notes:** T-helper cells (CD4+) include the Th1, Th2, Th17, and Tfh subtypes, each of which has different functions in regulating the immune response. These cells play a key role in activating other cells of the immune system and can contribute to the development of an autoimmune response if they are dysregulated.
 - **Th1:** Associated with inflammatory responses and may contribute to autoimmune processes.
 - **Th2:** Regulates responses to allergens and parasitic infections, but may also be involved in autoimmune reactions.
 - **Th17:** Important for maintaining inflammation and is associated with autoimmune diseases.
 - **Tfh:** Helps in the activation of B cells and the formation of antibodies.

2. Regulatory T cells (Tregs)

- **Role in pathogenesis:** Maintenance of immunological tolerance.
- **Notes:** Regulatory T cells help maintain a balance between activation and suppression of the immune response, preventing excessive reactions against one’s own tissues. Defects in Tregs function are associated with the development of autoimmune thyroiditis, as they cannot effectively control autoimmune processes.

3. Mast cells

- **Role in pathogenesis:** Inflammatory activity.
- **Notes:** Mast cells play a role in inflammation and allergic reactions. They have receptors for thyroxine (T3) and thyroid stimulating hormone

(TSH), which may contribute to their activation in the context of autoimmune thyroiditis. Mast cell activation may increase inflammation in thyroid tissue.

4. Cytokines (IL-2, IL-10)

- **Role in pathogenesis:** Regulation of the immune response.
- **Notes:** Cytokines IL-2 and IL-10 play a key role in the regulation of the immune response.
 - **IL-2:** Stimulates T-cell proliferation and maintains effector cell activity. Polymorphisms in genes encoding IL-2 may be associated with an increased risk of autoimmune diseases.
 - **IL-10:** It has anti-inflammatory effects and helps control inflammation. Polymorphisms in genes encoding IL-10 may also be associated with AIT.

Discussion

This table shows how different cells and molecules play a role in the development of autoimmune thyroiditis:

- T-helper cells and regulatory T cells: The balance between these cells is critical for maintaining immune tolerance. Disturbances in their function can contribute to the development of an autoimmune response.
- Mast cells: Their participation in inflammatory reactions and the presence of receptors for thyroid hormones can increase inflammation in the thyroid gland, contributing to the pathogenesis of the disease.
- Cytokines: They are important in regulating the immune response, and their genetic variations may increase the risk of developing autoimmune thyroiditis.

Conclusion

Understanding the role of these cells and molecules helps to uncover the mechanisms of development of autoimmune thyroiditis and may lead to the development of more targeted diagnostic and treatment methods.

Table 5. Genetic and environmental factors influencing the development of autoimmune thyroiditis

Factor	Type of influence	Description
Genetic polymorphisms	Interior	Include polymorphisms in the genes HLA, CTLA-4, PTPN22, IL-2RA, FOXP3
External triggers	External	Infections, stress, radiation
Epigenetic modifications	Internal External	DNA methylation, histone modifications

Table 5 describes the genetic and environmental factors that influence the development of autoimmune thyroiditis (AIT). These factors can be both intrinsic and extrinsic, and their interaction may contribute to the development of the disease.

1. Genetic polymorphisms

- **Type of influence:** Internal
- **Description:** Polymorphisms in certain genes can significantly increase the risk of developing autoimmune thyroiditis. The main genes mentioned in the table include:
 - **HLA:** A genetic complex involved in the regulation of the immune response.
 - **CTLA-4:** A gene encoding a protein that inhibits T cell activity.
 - **PTPN22:** A gene that regulates T cell signaling.
 - **IL-2RA:** A gene that regulates the activity of regulatory T cells.
 - **FOXP3:** A gene critical for regulatory T cell function.
- **Discussion:** Polymorphisms in these genes can disrupt normal regulation of the immune response and contribute to the development of autoimmune thyroiditis. Genetic predisposition plays a key role in the pathogenesis of the disease.

2. External triggers

- **Type of influence:** External
- **Description:** External factors can serve as triggers that initiate or aggravate autoimmune processes:
 - **Infections:** Viral or bacterial infections can initiate autoimmune reactions, disrupting the normal functioning of the immune system.
 - **Stress:** Physical or emotional stress can weaken the immune system or change its activity, contributing to the development of autoimmune diseases.

- **Radiation:** Exposure to ionizing radiation can damage tissues and alter their immunological environment, increasing the risk of autoimmune diseases.

- **Discussion:** These external factors may act as catalysts, accelerating the onset of the disease in people with a genetic predisposition. They may interact with internal factors to increase risk.

3. Epigenetic modifications

- **Type of influence:** Internal and external
- **Description:** Epigenetic modifications affect the expression of genes without changing their sequence. The main modifications include:
 - **DNA methylation:** The addition of methyl groups to DNA can alter gene activity, which affects the immune response and the development of autoimmune diseases.
 - **Histone modifications:** Changes in histone structure can alter DNA packaging and, consequently, its expression.
- **Discussion:** These modifications can be caused by both internal and external factors, and they may contribute to the development of autoimmune thyroiditis by affecting the regulation of genes associated with the immune response.

Conclusion

The table demonstrates that the development of autoimmune thyroiditis is caused by a complex interaction of various factors. Genetic polymorphisms create a predisposition to the disease, while environmental triggers can initiate its development. Epigenetic modifications represent an additional level of regulation that can link genetic and environmental factors, influencing gene expression and disease risk. Understanding these factors helps in developing strategies for the prevention and treatment of autoimmune thyroiditis.

Table 6. Modern methods of therapy for autoimmune thyroiditis and Graves' disease

Treatment method	Application	Advantages and disadvantages
Thyrostatic drugs	Treatment of hyperthyroidism in HD	Effective in controlling hormonal levels, possible side effects
Radioactive iodine	Treatment of hyperthyroidism in HD	High efficiency, hypothyroidism is possible after treatment
Thyroidectomy	Removal of the thyroid gland	Complete elimination of hyperthyroidism, risk of surgical complications
Hormone replacement therapy	Treatment of hypothyroidism with chemotherapy	Effective in compensating for hormonal deficiency, requires constant use

Table 6 describes current treatment options for autoimmune thyroiditis and Graves' disease, covering the various therapeutic approaches with their advantages and disadvantages.

1. Thyrostatic drugs

- **Application:** Treatment of hyperthyroidism in Graves' disease (GD).
- **Advantages:** Thyroid-blocking drugs are effective in controlling thyroid hormone levels by helping to reduce excessive production. They are often used in the early stages of hyperthyroidism treatment.
- **Flaws:** While these drugs can help stabilize the condition, they can cause side effects such as allergic reactions, liver dysfunction, and decreased white blood cell counts, making their use time-limited.

2. Radioactive iodine

- **Application:** Treatment of hyperthyroidism in Graves' disease.
- **Advantages:** Radioactive iodine effectively destroys thyroid cells, reducing its activity. This method is often preferred for patients who have not responded to other treatments.
- **Flaws:** After treatment, hypothyroidism may develop, since thyroid function may be completely suppressed, requiring further hormone replacement therapy.

3. Thyroidectomy

- **Application:** Complete removal of the thyroid gland.
- **Advantages:** The operation completely eliminates hyperthyroidism, since the gland that produces excess hormones is removed. This method is suitable for patients who have a

significantly enlarged gland or are at risk of cancer.

- **Flaws:** Like any surgery, thyroidectomy carries a risk of complications, such as damage to the vocal cords, parathyroid glands, and infection. After the surgery, patients require lifelong hormone replacement therapy.

4. Hormone replacement therapy

- **Application:** Treatment of hypothyroidism that occurs both in autoimmune thyroiditis and after treatment of hyperthyroidism (eg, with radioactive iodine or surgery).
- **Advantages:** Effectively compensates for the lack of thyroid hormones. Patients can maintain normal hormone levels by taking hormones in tablet form (most often levothyroxine) on a regular basis.
- **Flaws:** Ongoing treatment requires regular monitoring of hormone levels in the blood and adjustment of dosage. In addition, patients must take pills daily for life.

Discussion

All of the above methods have their own specific application depending on the form of the disease (hyperthyroidism or hypothyroidism), as well as the patient's condition. Thyrostatic drugs can be used in the early stages, while radioactive iodine or surgical intervention is used when radical measures are necessary. Hormone replacement therapy is inevitable in the case of hypothyroidism resulting from the treatment of hyperthyroidism or autoimmune thyroiditis.

These tables provide summary information on key aspects of autoimmune thyroiditis and Graves' disease, including epidemiology, genetic factors, clinical and immunological characteristics, the role of various cells and cytokines, and current therapies.

2. Materials and Methods

This study included a comprehensive review of the literature on the pathogenesis of AITD, including historical and contemporary perspectives. We reviewed primary scientific articles, meta-analyses, and recent experimental studies to provide a detailed synthesis of the genetic, epigenetic, and immunological factors involved in AITD. The role of autoantibodies and T cells in the development of AITD, as well as potential therapeutic approaches, has also been studied.

It is estimated that all possible associated genes, variants and polymorphisms are responsible for 75-80% of the heritability of CC. As a result, conclusions were drawn about the potential contribution of environmental and epigenetic factors to the pathogenesis of GC, including its initiation, development and progression.

Many analytical studies have summarized the contribution of genetic factors to the development of GC, but there are still some fundamental questions and concepts of the interaction of genetic, epigenetic and immunological factors that have not been discussed. Autoimmune thyroid diseases are complex multifactorial diseases based on the interaction of genetic and environmental factors. These diseases are characterized by different phenotypes, which are highly likely to occur in the same family. Some of the early research in this area involved direct study of patient records. To date, epidemiological rates and the contribution of genetic factors to familial clustering have been assessed in a number of populations, and extensive studies have been conducted in twin populations.

One of the main roles in the pathogenesis of AITD is assigned to autoantibodies (to thyroid peroxidase, to the TSH receptor of thyrocytes, to thyroglobulin). However, if in DTD the action of antibodies leads to stimulation of thyrocyte growth and hormone synthesis, then in AIT it leads to a direct cytotoxic effect in the presence of complement. In addition, the ability of thyrocytes to apoptosis is different in these two diseases. Consequently, despite a number of common mechanisms of etiopathogenesis of AIT and DTD, which allow them to be classified as a manifestation of type II hypersensitivity, the specificity of each of them is manifested by a different functional state of the thyroid gland and, accordingly, the level of thyroid hormones [2,4].

Despite the large number of hypotheses for the immunopathogenesis of AITD, it has been reliably established that the initial stage of the development of GD and AIT is the loss of tolerance to thyroid autoantigens, and the final stage is the development of autoantibodies to them [3, 5]. Autoantibodies stimulate or block thyroid function by binding to the TSH receptor (rTSH) and/or interacting with thyroid peroxidase (TPO), thyroglobulin (TG) [2-10]. Moreover, up to 75-80% of patients with HD have antibodies to TPO, less often - antibodies to TG, the increase of which is more typical for AIT [6,8]. In addition to classical autoantibodies to thyroid components, there is

a known classification of AIT according to the types of autoantibodies: IgG4-positive and IgG4-negative variants, which has important clinical and therapeutic significance, since it determines the possibility of binding specific autoantibodies to specific antigens and verifying the clinical phenotype of the disease using these markers [10]. The leading role of T cells in the pathogenesis of HD and AIT is associated with their participation in the responses of the immune system to viral and/or bacterial aggression, where, in addition to the main protective function, they act as initiators of cross-autoreactivity to thyroid autoantigens against the background of a genetically determined defect in the immunoregulatory system [1, 4, 5].

Studies in recent years have demonstrated the important role of Th17 cells (CD4 + IL 17 +), Tregs (CD4 + CD25 + high FoxP3 +), disturbances in the processes of apoptosis and their relationship with the development of hypo and hyperthyroidism [7]. Previously, it was believed that helper T cell clones, being antigen-specific and capable of recognizing the main thyroid autoantigens, are the main initiators of the development of AIT. When exposed to an external stimulus on the thyroid gland, thyrocytes provoke the expression of HLA class II molecules and their presentation of an organ-specific antigen directly to the T cells, which initiates the development of AIT [6, 8]. CD4 + T helper cells, in response to antigen-specific activation, produce large amounts of various cytokines and are defined as Th1, Th2, Th17 and Tfh cells based on the profiles of the cytokines they express [8]. It has also been shown that thyrocytes themselves can be a source of opposite cytokines and actively interact with intrathyroid T lymphocytes [9]. It is assumed that in AIT and GD, the use of anti-cytokine therapy based on the assessment of their serum and/or organ levels could most likely stop or complete the autoimmune inflammatory process.

In recent years, studies have increasingly appeared devoted to the study of the role of innate immune cells in the pathogenesis of AIT, where their influence on immunoregulatory processes and adaptive immunity is actively discussed [1]. The most intense debate is about the activation of intrathyroid mastocytes during the creation of exogenous thyrotoxicosis and acute gram-negative bacterial endotoxemia [8], which confirms their close relationship with thyroid hormones (TG) and the sympathoadrenal system [6,7]. It is known that mast cells, being highly specialized cells of the immune system, have receptors for T3 and TSH [5, 8]. Mast cells participate not only in the induction phase, but also in the effector phase of adaptive immunity [10]. The following can act as cofactors for mast cells: interleukin (IL) 3, IL10, IL4, IL33 [2, 9]. Mast cells, when activated, release through degranulation a certain profile of mediators and other factors: histamine, tryptases, chymases, carboxypeptidases A, proteoglycans, tumor necrosis factor α (TNF α), IL13, IL3, IL5, GM-CSF, GM-CSF, CXCL8/IL8, CCL3/MIP1 α , VEGFA, VEGFB, VEGFC and VEGFD, lipid mediators [1, 2, 7].

Of interest are the data obtained from the primary stimulation of mast cells with lipopolysaccharide complexes or bacterial endotoxins, which led to changes in thyroid status [2]. Exposure to a low-frequency electromagnetic field on the thyroid gland increased the number of intrathyroidal mastocytes and changed the amount of TG, leading to a decrease in both total T3 and total T4 [3]. However, it is still not known exactly which mechanism of mastocyte activation predominates in AITD. It has been shown that the number of mast cells in the group of experimental animals after thyroidectomy is significantly higher than in the control group 6 weeks after surgery [4]. These data have been confirmed in other studies [5], which may determine possible application points for AIT therapy in the future.

2.1. Prospects for AIT Therapy

Despite numerous studies and undoubted achievements in the field of experimental and clinical thyroidology, today there is no etiotropic treatment of AITD and no methods for reliable individual prediction of the results of pathogenetic therapy [6, 7]. This impressive gap between knowledge about the pathogenesis of diseases and the results of clinical practice is characteristic not only of AITD, but also of other pathologies. The need to reduce this distance is a reason to intensify research in the field of therapy.

Several methods are traditionally used to treat GD: therapy with thyreostatic drugs, treatment with radioactive iodine, and thyroidectomy. In case of AIT, during the period of manifestation of hypothyroidism, thyroid replacement therapy is used to adequately compensate for hormonal deficiency. Thus, the main goal of the therapeutic approach for AIT is to achieve and maintain a euthyroid state.

The division of patients with GD according to the adequacy of the response to traditional thionamide therapy into “complete and incomplete” shows that it poorly correlates with the final result of treatment [4, 7]. Therefore, in AIT, sensitive and specific markers are so necessary that would make it possible to more likely predict the clinical course of the disease and the development of relapses. At the same time, unified scientifically based approaches to solving this problem have not been formulated. Drug therapy, surgery and radioiodine therapy have their advantages and disadvantages, but not only the safety and effectiveness of traditional methods are relevant, but also the assessment of the results of their use in the long term, is associated with the risk of relapses and complications.

Recent studies on the role of neuropeptides in the regulation of the immune response are of interest [4, 6]. Data were obtained on the release of neuropeptides from the pituitary gland, adrenal glands, and thyroid gland into the blood under stressful conditions, as well as from the peripheral nervous system into innervated tissues, including lymphoid ones. In addition, it is known that

peptides are produced by cells of the APUD system, including lymphoid organs. The presence of specialized receptors, along with the ability of immunocompetent cells themselves to produce neuropeptides, creates the likelihood of their participation in intercellular cooperative processes. By analogy with the data on the influence of hormones and neurotransmitters on immunocytes, it can be assumed that neuropeptides act on them through specific receptors using cyclic nucleotides, which creates the possibility of targeted correction of these interactions.

Thus, further research into the mechanisms of immunopathogenesis of HD and AIT, understanding the role and place of interaction between innate and adaptive immune cells, immunoregulation, and molecules of intersystem signaling in the development of these diseases opens up prospects for the implementation of a modern strategy for their targeted therapy.

3. Detailed Discussion

Genetic factors in AIT: Genetic predisposition plays a decisive role in the development of AITD. Studies have identified various gene polymorphisms associated with an increased risk of AITD. TNF- α gene polymorphism is one such genetic factor associated with thyroid diseases. TNF- α , a proinflammatory cytokine, is involved in the inflammatory response and has been shown to play a role in the pathogenesis of AITD. IL-10 gene polymorphisms are also associated with AITD susceptibility. IL-10 is an anti-inflammatory cytokine that helps regulate the immune response. The relationship between these gene polymorphisms and AITD suggests that genetic factors make a significant contribution to the development of the disease.

Environmental triggers: Environmental factors also play a critical role in the pathogenesis of AITD. These factors can trigger autoimmune reactions in genetically predisposed people. Environmental triggers include infections, stress, dietary factors, and exposure to certain chemicals. These factors can lead to activation of the immune system and the production of autoantibodies targeting thyroid antigens. The interaction between genetic susceptibility and environmental factors is complex and requires further research to be fully understood.

Autoantibodies and their role: Autoantibodies are the hallmark of AITD. In HD, autoantibodies against the TSH receptor stimulate the thyroid gland, leading to hyperthyroidism. In AIT, autoantibodies against TPO and TG lead to the destruction of thyroid cells and hypothyroidism. The production of these autoantibodies is due to loss of immune tolerance to thyroid antigens. This loss of tolerance is a key step in the development of AITD. The presence of these autoantibodies in patients with AITD can serve as diagnostic markers and help in the treatment of the disease.

Role of T cells: T cells play a significant role in the

pathogenesis of AITD. CD4+ T helper cells, especially Th1 and Th17 cells, are involved in the immune response against thyroid antigens. Th1 cells produce pro-inflammatory cytokines such as IFN- γ , which promote inflammation and autoimmunity. Th17 cells produce IL-17, which is involved in the pathogenesis of a number of autoimmune diseases, including AITD. Regulatory T cells (Tregs) help maintain immune tolerance and prevent autoimmune reactions. Dysfunction or deficiency of Tregs may contribute to the development of AITD.

Innate immune cells: Innate immune cells such as mast cells also play a role in AITD. Mast cells are involved in both the initiation and effector phases of the immune response. They have receptors for thyroid hormones and TSH and can release mediators that affect thyroid function and inflammation. Activation of mast cells can occur through various mechanisms, including exposure to bacterial endotoxins and low-frequency electromagnetic fields. The role of mast cells in AITD is an area of active research and may provide new insights into disease mechanisms and potential therapeutic targets.

Therapeutic approaches: Modern treatments for AITD are aimed at eliminating symptoms and maintaining thyroid function. Treatment for HD includes thyroid drugs, radioactive iodine therapy, and thyroidectomy. These treatments aim to reduce the production of thyroid hormones and relieve symptoms of hyperthyroidism. In AIT, thyroid hormone replacement therapy is used to treat hypothyroidism. However, these treatments have limitations, including potential side effects and the risk of relapse. There is a need for more specific and effective treatments that target the underlying immune mechanisms of AITD.

Anticytokine therapy: Anticytokine therapy is a promising approach to the treatment of AITD. This therapy involves targeting specific cytokines involved in the inflammatory response. For example, targeting IL-17 or TNF- α may help reduce inflammation and autoimmunity in AITD. Neuropeptides that regulate immune responses are also potential therapeutic targets. Neuropeptides are released during times of stress and can influence immune function. Targeting neuropeptide receptors may help modulate immune responses and reduce autoimmunity in AITD.

3.1. Need for Further Research

Genetic mechanisms: Despite the discovery of genetic loci associated with autoimmune thyroiditis, a better understanding of their influence on the development and progression of the disease is required. Additional research may help identify new genetic factors and mechanisms regulating the immune response.

Environmental factors: Understanding the influence of external triggers such as infections, stress and radiation on the development of autoimmune thyroiditis also requires further research. This may include studying the

mechanisms by which these factors interact with genetic predispositions.

Clinical aspects: Various forms of autoimmune thyroiditis have their own clinical characteristics and require an individual approach to treatment. Further research should be aimed at identifying new clinical markers that will allow more accurate diagnosis and prognosis of the course of the disease.

Immunological mechanisms: Understanding the various cells and cytokines involved in the pathogenesis of autoimmune thyroiditis holds promise for the development of new treatments. Further research may help identify new targets for therapy and determine optimal methods of influencing the immune system.

Therapy methods: Despite the existing methods of treating autoimmune thyroiditis and Graves' disease, the emergence of new technologies and drugs requires an assessment of their effectiveness and safety in clinical practice.

Let's consider potential advantages and disadvantages of treating AIT using gene therapy.

Advantages of gene therapy in the treatment of AIT:

1. Gene therapy can be aimed directly at genes responsible for the development of an autoimmune response, which makes it possible to influence the root cause of the disease.
2. If successful, gene therapy may provide long-lasting or even permanent effects, eliminating the need for constant medication use.
3. Unlike systemic immunosuppressants, gene therapy can minimize side effects because it targets specific cells or genes.
4. Early intervention at the gene level can prevent further destruction of thyroid tissue and associated complications.

Disadvantages of gene therapy in the treatment of AIT:

1. Gene therapy for the treatment of autoimmune diseases such as AIT is still in the experimental stage. Its safety and effectiveness have not yet been fully proven.
2. Introducing genes can lead to unforeseen consequences, including activating other genes or causing mutations that could be harmful.
3. Gene therapy is an expensive treatment, and is currently not available to a wide range of patients.
4. The introduction of new genes can trigger an immune response, directed against the therapeutic agents themselves, which may reduce the effectiveness of treatment and cause complications.

4. Conclusions

AITD is a complex multifactorial disease involving genetic and environmental factors, autoantibodies, and

immune cells. Understanding the mechanisms underlying the pathogenesis of AITD is critical for the development of targeted therapies. Further research into the role of genetic and environmental factors, autoantibodies, T cells, and innate immune cells will help improve the treatment of AITD. Innovative therapeutic approaches such as anti-cytokine therapy hold promise for more effective treatment options. Bridging the gap between knowledge of pathogenesis and clinical practice will improve patient outcomes and quality of life.

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