Science Discovery
2026, Vol. 14, No. 2, pp. 24–34
https://doi.org/10.11648/j.sd.20261402.12

Review Article

The Butterfly Code: A Mechanistic Review of Thyroid Antibodies

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Abstract

Autoimmune thyroid diseases (AITDs) are common disorders marked by the presence of thyroid autoantibodies. This review summarizes their immunological roles, clinical relevance, and diagnostic value based on studies published up to January 2026. The main antibodies—anti-TPO, anti-Tg, and TSH receptor antibodies (TRAb) —serve different functions. TRAb play a direct pathogenic role, especially in Graves' disease, while anti-TPO and anti-Tg are primarily markers associated with autoimmune thyroid destruction, such as in Hashimoto's thyroiditis. Clinically, TRAb are important for diagnosis and monitoring of Graves' disease, whereas anti-TPO and anti-Tg help identify autoimmune origin and assess the risk of hypothyroidism. However, their diagnostic accuracy is limited by their presence in some healthy individuals. Overall, thyroid autoantibodies remain essential tools in clinical practice, though careful interpretation is necessary. Future approaches combining immunology with computational methods may improve disease prediction and management.

Keywords

Thyroid, Autoantibodies, Autoimmune Thyroid Diseases, Hashimoto's Thyroiditis, Graves' Disease

1. Introduction

The thyroid gland is particularly susceptible to autoimmune processes, making autoimmune thyroid diseases (AITDs) a major public health concern. Hashimoto's thyroiditis and Graves' disease constitute the two main clinical entities within this spectrum, presenting respectively with hypothyroidism and hyperthyroidism. The hallmark of these diseases is the presence of circulating autoantibodies directed against thyroid-specific antigens [1, 2].

Thyroid autoantibodies are widely used in clinical practice for diagnostic confirmation, assessment of disease activity and evaluation of autoimmune risk in asymptomatic individuals. However, their exact pathogenic role remains a subject of ongoing debate. Understanding the immunological basis and clinical significance of thyroid autoantibodies is essential for clinicians involved in endocrinology and internal medicine [3].

This review provides a comprehensive overview of thyroid antibodies, highlighting their pathogenetic mechanisms, utility, clinical implications, controversies and future perspectives.

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Received: 11 April 2026; **Accepted:** 21 April 2026; **Published:** 30 April 2026

2. Methodology

This narrative review was conducted to provide a comprehensive overview of thyroid autoantibodies and their clinical relevance. A literature search was performed using major electronic databases, including PubMed, Scopus, and Web of Science, covering studies published up to January 2026. Keywords used in various combinations included "thyroid autoantibodies," "anti-TPO," "anti-thyroglobulin," "TSH receptor antibodies," "Graves' disease," and "Hashimoto's thyroiditis."

Eligible articles included original research studies, systematic reviews, meta-analyses, and clinical guidelines published in English. Priority was given to high-impact and recent publications (primarily from the last 5–10 years), while seminal older studies were included where relevant for historical or mechanistic context. Case reports and studies with insufficient methodological quality were excluded unless they provided unique clinical insights.

Articles were selected based on their relevance to immunopathogenesis, diagnostic performance, prognostic value, and clinical applications of thyroid autoantibodies. The final selection was guided by the authors' clinical expertise and the objective of providing a balanced and up-to-date synthesis of current evidence.

3. Review of Literature

3.1. Immunogenetic and Environmental Mechanisms Underlying AITDs

AITDs arise from a complex interplay between genetic susceptibility, immune dysregulation and environmental triggers, leading to a breakdown of both central and peripheral immune tolerance to thyroid antigens (Figure 1).

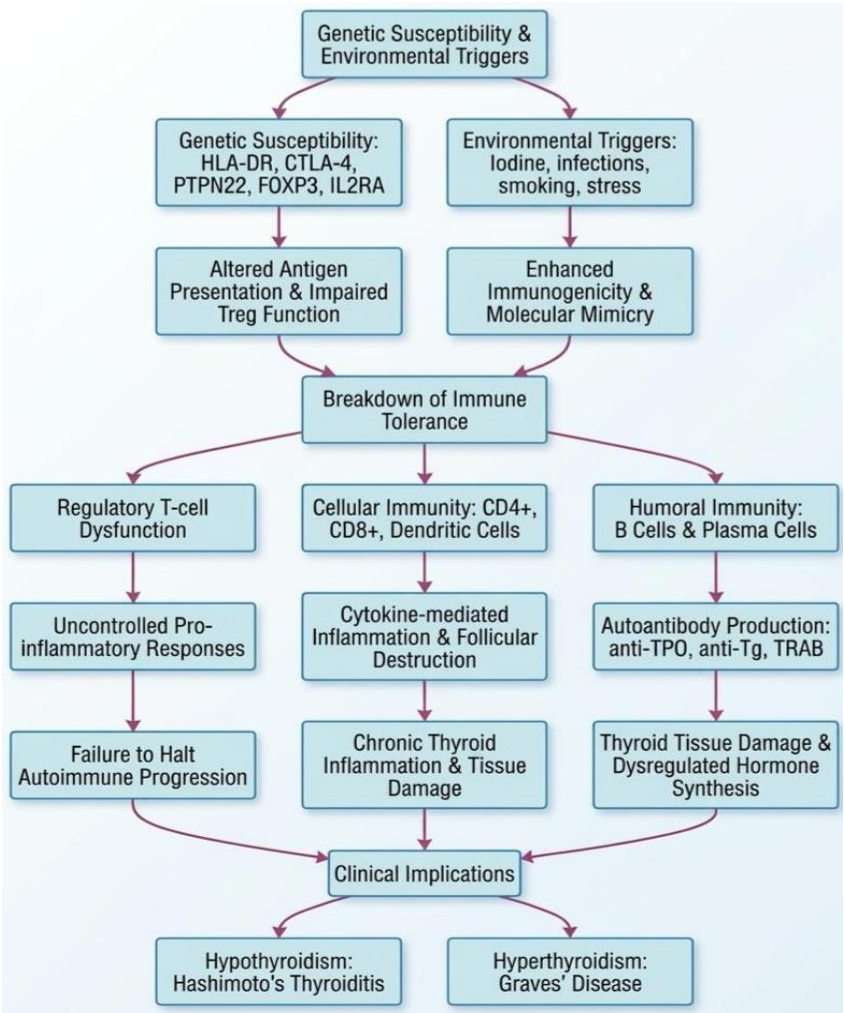

Figure 1. *Pathogenetic mechanisms in autoimmune thyroid diseases. HLA-DR: Human Leukocyte Antigen – DR isotype, CTLA-4: Cytotoxic T-Lymphocyte Associated protein 4, PTPN22: Protein Tyrosine Phosphatase Non-receptor type 22, FOXP3: Forkhead box P3, IL2RA: Interleukin-2 Receptor Alpha chain, Treg: Regulatory T-cell, CD4+: Cluster of Differentiation 4 (Helper T-cells), CD8+: Cluster of Differentiation 8 (Cytotoxic T-cells), anti-TPO: Anti-Thyroid Peroxidase antibodies, anti-Tg: Anti-Thyroglobulin antibodies, TRAb: TSH (Thyroid-Stimulating Hormone) Receptor Antibodies*

Genome-wide association studies and candidate gene analyses have consistently identified strong associations with immune-regulatory genes, including human leukocyte antigen (HLA) such as HLA-DR, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), forkhead box P3 (FOXP3) and interleukin-2 receptor alpha (IL2RA), highlighting the pivotal role of adaptive immune dysfunction in disease pathogenesis [4-6]. These genetic variants promote aberrant antigen presentation, altered T-cell receptor signaling and defective regulatory T-cell (Treg) function, facilitating the survival and activation of autoreactive lymphocytes.

Environmental factors such as excessive iodine intake, infections, psychosocial stress, smoking, pregnancy-related immune modulation and exposure to endocrine-disrupting chemicals act as critical triggers in genetically predisposed individuals [7, 8]. Iodine excess enhances thyroglobulin iodination, increasing its immunogenicity and promoting presentation by antigen-presenting cells, while infections may induce molecular mimicry and bystander activation, further amplifying immune tolerance failure [9].

At the cellular level, thyroid autoimmunity is characterized by dense lymphocytic infiltration of the thyroid gland, composed predominantly of $CD4^+$ T helper cells, $CD8^+$ cytotoxic T lymphocytes, B cells, plasma cells, and dendritic cells [10]. A predominance of Th1 and Th17 immune responses sustains chronic inflammation through the production of interferon-γ (IFN-γ), interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [11]. These cytokines induce aberrant expression of major histocompatibility complex (MHC) class II molecules on thyrocytes, enabling them to function as non-professional antigen-presenting cells and perpetuate autoimmune activation [12].

Concurrently, quantitative and functional defects in regulatory T cells, along with reduced levels of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), impair immune tolerance and fail to counterbalance pro-inflammatory responses [13]. Autoreactive $CD8^+$ T cells contribute directly to thyroid tissue damage through Fas–Fas ligand interactions and perforin–granzyme–mediated cytotoxicity, leading to progressive follicular destruction, particularly in Hashimoto's thyroiditis [14].

Humoral immunity also plays a central role through B-cell activation and plasma cell differentiation, resulting in the production of thyroid-specific autoantibodies, including anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), and Thyroid stimulating hormon (TSH) receptor antibodies (TRAb). Beyond their diagnostic utility (Figure 2), these antibodies exhibit variable pathogenic roles. Anti-TPO can mediate antibody-dependent cell-mediated cytotoxicity, while stimulating TRAb directly activate the TSH receptor, causing uncontrolled thyroid hormone synthesis in Graves' disease [15, 16]. Conversely, blocking TRAb may induce hypothyroidism, illustrating the functional heterogeneity of humoral immune responses

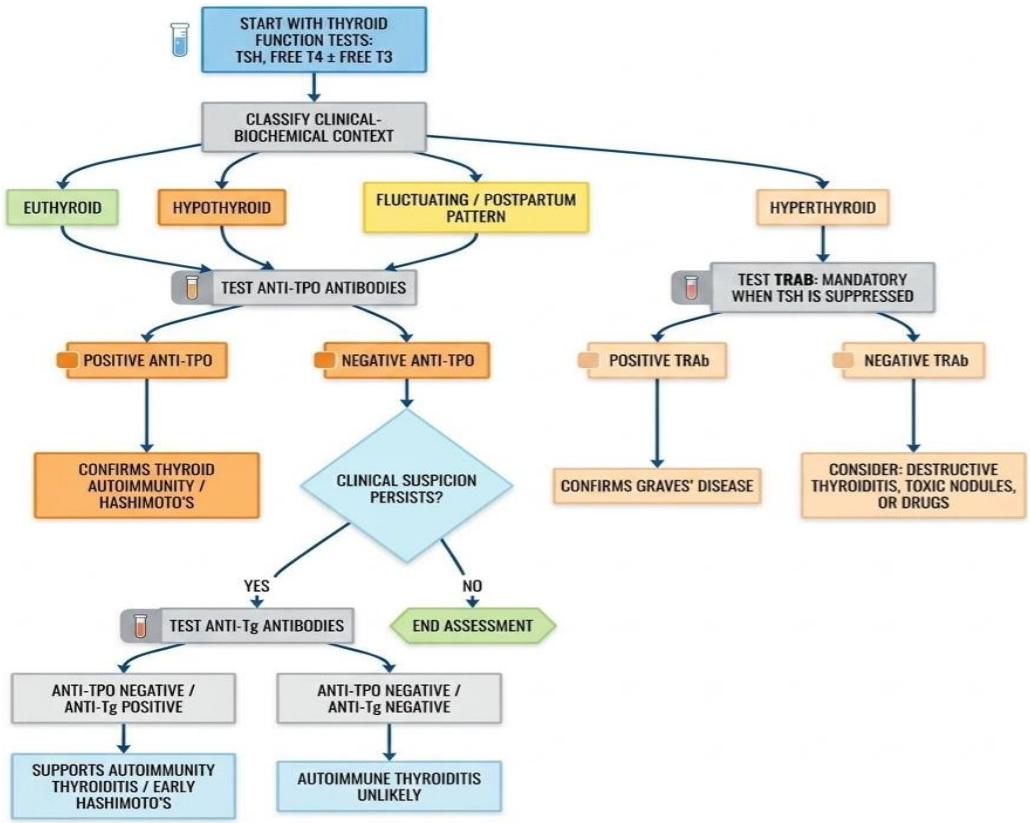

Figure 2. *Antibody-based diagnostic algorithm in autoimmune thyroid diseases.*

3.2. Thyroid Autoantibodies

3.2.1. Anti-thyroid Peroxidase (Anti-TPO)

Anti-TPO represent the most prevalent and clinically significant autoantibodies in AITDs. They are detected in approximately 90–95% of patients with Hashimoto's thyroiditis and in 70–80% of individuals with Graves' disease, making them the most sensitive serological hallmark of thyroid autoimmunity [5, 16, 17]. Thyroid peroxidase (TPO) is a membrane-bound enzyme essential for thyroid hormone biosynthesis, catalyzing iodide oxidation, iodination of thyroglobulin, and coupling of iodotyrosine residues. Immune targeting of this enzyme therefore occupies a central position in the autoimmune assault on thyroid tissue.

From a pathogenic perspective, anti-TPO are not merely passive markers of immune dysregulation. Experimental and clinical evidence suggests that they actively participate in thyroid injury through antibody-dependent cell-mediated cytotoxicity and complement activation, ultimately contributing to progressive follicular cell destruction [18, 19]. Their presence reflects an underlying T cell–mediated autoimmune response, in which B-cell activation and plasma cell differentiation perpetuate chronic inflammation within the thyroid microenvironment.

Clinically, anti-TPO serve several critical roles. They are highly sensitive indicators of AITD and are frequently detectable years before the onset of overt thyroid dysfunction. Longitudinal studies have consistently demonstrated that anti-TPO positivity in euthyroid individuals is associated with an increased risk of developing subclinical or overt hypothyroidism, particularly in the presence of additional risk factors such as female sex, pregnancy, iodine excess, or advancing age [20]. In patients with established Hashimoto's thyroiditis, anti-TPO are strongly associated with progressive thyroid failure and irreversible glandular damage [21].

Despite their diagnostic and prognostic value, anti-TPO titers do not reliably correlate with the clinical severity of disease, the degree of hypothyroidism or response to levothyroxine therapy [19, 22]. Antibody concentrations may fluctuate over time and often persist despite biochemical euthyroidism, limiting their utility for disease monitoring or therapeutic decision-making. Consequently, current clinical guidelines recommend anti-TPO measurement primarily for diagnostic confirmation and risk stratification rather than longitudinal follow-up [22].

3.2.2. Anti-thyroglobulin (Anti-Tg)

Anti-Tg are immunoglobulins directed against thyroglobulin, a large iodinated glycoprotein that functions as the molecular scaffold for thyroid hormone biosynthesis and storage within the thyroid follicular lumen. Thyroglobulin is one of the major autoantigens in AITDs, due in part to its abundant expression in the thyroid and its propensity for antigenic modification under inflammatory conditions [23].

Clinically, anti-Tg are detected in a significant proportion of patients with AITDs. In Hashimoto's thyroiditis, anti-Tg are present in approximately 60-80% of patients. In Graves' disease, anti-Tg are likewise detected but generally less frequently, with positivity reported in roughly 50-60% of patients in some cohorts [24].

Although anti-Tg lack the sensitivity of anti-TPO for diagnosing AITD, they provide important complementary diagnostic information, particularly in individuals with strong clinical or sonographic features of thyroiditis but negative anti-TPO status. In such contexts, the presence of anti-Tg supports an autoimmune etiology and reflects ongoing humoral immune activation within the thyroid gland [25].

Beyond their role in primary AITDs, anti-Tg carry significant clinical relevance in the follow-up of differentiated thyroid carcinoma (DTC). Because serum thyroglobulin (Tg) is widely used as a tumor marker after total thyroidectomy and radioiodine ablation, the presence of anti-Tg can interfere with immunometric Tg assays, often resulting in falsely low or undetectable thyroglobulin values, which may mask evidence of persistent or recurrent disease. Accordingly, anti-Tg themselves are monitored longitudinally in thyroid cancer patients. Rising or persistently elevated antibody titers during follow-up can serve as an indirect marker of residual or recurrent thyroid tissue and may prompt additional imaging, such as neck ultrasonography, especially when Tg levels are unreliable due to assay interference [26].

From a pathogenic standpoint, anti-Tg are generally regarded as markers rather than primary mediators of tissue injury. Unlike anti-TPO or TRAb, which have more direct pathogenic roles, anti-Tg exhibit limited capacity to induce direct cytotoxicity. Their presence primarily reflects humoral immune activation secondary to T-cell–mediated autoimmune responses rather than being principal effectors of follicular destruction. Nonetheless, the detection of anti-Tg underscores the breadth of antigenic targets involved in AITD and highlights the complexity of humoral immune responses directed against the thyroid gland [27].

3.2.3. TSH Receptor Antibodies (TRAb)

TRAb are central drivers of Graves' disease, exerting direct functional effects on thyroid follicular cells, unlike anti-TPO and anti-Tg, which primarily serve as markers of autoimmunity.

TRAb represent a heterogeneous population of immunoglobulins that can be classified based on their interaction with the TSH receptor and resulting functional consequences (Table 1) [16, 28, 29]:

Table 1. Classification and clinical relevance of TSH (Thyroid-Stimulating Hormone) Receptor Antibodies.

TRAb type	Mechanism of action	Effect on thyroid hormone production	Clinical significance
Stimulating (TSAb)	Binds TSH receptor, activates c Adenosine monophosphate (cAMP) signaling	↑ T4 and T3 → hyperthyroidism	Primary driver of Graves' hyperthyroidism; predicts relapse risk
Blocking (TBAb)	Competes with TSH for receptor binding	↓ T4 and T3 → hypothyroidism	Can cause hypothyroidism; relevant in postpartum thyroiditis
Neutral	Binds receptor without functional effect	No significant change	Clinical role unclear; research ongoing

Stimulating antibodies (TSAb) bind the extracellular domain of the TSH receptor, mimicking TSH, which leads to sustained activation of the cyclic adenosine monophosphate (cAMP) signaling pathway, driving excessive synthesis and secretion of thyroxine (T4) and triiodothyronine (T3), ultimately producing the clinical manifestations of hyperthyroidism.

Blocking antibodies (TBAb) competitively inhibit TSH binding, resulting in reduced receptor activation and decreased thyroid hormone production, potentially leading to hypothyroidism.

Neutral antibodies, though detectable in some patients, do not produce measurable effects on thyroid hormone synthesis or TSH receptor signaling; their biological significance remains uncertain, and research suggests potential modulation of receptor conformation without functional outcome.

The clinical utility of TRAb measurement is confirming diagnosis in ambiguous presentations, predicting relapse after cessation of antithyroid therapy and assessing maternal-fetal risk in pregnancy. Maternal TRAb can cross the placenta and stimulate or block fetal TSH receptors, leading to transient fetal or neonatal thyrotoxicosis or hypothyroidism. Moreover, TRAb titers often correlate with disease activity, providing a dynamic biomarker for treatment monitoring and prognosis [30].

3.2.4. Special Clinical Contexts

(i). Pregnancy

The presence of thyroid antibodies during pregnancy (most notably anti-TPO and anti-Tg) has emerged as a significant immuno-endocrine factor influencing maternal and fetal outcomes, even in women who remain biochemically euthyroid. Pregnancy constitutes a unique immunological condition characterized by finely regulated tolerance mechanisms aimed at protecting the semi-allogeneic fetus; however, pre-existing thyroid autoimmunity may perturb this delicate balance and predispose to adverse obstetric events. A substantial body of observational and prospective evidence demonstrates that euthyroid pregnant women who are positive for thyroid autoantibodies face an increased risk of early pregnancy loss and miscarriage compared with antibody-negative counterparts. This association has been consistently reported across different populations and study designs [31, 32].

The underlying mechanisms are likely multifactorial, involving both subtle thyroid hormone insufficiency in response to the increased metabolic demands of pregnancy and a more generalized immune dysregulation. In this regard, thyroid autoantibodies may represent a surrogate marker of systemic autoimmunity rather than acting solely as direct mediators of thyroid dysfunction. In addition to their association with pregnancy loss, thyroid autoantibodies are a well-established risk factor for the development of postpartum thyroiditis, an autoimmune inflammatory disorder of the thyroid occurring within the first year after delivery. Pregnancy-induced immunological tolerance is followed by a postpartum immune rebound, which may precipitate renewed autoimmune activity against thyroid antigens [33]. Women with detectable anti-TPO during pregnancy have a markedly elevated risk (reported to be as high as 30–50% of developing postpartum thyroiditis), whereas the condition remains rare among antibody-negative women [34].

Emerging data also suggest a link between thyroid autoimmunity, preterm delivery and other obstetric complications including placental dysfunction and impaired fetal growth. Even in the absence of overt hypothyroidism, subtle alterations in thyroid hormone bioavailability at the placental and fetal level, combined with immune-mediated inflammatory processes, may adversely influence placental development and gestational duration [35].

In fact, thyroid autoantibody profiling is central to the evaluation of AITDs. Combined assessment of anti-TPO, anti-Tg, and TRAb helps characterize the autoimmune pattern and differentiate major AITD phenotypes (Table 2).

Table 2. Interpretation of anti-thyroid peroxidase, anti-thyroglobulin and TSH receptor antibodies profiles in autoimmune thyroid diseases.

Anti-TPO	Anti-Tg	TRAb	Likely Diagnosis
+	±	—	Hashimoto's thyroiditis
+	±	+	Graves' disease
—	+	—	Seronegative Hashimoto's
+	—	—	Euthyroid AITD
—	—	+	Graves' disease (early or isolated)
±	±	—	Postpartum thyroiditis

(ii). Other Autoimmune Diseases

Thyroid autoantibodies, principally anti-TPO and anti-Tg, are detected with increased frequency in patients affected by systemic autoimmune diseases, including systemic lupus (SL), type 1 diabetes (T1D) and rheumatoid arthritis (RA) (Table 3). Their presence reflects not a coincidental overlap but rather a convergence of shared immunogenetic susceptibilities and overlapping pathogenic pathways that transcend the boundaries between organ-specific and systemic autoimmunity.

Table 3. Association of thyroid autoantibodies with other systemic autoimmune diseases.

Systemic autoimmune disease	Prevalence of Anti-TPO / Anti-Tg	Shared genetic susceptibility	Immunopathogenic mechanisms	Clinical implications	References
SL	↑↑ compared to general population, even in euthyroid patients	HLA-DR, HLA-DQ, CTLA-4, PTPN22, FOXP3	Chronic B-cell hyperactivity, impaired apoptotic debris clearance, type I IFN signaling	Subclinical thyroid dysfunction may exacerbate fatigue, cognitive and metabolic symptoms	[37]
T1D	~30% may have anti-TPO / anti-Tg, often preceding clinical AITDs	HLA-DR, HLA-DQ	Autoreactive T lymphocyte-mediated beta cell and thyroid attack	Supports early thyroid monitoring; reflects polyautoimmunity	[38, 39]
RA	Elevated vs. matched controls	HLA-DR, PTPN22	Th1/Th17 polarization, epitope spreading	Associated with higher RA severity and extra-articular manifestations	[40]

From an immunogenetic standpoint, these associations are largely driven by common HLA haplotypes, particularly within the HLA-DR and HLA-DQ loci, which confer susceptibility to both thyroid and non-thyroid autoimmune disorders. Moreover, polymorphisms in immune-regulatory genes such as CTLA-4, PTPN22, and FOXP3 contribute to defective central and peripheral immune tolerance, thereby facilitating the development of polyautoimmunity [4, 36]. In this framework, anti-TPO and anti-Tg may be interpreted as serological manifestations of a broader autoimmune diathesis rather than isolated indicators of thyroid-restricted pathology.

In SL, numerous studies have reported a significantly higher prevalence of anti-TPO and anti-Tg compared with the general population, even in patients who remain clinically euthyroid. Hallmark features of SL (including chronic B-cell hyperactivity, impaired clearance of apoptotic debris, and sustained type I interferon signaling) create a permissive immunological environment for the diversification of autoreactive antibody repertoires, encompassing thyroid antigens [37]. Subclinical thyroid dysfunction associated with thyroid antibodies may further exacerbate fatigue, neurocognitive symptoms and metabolic disturbances, complicating clinical assessment in lupus patients.

The coexistence of thyroid autoimmunity with T1D represents one of the most robust examples of autoimmune clustering. Anti-TPO and anti-Tg are detected in up to one-third of individuals with T1D, often preceding the onset of clinically

apparent AITDs. Both conditions share strong HLA associations and are mediated predominantly by autoreactive T lymphocytes, underscoring the interconnected nature of endocrine autoimmunity and supporting the rationale for longitudinal thyroid surveillance in diabetic populations [38, 39].

In RA, the prevalence of anti-TPO and anti-Tg is also significantly elevated relative to matched controls. Persistent systemic inflammation, dysregulated T-helper cell polarization—particularly Th1 and Th17 responses—and mechanisms of epitope spreading may promote secondary autoimmune targeting of thyroid antigens [40]. Notably, thyroid autoimmunity in RA has been associated with increased disease severity and a higher burden of extra-articular manifestations, suggesting a potential modulatory role of thyroid-directed immune responses in systemic inflammatory disease.

4. Controversies

Despite their established diagnostic and prognostic value in AITDs, thyroid antibodies (most notably anti-TPO and anti-Tg) exhibit important limitations that constrain their utility as standalone clinical tools. A critical appraisal of their interpretative boundaries is therefore essential to avoid overdiagnosis, unnecessary intervention and misallocation of healthcare resources [25, 41].

One of the principal limitations lies in the detection of thyroid autoantibody positivity in otherwise healthy individuals. Population-based studies have consistently demonstrated that a substantial proportion of euthyroid subjects harbor detectable thyroid antibodies without manifesting clinical or biochemical evidence of thyroid disease. This phenomenon is particularly prevalent among women, older individuals and populations with a genetic predisposition to autoimmunity. In such contexts, antibody positivity may represent latent or indolent autoimmunity that never progresses to overt thyroid dysfunction, thereby limiting the specificity of these markers when applied indiscriminately [42].

Furthermore, antibody titers do not invariably correlate with disease activity, severity or progression. While high titers are often associated with autoimmune thyroiditis, longitudinal studies reveal considerable intra-individual variability, with antibody levels fluctuating independently of thyroid hormone concentrations or clinical symptomatology. In established disease, declining or persistently elevated antibody titers may coexist with stable thyroid function, rendering serial measurements of limited value for disease monitoring or therapeutic decision-making [43].

The question of routine screening for thyroid autoantibodies in asymptomatic populations remains a subject of ongoing debate. Although early identification of thyroid autoimmunity may theoretically permit anticipatory monitoring, current evidence does not demonstrate a clear benefit in terms of morbidity reduction or prevention of disease progression. On the contrary, widespread screening risks generating anxiety, unnecessary follow-up testing and overtreatment, particularly in individuals unlikely to develop clinically meaningful thyroid dysfunction. Crucially, current clinical evidence does not support treatment decisions based solely on the presence or magnitude of thyroid autoantibody titers in the absence of overt clinical or biochemical thyroid abnormalities. Major professional guidelines emphasize that therapeutic intervention should be guided by thyroid function tests and clinical context rather than antibody status alone. Initiating treatment on the basis of seropositivity alone may expose patients to unwarranted pharmacological therapy without demonstrable benefit, underscoring the importance of integrating serological findings within a broader clinical framework [24, 44].

5. Measurement of Thyroid Autoantibodies and Clinical Implications

Thyroid autoantibodies are measured using a range of immunoassays, including enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and, more recently, automated chemiluminescent immunoassays (CLIA). The latter offer improved sensitivity, reproducibility, and suitability for high-throughput testing, making them widely used in current clinical practice.

For TSH receptor antibodies (TRAb), two principal assay types are available. Binding immunoassays—commonly referred to as TSH-binding inhibitory immunoglobulin (TBII) assays—detect antibodies that interfere with TSH binding to its receptor. In contrast, functional bioassays assess the biological activity of these antibodies, distinguishing between stimulating and blocking forms. Although functional assays provide more detailed clinical information, their availability remains limited due to technical complexity [45-47].

The choice of assay has important implications for clinical decision-making. Variations in sensitivity, specificity, and assay standardization can influence diagnostic accuracy, particularly in borderline or subclinical cases. In addition, inter-assay variability reduces the comparability of antibody titers between laboratories, underscoring the importance of interpreting results within assay-specific reference ranges.

6. Future Directions

Emerging research in 2025 and early 2026 has begun to refine our understanding of thyroid autoantibodies, both in terms of novel clinical associations and advanced diagnostic tools. Recent studies have explored the application of machine learning algorithms to predict thyroid autoantibody positivity in related autoimmune conditions, such as primary Sjögren's disease, where Random Forest models identified clinical predictors for anti-TPO and anti-Tg positivity with moderate accuracy, highlighting the potential utility of AI-augmented risk stratification in identifying at-risk populations early in the clinical course [48].

Alongside predictive modeling, metabolomic profiling in patients with Hashimoto's thyroiditis and positive anti-Tg or anti-TPO has revealed distinct serum metabolite signatures, suggesting that metabolic alterations may complement autoantibody profiling for disease characterization and progression monitoring [49]. Research has also underscored the systemic impact of thyroid autoimmunity beyond the thyroid gland (for example, large cohort studies in 2025 have documented the prevalence and clinical impact of thyroid dysfunction in RA, indicating intertwined autoimmune pathways) [50].

In specialized populations, the prevalence of anti-TPO in women with polycystic ovary syndrome (PCOS) underscores the need to investigate endocrine–immune cross-talk in conditions with overlapping reproductive and metabolic phenotypes [51].

Moreover, retrospective analyses in patients with inborn errors of immunity emphasize the diverse clinical contexts where AITDs and associated autoantibodies emerge, reinforcing the need for tailored immunological surveillance in these groups [52].

Basic and translational research is also expanding the horizon of measurable autoantibodies: newly developed chemiluminescent assays for autoantibodies against T3 and T4 hormones have shown potential as independent biomarkers that may interfere with standard thyroid hormone tests and provide additional insight into immune-mediated thyroid dysfunction, particularly in contexts such as immune checkpoint blockade therapies [53].

Together, these studies point toward a future where integrative biomarkers, AI-assisted diagnostics, and precision-based approaches combining immunological, metabolic and clinical data could enable improved prediction, stratification and individualized management of AITDs. Further longitudinal and interventional studies are needed, especially to validate these emerging biomarkers and computational models in diverse populations and across different stages of thyroid autoimmunity (Figure 3).

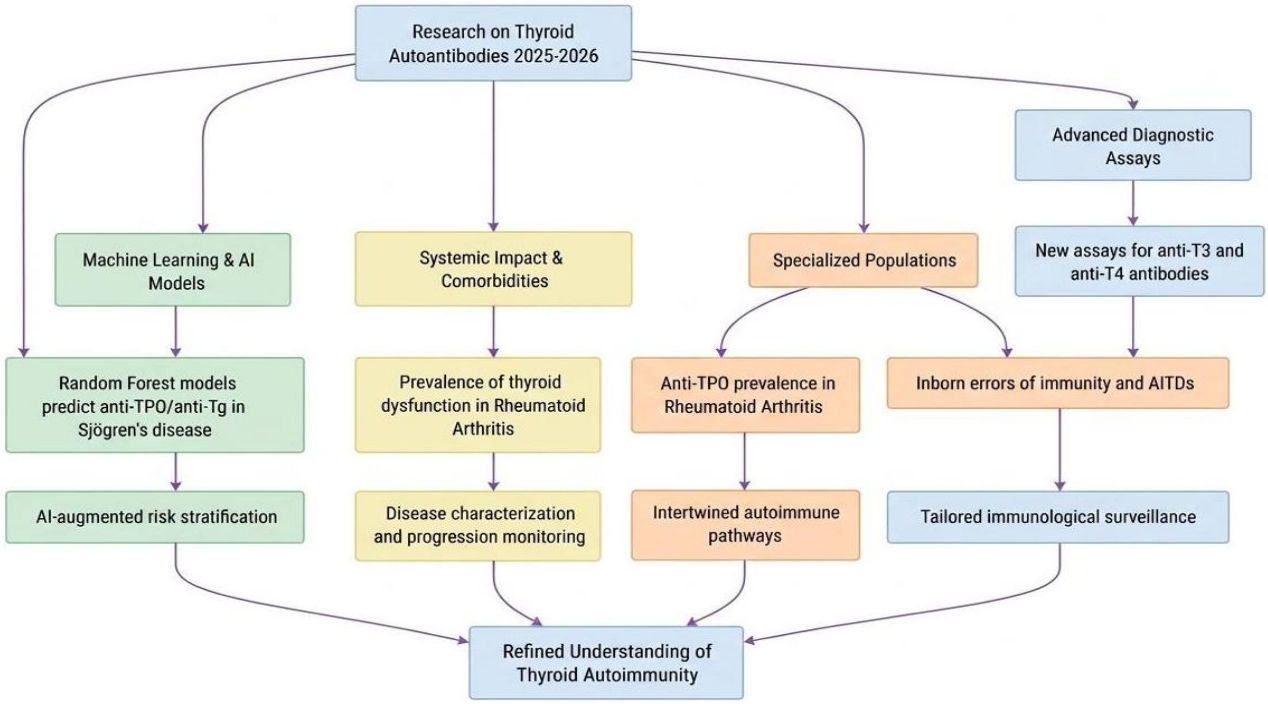

Figure 3. *Research perspectives proposed for improving the understanding of thyroid autoimmunity.TSH: Thyroid-Stimulating Hormone, Free T4: Free Thyroxine, Free T3: Free Triiodothyronine, Anti-TPO: Anti-Thyroid Peroxidase Antibodies, Anti-Tg: Anti-Thyroglobulin Antibodies, TRAb: TSH Receptor Antibodies, AITDs: Autoimmune Thyroid Diseases, AI: Artificial Intelligence. Machine Learning: A subset of AI focused on building systems that learn from data. Random Forest: A specific machine learning algorithm that uses an ensemble of decision trees to make predictions.*

7. Conclusion

Thyroid autoantibodies constitute fundamental biomarkers in autoimmune thyroid diseases, offering valuable insights into diagnosis, prognosis and disease mechanisms. Anti-TPO and anti-Tg primarily serve as markers of thyroid autoimmunity, whereas TSH receptor antibodies play a direct pathogenic role in Graves' disease. Although widely used in clinical practice, their predictive and therapeutic value remains limited by variability in expression and clinical impact. Future research should focus on clarifying their role in disease progression,

identifying novel immunological targets and integrating antibody profiles into personalized management strategies for AITDs.

Abbreviations

AITDs	Autoimmune Thyroid Diseases
TPO	Thyroid Peroxidase
Tg	Thyroglobulin
TRAb	TSH Receptor Antibodies
TSAb	Thyroid-Stimulating Antibodies
TBAb	Thyroid-Blocking Antibodies
TSH	Thyroid-Stimulating Hormone
T3	Triiodothyronine
T4	Thyroxine
HLA	Human Leukocyte Antigen
CTLA-4	Cytotoxic T-lymphocyte-associated Protein 4
PTPN22	Protein Tyrosine Phosphatase Non-receptor Type 22
FOXP3	Forkhead Box P3
IL	Interleukin
IFN-γ	Interferon Gamma
TNF-α	Tumor Necrosis Factor Alpha
RA	Rheumatoid Arthritis
T1D	Type 1 Diabetes
SL	Systemic Lupus
DTC	Differentiated Thyroid Carcinoma
ELISA	Enzyme-linked Immunosorbent Assay
RIA	Radioimmunoassay
CLIA	Chemiluminescent Immunoassay

Acknowledgments

The authors acknowledge the support of the Department of Internal Medicine at Ibn Rochd University Hospital, Casablanca, for providing the academic and infrastructural environment that facilitated this work.

Author Contributions

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Leila Barakat: Writing – review & editing
Hassan Elkabli: Supervision

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Conflicts of Interest

The authors declare no conflicts of interests.

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