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AUTOIMMUNE BASIS OF HYPERTHYROIDISM AND ITS LABORATORY DIAGNOSIS: AN OVERVIEW

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ABSTRACT
This review explores hyperthyroidism, an endocrine disorder marked by excessive secretion of thyroid hormones, using Graves' disease as a case study, the most common autoimmune cause. While hyperthyroidism can arise from several etiologies, Graves' disease is distinguished by its autoimmune nature, where the body produces thyroid – stimulating immunoglobulin (TSI) that bind to and activate thyroid – stimulating hormone receptors (TSHR) on the thyroid gland. This abnormal immune response result in unregulated stimulation of thyroid hormone production and release, leading to the clinical manifestation of hyperthyroidism. Graves' disease exemplifies a Type V hypersensitivity reaction, a subclass of hypersensitivity defined by stimulatory autoantibodies that mimic physiological ligands rather than destroy cells or tissues. This mechanism sets it apart from the known Type II hypersensitivity reactions, which involves cytotoxic antibody – mediated destruction. The Type V classification is critical to understanding the disease mechanism in Graves' disease, as it explains the persistent hormonal overstimulation seen in affected individuals. This review details the immunopathological basis of Graves' disease, beginning with the loss of immune tolerance, the role of antigen – presenting cells, T – helper cell differentiation, B – cell activation, and subsequent autoantibody production. It explores the molecular and cellular events that underpin this autoimmune activation and how they contribute to the thyroid gland. Special emphasis is placed on the role of TSHR autoantibodies, cytokine imbalances, and the involvement of genetic and environmental triggers that contribute to disease onset and progression. In addition, this work presents a comprehensive overview of laboratory diagnosis of hyperthyroidism and Graves' disease, including thyroid function tests (T3, T4 TSH level), thyroid autoantibody assays (TRAb, TSI), imaging techniques like ultrasonography and other confirmatory investigations.

KEYWORDS: Hyperthyroidism, Autoantibody, autoimmune activation, Grave's disease, Thyroid – stimulating hormone receptors, Type V hypersensitivity reaction, Thyroid hormones.

INTRODUCTION
The human endocrine system operates as a complex and integrated network of glands and hormones, essential for the maintenance of metabolic homeostasis, development, and overall physiological regulation. Central to this network is the thyroid gland, a pivotal endocrine organ located anteriorly in the neck, responsible for synthesizing the hormones triiodothyronine (T3) and thyroxine (T4), which exert wide-ranging effects on basal metabolic rate, thermogenesis, and growth (Shahid *et al*., 2023). The synthesis and release of these hormones are tightly controlled by the hypothalamic-pituitary-thyroid (HPT) axis through negative feedback mechanisms involving thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). Hyperthyroidism, a pathological state characterized by excessive production and secretion of thyroid hormones, results in a hypermetabolic condition. Symptoms typically include weight loss, increased heart rate, anxiety, irritability, tremors, and heat intolerance (Stern *et al*., 2023; Blick *et al*., 2025). The condition can arise from several etiologies, including toxic multinodular goiter, solitary toxic adenomas, thyroiditis, and, most predominantly, Graves' disease, an autoimmune disorder that accounts for 60–80% of hyperthyroidism cases worldwide (Pokhrel and Bhusal, 2023; Jinesh *et al*., 2022).

Graves' disease represents a unique subset of autoimmune thyroid disorders. It is characterized immunopathologically by the generation of thyroid-stimulating immunoglobulins (TSIs), particularly TSH receptor antibodies (TRAbs), which aberrantly stimulate the TSH receptor (TSHR) on thyroid follicular cells. Unlike other autoimmune conditions that mediate tissue destruction through cytotoxicity or complement activation, the TRAbs in Graves' disease mimic the action of TSH, resulting in persistent thyroid hormone synthesis and secretion. This phenomenon aligns with the classification of Graves' disease as a Type V hypersensitivity reaction, where autoantibodies stimulate rather than destroy target cells (Kim *et al*., 2024). Type V hypersensitivity, a relatively newer subclass in immunopathological taxonomy, involves antibody-mediated stimulation of cell surface receptors. This contrasts with Type II hypersensitivity, where antibodies typically bind to antigens on target cells and elicit cellular damage through mechanisms like antibody-dependent cellular cytotoxicity (ADCC) and complement activation. In Graves' disease, the TRAbs activate the TSHR, mimicking physiological TSH and triggering uncontrolled hormone synthesis, thereby making hyperthyroidism in this context a quintessential example of Type V hypersensitivity (Kustrimovic *et al*., 2023; Davies *et al*., 2020).

The immunopathological basis of Graves' disease entails a breakdown in both central and peripheral tolerance mechanisms, leading to the survival and proliferation of autoreactive T and B lymphocytes. Genetically predisposed individuals with polymorphisms in immune-regulatory genes such as HLA-DR3, CTLA-4, and PTPN22 exhibit increased susceptibility to loss of self-tolerance (Tizaoui *et al*., 2022; Bufalo *et al*., 2021; Bottini and Peterson, 2014). Environmental factors such as infections, stress, and smoking further modulate immune responses, contributing to the pathogenesis of the disease. Cytokine profiling in Graves' disease reveals a predominance of Th2-type immune responses, which favor B-cell activation and antibody production. Moreover, impaired regulatory T cell (Treg) function contributes to the persistence of the autoimmune response (Toro-Tobon and Stan, 2024; Rydzewska *et al*., 2018). The overexpression of costimulatory molecules and dysregulated antigen presentation further perpetuate immune activation (Scappaticcio *et al*., 2021*;* Kustrimovic *et al*., 2023). These complex immunological interactions culminate in chronic stimulation of the thyroid gland, causing diffuse goiter and sustained thyrotoxicosis. From a clinical perspective, understanding the immunological underpinnings of hyperthyroidism—particularly within the framework of Graves' disease—is vital for accurate diagnosis, therapeutic decision-making, and long-term management. Laboratory evaluation typically reveals elevated levels of free T3 and T4 with suppressed TSH. The detection of TRAbs and TSI provides confirmatory evidence of Graves' disease. Advanced imaging modalities such as radioactive iodine uptake (RAIU) scans and thyroid ultrasonography further aid in differentiating autoimmune hyperthyroidism from other causes of thyrotoxicosis (Giovanella *et al*., 2022; Alswat *et al*., 2020).

Management strategies for Graves' disease include antithyroid medications (e.g., methimazole, propylthiouracil), radioactive iodine therapy, surgical thyroidectomy, and adjunctive beta-blocker therapy to control adrenergic symptoms. Recent therapeutic advancements have focused on immunomodulatory approaches targeting B cells and costimulatory pathways. Monoclonal antibodies like rituximab have shown potential in refractory cases (Lee & Kahaly, 2022). Given the intersection between immunology and endocrinology in Graves' disease, this seminar aims to explore the immunopathological mechanisms and laboratory diagnostic protocols that define hyperthyroidism as a Type V hypersensitivity reaction. By synthesizing current evidence, the seminar highlights the diagnostic criteria, pathophysiological processes, and immunological markers relevant to this autoimmune endocrine disorder. A detailed understanding of these dynamics not only facilitates improved clinical outcomes but also opens avenues for targeted immunotherapies and precision medicine.

OVERVIEW OF HYPERTHYROIDISM

Hyperthyroidism is a clinical condition characterized by excessive synthesis and secretion of thyroid hormones—primarily triiodothyronine (T3) and thyroxine (T4)—from the thyroid gland. This hormonal excess leads to a hypermetabolic state that affects virtually every system in the body. The thyroid gland, located in the anterior neck, plays a pivotal role in regulating metabolism, thermogenesis, and protein synthesis through the secretion of these hormones (Shahid *et al*., 2023; Ogbodo *et al*., 2019). The primary causes of hyperthyroidism include Graves' disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. Among these, Graves' disease is the most prevalent cause, particularly in iodine-sufficient regions, accounting for approximately 60–80% of cases (Pokhrel and Bhusal, 2023; Jinesh *et al*., 2022)). The pathophysiology of hyperthyroidism varies with its underlying cause. In Graves' disease, thyroid-stimulating immunoglobulins (TSIs) bind to the thyrotropin (TSH) receptor on thyroid follicular cells, mimicking the action of TSH and resulting in continuous stimulation of thyroid hormone production. In contrast, toxic adenoma and toxic multinodular goiter result from autonomous functioning thyroid nodules, independent of TSH regulation (Krishnan *et al*., 2023; Toro-Tobon and Stan, 2024).

Clinically, patients with hyperthyroidism may present with a range of symptoms due to the elevated basal metabolic rate, including unintentional weight loss, heat intolerance, palpitations, increased appetite, nervousness,

tremors, fatigue, and menstrual disturbances. Signs often observed on physical examination include tachycardia, goiter, hyperreflexia, and, in the case of Graves' disease, ophthalmopathy or dermopathy.

Biochemically, hyperthyroidism is confirmed by suppressed serum TSH levels and elevated levels of free T4 and/or T3. TSH receptor antibodies (TRAb) may be detectable in autoimmune-related cases, especially in Graves' disease. Thyroid ultrasound and radioactive iodine uptake (RAIU) tests are useful adjuncts for determining the etiology ((Giovanella *et al*., 2022; Alswat *et al*., 2020). Epidemiologically, hyperthyroidism affects about 1.3% of the U.S. population, with higher prevalence in women and increasing incidence with age (de Jongh *et al*., 2011; Hollowell *et al*., 2002). It is also more common in populations with higher iodine intake, although iodine deficiency can influence the pattern of thyroid disorders in certain regions.

Management strategies depend on the etiology and may include antithyroid medications (such as methimazole or propylthiouracil), radioactive iodine therapy, or thyroidectomy. Beta-blockers are commonly used to control adrenergic symptoms during the initial stages of treatment (Blick *et al*., 2025).

Hyperthyroidism can have serious complications if left untreated, including atrial fibrillation, osteoporosis, and thyrotoxic crisis (thyroid storm), which is a medical emergency. Long-term follow-up is necessary to monitor treatment response and manage relapses or progression to hypothyroidism.

Hyperthyroidism refers to the clinical condition resulting from an excess of thyroid hormones in the bloodstream, leading to an overall increase in metabolic activity. The condition can manifest in various forms including diffuse toxic goiter (Graves' disease), toxic multinodular goiter, and toxic adenoma. Clinically, hyperthyroidism presents with signs and symptoms such as weight loss, heat intolerance, anxiety, palpitations, and tremors (Stern *et al*., 2023; Blick *et al*., 2025).

Graves' disease remains the most common etiology of hyperthyroidism, accounting for 60–80% of cases ((Pokhrel and Bhusal, 2023; Jinesh *et al*., 2022). This autoimmune disorder is characterized by the production of thyroid-stimulating immunoglobulins (TSI) that mimic the action of TSH on the thyroid gland. Consequently, there is increased synthesis and release of T3 and T4, resulting in thyrotoxicosis. The thyroid gland becomes diffusely enlarged, and ophthalmopathy is frequently observed due to retro-orbital inflammation. Hyperthyroidism, particularly that caused by Graves' disease, is increasingly recognized as a significant endocrine disorder with important public health implications, especially in developing countries like Nigeria. As an organ-specific autoimmune disease, Graves' disease is a hallmark example of a Type V hypersensitivity reaction, wherein autoantibodies—thyroid-stimulating immunoglobulins (TSIs)—bind to and stimulate the TSH receptor, causing unregulated thyroid hormone production. In developed nations, autoimmune thyroid disorders have been widely studied and diagnosed due to the availability of routine thyroid screening and autoantibody testing. However, in sub-Saharan Africa, including Nigeria, the epidemiological data remain limited. The burden of thyroid diseases in Nigeria just like other west African countries is likely underreported due to poor diagnostic infrastructure, limited access to specialist care, lack of awareness, and overlapping symptoms with other common diseases like malaria, HIV, and tuberculosis (Okechukwu *et al*., 2024; Díez and Iglesias, 2023). Although exact national prevalence rates for autoimmune hyperthyroidism in Nigeria are not well documented, several hospital-based studies suggest that thyroid disorders are not uncommon and that Graves' disease accounts for a majority of thyrotoxicosis cases. For instance, a retrospective study at the University College Hospital, Ibadan, indicated that Graves' disease was responsible for over 70% of the hyperthyroidism cases evaluated (Ogun and Adeleye, 2016). Ezeani and Ogbonna (2024) reported a prevalence of 12.4% in diabetics and 1.7% in healthy controls adding that females had higher prevalence of hyperthyroidism. Women are disproportionately affected, with a female-to-male ratio as high as 5:1, which aligns with global trends showing autoimmune diseases are more prevalent in females due to genetic, hormonal, and immunological factors (Kronzer *et al*., 2020; Angum *et al*., 2020). Patients commonly present with classical symptoms such as weight loss, palpitations, exophthalmos, goiter, and heat intolerance, but often with delayed diagnosis due to poor access to endocrine services. In summary, hyperthyroidism represents a spectrum of disorders that lead to thyroid hormone excess, with Graves' disease being the most prominent autoimmune form. Accurate diagnosis, understanding of underlying pathophysiology, and individualized treatment approaches are essential for optimal outcomes.

Comparative Analysis: Type II vs. Type V Hypersensitivity

Hypersensitivity reactions are classified into distinct types based on their immunological mechanisms. Type II and Type V hypersensitivity reactions both involve IgG or IgM antibodies, but they differ fundamentally in their mechanisms, targets, and clinical outcomes.

Definition and Mechanism

Type II Hypersensitivity (Cytotoxic Antibody-Mediated)

- Involves IgG or IgM antibodies directed against antigens present on the surface of cells or extracellular matrix components.
- Leads to cell destruction via complement activation, opsonization, or antibody-dependent cellular cytotoxicity (ADCC).

- The reaction results in tissue damage or cell lysis.

Example: Hemolytic anemia due to antibody binding to red blood cells, leading to their destruction (Wang *et al*., 2024).

Type V Hypersensitivity (Stimulatory/Blocking Antibody-Mediated)

- It is a proposed subtype of Type II, but often treated as a distinct mechanism.
- It Involves non-cytotoxic IgG antibodies that bind to cell surface receptors and alter their function by either stimulating or blocking them.
- Does not lead to cell destruction, but instead results in dysregulated cellular function.

Example: Graves' disease, where autoantibodies stimulate the thyroid-stimulating hormone receptor (TSHR), causing hyperthyroidism (Davies, 2025).

Immunological Differences

Feature	Type II Hypersensitivity	Type V Hypersensitivity
Antibody type	IgG or IgM	IgG
Target	Cell- surface or matrix antigen	Cell surface receptors
Outcome	Cell death or tissue damage via lysis or phagocytosis	Cellular dysfunction due to overstimulation or inhibition
Complement activation	Present	Typically absent
Examples	Autoimmune hemolytic anemia, Hemolytic disease of the new born	Graves' disease, Myasthenia gravis
Pathological hallmarks	Cell destruction	Abnormal cell dysfunction without destruction

Clinical Implications

Type II reactions tend to present with acute inflammation and cytolysis, leading to signs like anemia, bleeding, or renal failure depending on the organ affected. Type V reactions may present with chronic disease due to prolonged stimulation or receptor blocking, such as persistent hyperthyroidism in Graves' disease or muscle weakness in Myasthenia gravis. Though Type V is sometimes classified under Type II, their clinical behavior and underlying mechanisms justify considering Type V as a functionally distinct reaction. Type V lacks the cytotoxicity characteristic of Type II and instead affects receptor-mediated signaling pathways.

While both Type II and Type V hypersensitivity reactions involve antibody responses, their pathomechanisms differ.

- **Type II** involves antibody binding that leads to cell destruction via complement activation or ADCC.
- **Type V** involves antibody binding that result in receptor stimulation without cell damage.

In Graves' disease, TRAbs stimulate the TSH receptor, enhancing thyroid hormone output, thereby qualifying it as Type V hypersensitivity.

Normal Thyroid Function

The thyroid gland is a vital endocrine organ located in the anterior neck, responsible for the regulation of metabolism, growth, and development through the secretion of thyroid hormones. Its proper functioning is critical to maintaining homeostasis in virtually every organ system.

Anatomy and Structure

The thyroid gland is a butterfly-shaped organ located inferior to the larynx and anterior to the trachea. It consists of two lobes connected by an isthmus and is richly vascularized. The functional unit of the thyroid is the thyroid follicle, composed of follicular cells (that produce thyroid hormones) and parafollicular cells (that secrete calcitonin, a calcium-regulating hormone) (Khan and Farhana, 2025; Morgan, 2021).

Hormone Synthesis and Secretion

The thyroid gland synthesizes two main hormones: thyroxine (T4) and triiodothyronine (T3). These hormones are iodine-containing amino acid derivatives synthesized from tyrosine on the glycoprotein thyroglobulin.

The synthesis of thyroid hormones involves several steps.

- Iodide uptake from the bloodstream via the sodium-iodide symporter (NIS).
- Oxidation of iodide to iodine and iodination of tyrosine residues on thyroglobulin (organification).
- Coupling of iodotyrosines (MIT and DIT) to form T3 and T4.
- Storage in the colloid and release into the bloodstream after endocytosis and proteolysis.

Approximately 80% of the hormone produced is T4, which is converted peripherally into T3, the more biologically active form (Gelen *et al*., 2023; Shahid *et al*., 2023; Morgan, 2021; Ogbodo *et al*., 2019).

Regulation of Thyroid Hormone Production

Thyroid function is primarily regulated by the hypothalamic-pituitary-thyroid (HPT) axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH).

TSH then acts on the thyroid gland to promote synthesis and release of T3 and T4.

Negative feedback from elevated T3 and T4 levels inhibits TRH and TSH production to maintain hormone balance (Pirahanchi *et al*., 2023; Shahid *et al*., 2023; Ogbodo *et al*., 2019).

This finely tuned feedback loop ensures thyroid hormone levels remain within a narrow physiological range.

In fetuses and infants, thyroid hormones are vital for neurological development, and deficiency can lead to cretinism, a preventable cause of intellectual disability (Bernal, 2022; Patel *et al*., 2011).

The normal thyroid function is a complex, yet highly regulated, system involving hormone synthesis, secretion, and systemic action. Disruption in any component of this system can lead to significant metabolic and systemic disturbances, as seen in conditions like hyperthyroidism, hypothyroidism, and thyroiditis. Understanding the normal physiology of the thyroid gland is essential for diagnosing and managing its associated disorders.

2.2 Autoimmune Basis of Hyperthyroidism

Graves' disease is an organ-specific autoimmune disorder. It primarily targets the thyroid gland through autoreactive B cells that produce antibodies against the TSH receptor. These antibodies bind to the receptor and stimulate thyroid hormone production rather than inhibiting it. Thus, Graves' disease is distinguished by a stimulating autoimmune response rather than a destructive one (Lane *et al*., 2023). Autoimmune hyperthyroidism, primarily represented by Graves' disease, is the most common cause of hyperthyroidism globally and is classically characterized by the presence of autoantibodies that target components of the thyroid gland (Kyritsi and Kanaka-Gantenbein, 2020). It is the archetype of a Type V hypersensitivity reaction, a subtype of hypersensitivity where autoantibodies stimulate rather than destroy, leading to overactivity of the target organ—in this case, the thyroid gland.

Immune Dysregulation and Loss of Tolerance

The pathogenesis of autoimmune hyperthyroidism begins with the loss of immune tolerance to self-antigens expressed by thyroid follicular cells, particularly the thyrotropin receptor (TSHR). In genetically predisposed individuals, T cells fail to recognize TSHR as "self", leading to activation of autoreactive B cells and production of thyroid-stimulating immunoglobulins (TSIs). These autoantibodies mimic the action of TSH by binding to the TSH receptor and stimulating thyroid hormone synthesis and secretion, resulting in elevated levels of free T3 and T4 despite suppressed TSH levels (Paluchamy, 2021).

Role of T Helper Cells and Cytokine Profiles

Immunopathologically, CD4+ T helper cells (particularly Th1 and Th17) play central roles in driving the autoimmune process. Th1 cells secrete interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), promoting antigen presentation and local inflammation, while Th17 cells produce IL-17, which has been implicated in tissue remodeling and chronicity of inflammation (Paroli *et al*., 2022). Meanwhile, regulatory T cells (Tregs), which normally maintain peripheral tolerance, are functionally impaired or numerically reduced in patients with Graves' disease (Kustrimovic *et al*., 2023).

Genetic and Environmental Triggers

Genetic susceptibility plays a substantial role in the autoimmune basis of hyperthyroidism. The HLA-DR3 allele, CTLA4, and PTPN22 gene polymorphisms are consistently associated with increased risk of Graves' disease (Grixti *et al*., 2024; Touil *et al*., 2023). However, genetic predisposition alone is insufficient; environmental triggers such as viral infections, stress, iodine repletion, smoking, and female sex hormones contribute to disease onset (Touil *et al*., 2023; Paluchamy, 2021; Ferrari *et al*., 2017).

Autoantibodies in Hyperthyroidism

The hallmark of the autoimmune nature of Graves' disease is the presence of TSH receptor autoantibodies (TRAbs), particularly stimulating TRAbs. These autoantibodies are functional, meaning they actively stimulate the TSH receptor, in contrast to blocking or neutral TRAbs. Their detection in serum is not only diagnostic but also prognostic, as levels correlate with disease activity and likelihood of relapse (Yang and Chen, 2025; Diana *et al*., 2018). Other thyroid-specific autoantibodies such as anti-thyroglobulin (TgAb) and anti-thyroid peroxidase (TPOAb) are also frequently found, reflecting broader autoimmune dysregulation. Although they are more common in Hashimoto's thyroiditis, their presence in Graves' disease reinforces the autoimmune basis of the disorder (Dwivedi *et al*., 2023).

Organ-Specific Autoimmunity

Graves' disease is an organ-specific autoimmune disorder, primarily targeting the thyroid, unlike systemic autoimmune diseases such as lupus. However, extra-thyroidal manifestations such as Graves' orbitopathy, dermopathy, and acropachy occur due to shared autoantigen expression in fibroblasts and other tissues, often mediated by the same autoantibodies (Toro-Tobon and Stan, 2024; Diana *et al*., 2021).

Immunopathology of Graves' Disease

Hyperthyroidism, particularly in the context of Graves' disease, is a classic example of an organ-specific autoimmune disorder. Its immunopathology involves a complex interplay between genetic predisposition, immune dysregulation, environmental factors, and the production of specific autoantibodies, which ultimately result in excessive thyroid hormone production.

1. Loss of Immune Tolerance

In genetically susceptible individuals, immune tolerance to self-antigens, especially the thyroid-stimulating hormone receptor (TSHR), is lost. Autoreactive CD4+ T helper cells that should be eliminated during thymic development escape into peripheral circulation and get activated by antigen-presenting cells (APCs) that present thyroid antigens. This breach in tolerance facilitates B cell activation and subsequent autoantibody production (Chopp *et al*., 2023; Sun *et al*., 2023).

2. Autoantibody Production

The hallmark of Graves' disease is the development of thyroid-stimulating immunoglobulins (TSI), a subset of TSH receptor antibodies (TRAb). These TSIs bind to and stimulate the TSHR on thyroid follicular cells, leading to:

- Unregulated synthesis and release of thyroxine (T4) and triiodothyronine (T3),
- Thyroid follicular cell proliferation (resulting in goiter),
- Suppression of pituitary TSH through negative feedback (Pirahanchi *et al*., 2023; Shahid *et al*., 2023).

Unlike TSH, which is subject to physiological regulation, TSIs act continuously, driving thyroid overactivity.

3. Role of T Cells and Cytokines

Activated Th2-type CD4+ T cells support B cell maturation into plasma cells that produce TSIs. However, Th1 responses also contribute to the disease by producing pro-inflammatory cytokines such as:

- Interferon-gamma (IFN-γ)
- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-6 (IL-6)

These cytokines promote inflammation and further stimulate the autoimmune response (Ferrari *et al*., 2023; Chao-Wen *et al*., 2021).

4. Genetic Predisposition

Genetic susceptibility to Graves' disease is well documented, involving loci such as:

- HLA-DR3
- CTLA-4
- PTPN22
- CD40 gene polymorphisms

These genes influence antigen presentation, T cell signaling, and immune checkpoint pathways, contributing to autoimmunity (Vargas-Uricoechea, 2023; Khan *et al*., 2021).

5. Environmental and Epigenetic Triggers

Factors such as smoking, stress, infections (e.g., Yersinia enterocolitica), and excessive iodine intake have been associated with disease onset. These triggers may induce epigenetic changes that dysregulate immune function (Xie *et al*., 2016).

6. Histological Changes in the Thyroid

Histologically, the thyroid gland in Graves' disease shows:

- Diffuse follicular hyperplasia,
- Lymphocytic infiltration (mainly CD4+ and CD8+ T cells),
- Scant colloid in hyperactive follicles,
- Fibrosis in long-standing cases.

These findings reflect sustained immune-mediated thyroid stimulation (Akamizu and Amino, 2017; Khan *et al*., 2022).

7. Orbital Autoimmunity (Thyroid Eye Disease)

In some patients, TSIs cross-react with orbital fibroblasts expressing TSHR and IGF-1 receptors, leading to thyroid eye disease (TED). This extrathyroidal manifestation is characterized by inflammation, edema, and tissue remodeling in the orbit (Girnita *et al*., 2022).

The immunopathology of Graves' disease is primarily mediated by the breakdown of central and peripheral tolerance. Central tolerance failure in the thymus allows autoreactive T cells to escape deletion, while peripheral tolerance breakdown facilitates the activation of these T cells in peripheral tissues (Han *et al*., 2025). Understanding these mechanisms is crucial for accurate diagnosis and targeted therapy.

2.5 Physical and Laboratory Diagnosis of Hyperthyroidism and Graves' Disease

2.5.1 Physical Examination

Graves' disease can cause an enlarged thyroid gland, rapid heart rate, agitation, tremor, fast reflexes, and possibly moist, smooth skin. These are all signs of hyperthyroidism, but they do not confirm that you have Graves' disease.

A goiter suggests that you may have Graves' disease, but does not rule out another thyroid condition. Ophthalmopathy or dermopathy are more common with Graves' disease than with other causes of hyperthyroidism.

The combination of goiter, ophthalmopathy, dermatopathy is suggestive of Graves' disease.

Graves' disease may present clinically with one or more of these characteristic signs:

- Rapid heartbeat (80%)
- Diffuse palpable goiter with audible bruit (70%)
- Tremor (40%)
- Exophthalmus (protuberance of one or both eyes), periorbital edema (25%)
- Fatigue (70%), weight loss (60%) with increased appetite in young people and poor appetite in the elderly, and other symptoms of hyperthyroidism thyroxicosis
- Heat intolerance (55%)
- Tremulousness (55%)
- Palpitations (50%) (Retrieved from: https://www.findzebra.com/details/jrZ4E8v-graves-disease?q=cowden+syndrome (on 21 June 2025).

LABORATORY INVESTIGATIONS

1. Thyroid Function Tests (TFTs)

This is one of the first tests for the diagnosis of Graves' disease.

- Thyroid – stimulating Hormone (TSH) test:

The first test for diagnosis of hyperthyroidism is the thyroid-stimulating hormone (TSH) test. Thyroid-stimulating hormone (TSH) is produced by the pituitary gland situated at the base of the brain. It acts as a chemical messenger, telling the thyroid gland when to start producing thyroid hormones.

When thyroid hormone levels are low, more TSH is produced to stimulate production. When levels are normal, the pituitary gland stops producing TSH. The TSH test measures how much or how little TSH there is in the bloodstream.

- Free Thyroxine (Free T4) and Free Triiodothyronine (Free T3) Tests:

Thyroxine (T4) is one of two hormones produced by the thyroid gland. It is an inactive thyroid hormone that freely circulates in the bloodstream, ready to be converted to the active form called T3. There are two types of T4: bound T4 (which is attached to proteins that prevent it from entering tissues) and free T4 (which is not attached to proteins and can enter tissues freely).

When measuring T4, the lab will look at two different values:

- **Total T4**: The total amount of T4 (bound and unbound) in your bloodstream
- **Free T4**: The total amount of unbound T4 available for use in tissues

  Free T4 is arguably more important to measure because it is the type that will be more active once converted to T3.

  Triiodothyronine (T3) is the active thyroid hormone converted from T4. As with T4, there is both bound and free T3. (Shahid *et al*., 2023; Ogbodo *et al*., 2019).

If TSH is suppressed, one needs to order Free T4 (FT4) and Free T3 (FT3). If free hormone assays are not available, total T4 (Thyroxine) and total T3 (Triiodothyronine) can be ordered. Suppressed TSH with high FT4 or FT3 or both will confirm the diagnosis of hyperthyroidism. In subclinical hyperthyroidism, only TSH is suppressed, but FT4 and FT3 are normal (Praw and Brent, 2023; Koulouri and Gurnell, 2013).

2. Thyroid Autoantibody Tests

Some thyroid diseases like Hashimoto's thyroiditis and Graves' disease are autoimmune disorders. These are diseases in which the immune system targets and attacks normal thyroid cells.

There are three common antibodies associated with autoimmune thyroid disease.

- Thyroid Peroxide Antibody (TPOAb): The type of antibody is detected in 90% of people with Hashimoto's. For those with Graves' disease, the frequency of TBOAb has been varied with estimates of 50% to 90%. (Esfandiari and Papaleontiou, 2017). A high TPOAb is also seen after childbirth in people postpartum thyroiditis.
- **Thyroid-stimulating hormone receptor antibodies (TRAb)**: These are found in up to 100% of Graves' disease cases, depending on the method used to detect the antibodies. TRAb may also be found in people with Hashimoto's disease but in significantly fewer cases (Ruan *et al*., 2024).
- **Anti - Thyroglobulin antibodies (TgAb)**: These are produced by your body in response to the presence of Tg. One in four people with thyroid cancer will have elevated TgAb. It is also detected in 60% to 80% of people with Hashimoto's and between 50% to 60% of those with Graves' disease (Shomon, 2025).

3. Thyroid Binding Proteins

These blood tests measure the amount of proteins that can bind to T3 and T4. They can help determine the cause of a thyroid problem if your thyroid gland is functioning normally.

The tests include

- **Thyroid binding globulin (TBG)**: This is the specific protein that binds to T4 and T3.
- **T3 resin uptake (T3RU)**: This calculates the percentage of TBG in the blood.

4. Radioactive Iodine Uptake Test

Because T4 contains iodine, the thyroid gland must pull a large amount of iodine from the bloodstream in order to make an appropriate amount of T4. The thyroid has developed a very active mechanism for doing this. Therefore, this activity can be measured by having an individual swallow a small amount of iodine, which is radioactive. The radioactivity allows the doctor to track where the iodine goes. By measuring the amount of radioactivity that is taken up by the thyroid gland (radioactive iodine uptake, RAIU), doctors may determine whether the gland is functioning normally. A very high RAIU is seen in individuals whose thyroid gland is overactive (hyperthyroidism), while a low RAIU is seen when the thyroid gland is underactive (hypothyroidism). In addition to the radioactive iodine uptake, a thyroid scan may be obtained, which shows a picture of the thyroid gland and reveals what parts of the thyroid have taken up the iodine.

In Graves' disease, the uptake will be high and diffuse whereas, in a toxic nodule, the uptake will be focal known as a hot nodule. Toxic multinodular goiter will have heterogeneous uptake. The radioactive iodine uptake in subacute or silent thyroiditis, factitious hyperthyroidism, and recent iodine load will be low (Giovanella et al., 2022; Pokhrel and Bhusal, 2023).

5. Thyroid Ultrasonogram with Doppler

This is an imaging modality to assess the thyroid gland's structure and vascularity. It's useful during pregnancy or when RAIU is contraindicated.

- Increased vascularity: The thyroid gland in Graves' disease is usually hypervascular.
- Nodules: The presence of nodules may suggest toxic multinodular goiter or thyroid adenoma.

Other Tests

- Full Blood Count (FBC)

This may show anemia or leukopenia

- Liver Function Test (LFTs)

This provides access to hepatic function, this is because hyperthyroidism can affect liver enzymes.

- Calcium Levels:

Hypercalcemia can occur due to increased bone turnover

- T3/T4 ratio greater than20 (ng/mcg) or FT3/FT4 ratio:

Ratio greater than 0.3 (SI unit) suggests Graves' disease and can be used to differentiate Graves' disease from thyroiditis induced thyrotoxicosis.

Management Strategies

Graves' disease is an autoimmune disorder characterized by the overproduction of thyroid hormones (hyperthyroidism), driven by stimulating autoantibodies against the thyrotropin (TSH) receptor. Its management aims to restore euthyroidism, prevent complications, and improve quality of life. Treatment modalities include antithyroid drugs, radioactive iodine therapy, thyroidectomy, and supportive care. Each strategy has unique indications, benefits, and limitations depending on the patient's profile and disease severity.

1. Antithyroid Drugs (ATDs)

Antithyroid medications, particularly thionamides, are often the first line of treatment, especially in younger patients and those with mild disease.

- Methimazole (MMI) and propylthiouracil (PTU) inhibit thyroid hormone synthesis by blocking thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin (Awosika *et al*., 2023).
- PTU also inhibits peripheral conversion of T4 to T3, making it preferable in thyroid storm or first trimester of pregnancy.
- Duration of therapy typically lasts 12–18 months, with periodic monitoring of thyroid function tests (TFTs) to assess response.

2. Radioactive Iodine (RAI) Therapy

RAI therapy using Iodine-131 is a definitive and non-surgical method to ablate thyroid tissue.

- It's administered orally and selectively taken up by the thyroid, leading to gradual gland destruction and decline in hormone production.
- RAI is generally contraindicated in pregnancy and breastfeeding, and used cautiously in active Graves' orbitopathy (Campennì *et al*., 2023; Padda and Nguyen, 2023).

Approximately 70–90% of patients become hypothyroid within 3–6 months post-RAI and require lifelong levothyroxine replacement.

3. Thyroidectomy

Surgical intervention is preferred in cases of.

- Large goiters
- Suspicion of malignancy
- Severe ophthalmopathy
- Patients desiring pregnancy within 6 months
- Failure or intolerance to ATDs or RAI

Total or near-total thyroidectomy offers rapid resolution of hyperthyroidism, though it requires experienced surgical hands to minimize complications like hypoparathyroidism and recurrent laryngeal nerve injury (Smithson *et al*., 2019).

Patients require lifelong thyroid hormone replacement therapy post-surgery.

4. Management of Graves' Orbitopathy

Graves' orbitopathy (GO), an inflammatory condition of the orbit, may occur independently or with hyperthyroidism. Its management involves:

- Smoking cessation (a major risk factor)
- Selenium supplementation for mild GO
- Intravenous glucocorticoids for moderate to severe GO
- Teprotumumab, an IGF-1 receptor antagonist, approved for active moderate-to-severe orbitopathy (Fox *et al*., 2025)

5. Beta-Adrenergic Blockers (Symptomatic Management)

Beta-blockers like propranolol are used for symptom control by:

- Reducing tachycardia
- Alleviating tremors
- Controlling heat intolerance and anxiety

They do not address the underlying autoimmune process, but significantly improve quality of life during the acute phase.

6. Long-Term Monitoring and Patient Education

Even after euthyroidism is achieved:

- Periodic monitoring of TSH, T3, and T4 is essential.
- Patients should be educated about symptoms of recurrence, medication adherence, and importance of follow-up.
- Screening for other autoimmune diseases (e.g., type 1 diabetes, celiac disease) may be warranted.

Graves' disease requires a multifaceted and individualized treatment approach. Factors influencing management choices include patient age, severity of disease, comorbidities, pregnancy status, and presence of orbitopathy. Current advances, such as biologics for orbitopathy, reflect ongoing improvements in understanding and managing this complex autoimmune disorder.

CONCLUSION

Hyperthyroidism, particularly in the contest of Graves' disease, exemplifies a classic model of Type V hypersensitivity, where stimulating autoantibodies – specifically thyroid – stimulating immunoglobulins (TSI), mimics the action of the thyroid – stimulating hormone (TSH), leading to unregulated thyroid hormone production. This autoimmune stimulation underscores the intricate interface between endocrine regulation and immune system dysfunction. As we look through the immunopathology, Graves' disease reveals how a breakdown in immune tolerance through mechanisms such as; genetic susceptibility, environmental triggers, and loss of regulatory T cell control, all these leads to the production of autoantibodies which targets the TSH receptors. The result of this is persistent thyrotoxicosis with multi system involvement ranging from cardiovascular and metabolic effects to dermatologic and ophthalmologic complications. Effective laboratory diagnosis relies on a combination of thyroid function tests (TSH, free T4, free T3), autoantibody screening (TSI, TRAb), and functional imaging (RAIU, ultrasound Doppler), proving the basis for accurate clinical classification and timely intervention. Therapeutic strategies, whether pharmacological (methimazole, PTU), radioactive iodine ablation, or thyroidectomy, must be carefully designed based on disease severity, patients age, comorbidities and reproductive status.

Additionally, managing associated features such as Graves' orbitiopathy requires a multidisciplinary approach and emphasizes the importance of early and precise treatment. In conclusion, understanding hyperthyroidism as a Type V hypersensitivity reaction not only enhances our comprehension of its immune – driven pathogenesis but also reinforces the need for early diagnosis, targeted therapy, and patient centered care. As research advances, continued exploration of immunological mechanisms holds promise for more precise, less invasive and durable treatment in autoimmune thyroid disease.

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