



GRAVES' DISEASE AND THE MANIFESTATIONS OF THYROTOXICOSIS

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ABSTRACT

Graves' disease (GD) is an autoimmune disorder characterized by hyperthyroidism and various systemic manifestations, including thyroid eye disease (TED) and, less commonly, dermatopathy. This chapter provides an in-depth review of GD, covering its history, epidemiology, risk factors, and the molecular mechanisms underlying autoimmune hyperthyroidism. Emphasis is placed on emerging insights into the genetic, environmental, and immunological factors contributing to GD's multifactorial pathogenesis. The chapter also explores the pathogenic role of TSH receptor antibodies and their significance in diagnosis and treatment, alongside key clinical features of thyrotoxicosis.

INTRODUCTION

Graves' disease (GD) is an autoimmune form of hyperthyroidism characterized by multisystemic manifestations of thyrotoxicosis and, in some cases, extrathyroidal manifestations of thyroid autoimmunity including, frequently, thyroid eye disease (TED) and rarely pretibial dermatopathy. There are therefore diverse phenotypic presentations of thyroid autoimmunity, and patients do not necessarily present with thyrotoxicosis as the main manifestation of their

autoimmune phenomena. Autoimmune thyroid disease (AITD) typically includes two major categories of manifestations. Those specific to GD, and caused by the autoimmunity per se, including goiter, TED, and dermatopathy (TED and dermatopathy are discussed in the chapter "Graves' disease: Complications"). The second set of problems is caused by the excess thyroid hormone and its widespread disturbance in metabolism. These thyrotoxic manifestations do not differ from those induced by any other cause of excess of thyroid hormone. Alternative etiologies of thyrotoxicosis are described in other chapters.

HISTORY

The triad of goiter, tachycardia, and ophthalmopathy was independently described by Caleb Parry (1755-1822) and Karl A. Von Basedow (1799 - 1854), but it is the description by the Irish physician Robert James Graves (1796 - 1853) (Figure 1) (1) that is the source of the acronym in the English literature, Graves' disease (GD). However, in many countries, the term Morbus Basedow is widely used to describe autoimmune hyperthyroidism. The autoimmunity reflected in GD is related to antibodies directed against the TSH receptor (TSH-R) expressed at the basolateral membrane of thyroid follicular cells. Initially, serum factors that were thought to be a modified TSH molecule and produced exophthalmos

in experimental animal models were given the eponym exophthalmos producing substance (2, 3). Later, Adams et al. identified a factor in human serum that could stimulate the release of thyroid hormone in guinea pigs and a human subject (Figure 2) (4, 5). Because of the time course of its action being longer than TSH, this material was named Long-Acting Thyroid Stimulator, or LATS. Subsequent studies better characterized this substance as an immune

gamma globulin that acts on a thyroid antigen, and mimics the action of the natural thyroid stimulator, TSH. Nearly three decades later, the antigen to which this antibody was directed was identified as the TSH-R (6, 7). Over the past four decades, there has been improved understanding of the accurate identification, quantitation, and pathophysiologic importance of the thyroid receptor antibodies (8-10), as will be further detailed throughout this chapter.



Figure 1. Robert James Graves, Statue. Marble statue of Robert James Graves, former president (1843–1849) of the Royal College of Physicians of Ireland. The statue was commissioned by John Henry Foley who died before completing it. Graves Hall, the Royal College of Physicians of Ireland, No. 6, Kildare Street, Dublin, Ireland. Photographer: Osama Shukir Muhammed Amin FRCP(Glasgow). Copyrighted work available under Creative Commons Attribution only license CC BY 4.0.

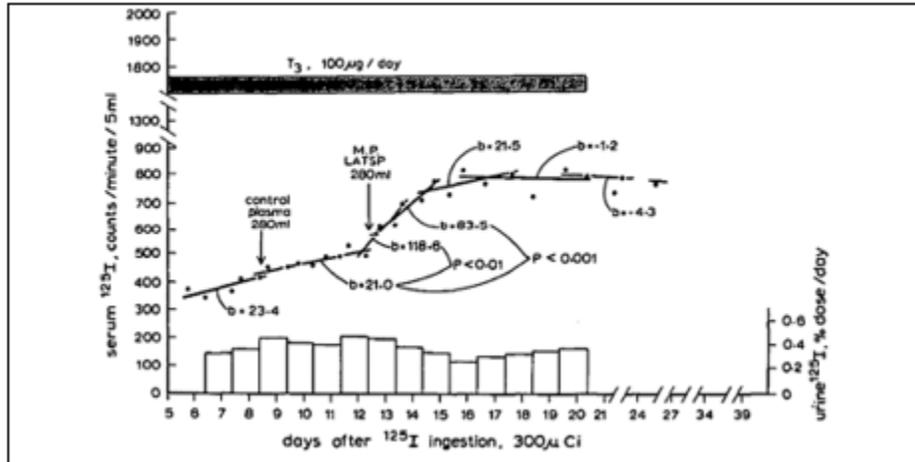


Figure 2. Stimulation of thyroid hormone secretion by LATS-P. The subject's thyroid iodine was labeled by administration of I^{131} , and serial observations were made on the appearance of I^{131} -labeled hormone in blood (Y axis) over one month (X axis). An infusion of 280 ml control plasma had no effect, but 280 ml plasma from a patient with Graves' disease caused a marked stimulation of secretion of hormone from the thyroid. (Adapted from: D.D. Adams et al., *J. Clin. Endocrinol. Metab.*, 39:826, 1974).

EPIDEMIOLOGY

GD has an estimated incidence of 30 to 80 cases per 100,000 persons per year and occurs more frequently in the white population while it appears to be less frequent in the Asian and Sub-Saharan African populations (3.8 to 5, and 0.7 to 51 cases per 1000,000 persons per year, respectively) (11-13). Female (lifetime risk 3%, eight-folds greater than in men) and middle-aged individuals (30 to 50 years of age) are at higher risk. The manifestations of disease tend to be more pronounced in patients younger than 65 years, while older patients tend to have an abbreviated presentation, with mainly cardiac manifestations (14, 15). Around 50% of patients with GD have a family history of autoimmune thyroid disease (AITD). Aside from the infrequent occurrence of postnatal thyrotoxicosis due to maternal antibodies, the incidence of spontaneous GD in children before the age of ten is unusual, but the incidence climbs with each decade until about age 60 (16-20).

RISK FACTORS

GD is a consequence of autoimmunity against the TSH-R. The next question revolves around the trigger for this specific autoimmunity. Contemporary understanding is that a multi-factorial process allows thyroid self-reactivity to occur. While our immune system is designed to prevent self-reactivity, to some extent, exceptionally low levels of self-reactivity are normally present (21). Sex, environmental, immunologic, and genetic factors interact to augment this immune response to a degree that predisposes to clinically manifest autoimmunity (Figure 3). Several such factors have been identified with some certainty, and others have been suggested.

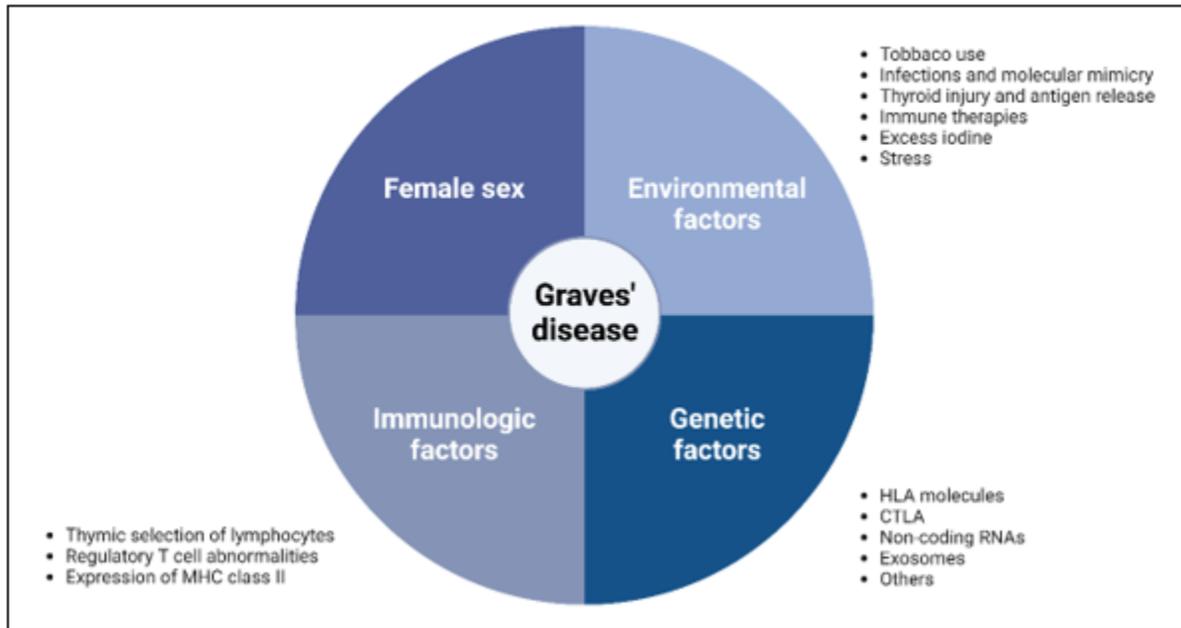


Figure 3. Risk factors for Graves' disease. MHC: Major histocompatibility complex; HLA: Human leukocyte antigen; CTLA: Cytotoxic T-lymphocyte-associated protein; RNA: Ribonucleic acid. (Created with Biorender.com)

Sex

The clearest association with any autoimmune condition is female sex, which carries a 10-20-fold risk compared to men (22). Although, the mechanism behind the increased incidence of autoimmune conditions in female is not fully understood, several factors leading to greater autoreactivity towards the thyroid have been proposed. Polymorphisms in the estrogen receptor genes might be at least partially responsive for the increased susceptibility of female to developing GD (23). In addition, marked fluctuations in leptin and other hormonal secretion patterns throughout the different endocrine states during the female lifespan (Including puberty, pregnancy, and menopause) have been linked with changes in the regulation of the innate and adaptive immune systems, and disbalance between pro and anti-inflammatory states, which altogether increase the risk of developing autoimmune diseases (22, 24).

The post-partum period is associated with a higher risk of developing GD. This relates to the transition from a

skewed T helper 2 (Th2) cell response that suppresses the immune response and antibody production (Including TSH-R antibodies) during pregnancy, to a post-partum state in which the proinflammatory Th1 cell response returns to normal (25). Furthermore, it has been shown that fetal cells from male infants can persist in the maternal circulation for up to 20 years (fetal micro chimerism). These cells have been found in frozen thyroid tissue specimens from patients with GD and thyroid nodules, and it is hypothesized that they could modulate AITD by induction of immune response or development of a graft-versus-host immune response to the mother (26).

Environmental Factors

Considerable information has accumulated about factors in the environment that can induce GD. Cigarette smoking increases the risk of GD and complicates its extra thyroidal manifestations through direct cell damage, downregulation of the innate immune system, and induction of epigenetic changes

(27-31). Conversely, moderate alcohol use and obesity seem to decrease the risk of developing the disease (32), while physical activity seems neutral in that respect (33). Other factors include:

INFECTIONS AND MOLECULAR MIMICRY

A persistent theory on the etiology of autoimmune diseases is that exposure to a particular peptide epitope in an environmental antigen might lead to immune reactivity to an amino acid sequence identical to that present in a human antigen such as the TSH-R, thyroperoxidase (TPO), or thyroglobulin (Tg). Through this molecular mimicry, exposure to a virus or bacteria could produce heightened immune reactivity towards these autoantigens. This sequence is believed to play a role in rheumatic fever and glomerulonephritis. There is some evidence that proteins present in a common intestinal parasite, *Yersinia enterocolitica*, may induce antibody reactivity to the TSH-R (34-36). While a clear association has not been established, a higher proportion of patients with GD have been infected with this bacteria than people without the disease (34) and exposure to the bacteria can induce TSH-R antibodies (TRAb) (35).

There is also evidence that autoimmunity to the thyroid can be induced by infection with the human T-lymphotropic virus type 1 (HTLV-1), which causes lymphocytic leukemia (37). Whether this is due to molecular mimicry of the virus, viral damage to the thyroid, or stimulation through another mechanism such as cytokine secretion, remains uncertain. In addition, it has been suggested that *Helicobacter pylori* (*H. pylori*) antigens may be involved in the development of AITD, and one study reported that up to 85% of patients with autoimmune atrophic thyroiditis have *H. pylori* infections (38). While molecular mimicry remains a tantalizing explanation, the factual evidence for its role in the pathogenesis of GD is minimal.

THYROID INJURY AND ANTIGEN RELEASE

It is accepted that certain types of injury to the thyroid are followed by the development of thyroid autoimmunity, including GD. In fact, this is one of the few proven causes of GD. The release of thyroid antigens following destruction of thyroid tissue may add a significant stimulation to a latent low level of thyroid autoimmunity, causing the development of GD. Radiation to the thyroid has been associated with a subsequent higher incidence of positive thyroid antibody tests (39), and an increased risk of GD, Hashimoto's thyroiditis, and TED (40, 41). Around 1% of patients with autonomous thyroid nodules who undergo radioactive iodide treatment or ethanol injection can subsequently develop GD (42, 43), with a tenfold higher risk if anti-TPO antibodies are present (44). Whether viral injury, as in the case of HTLV-1 and SARS-CoV (45, 46), plays a similar role in human AITD is uncertain. However, Covid-19 disease caused by the SARS-CoV has been associated with higher risk of developing subacute thyroiditis, GD, and TED.

IMMUNE THERAPIES

Administration of cytokines such as INF- α , IL-2, and GM-CSF can augment AITD, or in some cases appear to induce it *de novo* (47-49). Alemtuzumab therapy, used for depletion of circulating lymphocytes in the therapy of multiple sclerosis is followed by development of GD in a third of such treated patient within 6 months of recovery from T cell depletion (50). This and other immunosuppressive treatments may deviate the immune system from a Th1 to a Th2 type of response, reducing the number of regulatory T cells or altering the balance between T helper 17 (Th17) cells and regulatory T cells, and leading to overexpression of pro-inflammatory cytokines IL-17, IL-22, IL-23R, and IL-32 that are commonly seen in patients with AITD (51-55). In addition, treatment with INF- α for chronic hepatitis or INF- β for multiple sclerosis has also been suggested to cause AITD and destructive thyroiditis, especially in females (RR: 4.4) and people with pre-existing anti-TPO antibodies (RR: 3.9) (56); however, a definitive association has not been established (57). In addition, while immune check

point inhibitors can commonly induce hypothyroidism and thyrotoxicosis due to destructive thyroiditis (58), in rare instances they can also induce GD (59, 60).

EXCESS IODINE

Excess iodide can induce hyperthyroidism in patients with multinodular goiter (61, 62), a phenomenon known as “Jod Basedow”. Presumably, autonomous nodules in the goiter are in a subclinical state and unable to produce an excess of thyroid hormones as their synthesis is limited by iodide supply; yet, when the iodine supply is high, the autonomous nodules produce an excess of hormone. Well studied epidemics of iodide-induced thyrotoxicosis occurred for example in Tasmania, Denmark, and India after the introduction of salt iodization and were clearly associated with multinodular goiters rather than typical GD (63-66). In addition, increased iodine intake can actually augment thyroid autoimmunity through other mechanisms such as heavy iodination of Tg which appears to increase immunogenicity in animal studies (67), or hypothetical induction of follicular thyroid cell injury with secondary liberation of thyroid related antigens (68, 69). On the other hand, the addition of 2 - 6 mg per day of iodide to the intake of most patients with GD causes a dramatic, but probably temporary, reduction in hormone release, a phenomenon referred to as Plummer effect (70-73). Overall, whether an excess of iodine can induce true GD and autoimmunity remains unknown.

STRESS

The incidence of GD increased in Denmark during World War II (74), and in Serbia during the civil war in the former Yugoslavia (75). In general, studies have shown mixed results; however, meta-analysis suggests physical trauma and psychologic stress are possible environmental triggers of GD (76). Some authors indicated that patients with GD had suffered on average more stressful episodes than control subjects, but other similar studies failed to show this relationship (77-80). Stress induces a variety of

physiologic responses including anxiety, tachycardia, and restlessness, among others, which are not unlike symptoms of GD. Its role remains enigmatic in causation of GD to this date. Theoretically, stress might cause activation of the adrenal cortex or the sympathetic nervous system which might cause stimulation of thyroid secretion, as has been shown in experimental animals (81). Other specific stressors have been reported. Aggressive weight loss programs that involve using exogenous thyroid hormone have been reported to induce GD (82).

Immunologic Factors

THYMIC SELECTION OF LYMPHOCYTES

Lymphocytes develop from precursors present in the bone marrow that undergo progressive maturation and selection in the thymus. Lymphocytes which fail to recognize endogenous human leukocyte antigens (HLA) undergo negative selection, as do those which strongly react with endogenous epitopes presented by HLA molecules (83, 84). In this process, more than 95% of all lymphocytes undergo apoptosis. As with other human molecules, thyroid molecules like the sodium iodine symporter (NIS), TSH-R, TPO, and Tg-RNAs are presented as immunoreactive peptides in the human thymus as part of the lymphocyte selection process (85, 86). Pre-T lymphocytes are thus educated in the thymus to recognize thyroid-related epitopes, and to generate self-tolerance against them. Expression of these thyroid antigens in the fetal thymus is under control of the AIRE gene, and absence of this gene leads to polyglandular autoimmune syndrome type 1 whose hallmarks are adrenal insufficiency, hypoparathyroidism and mucocandidiasis. In Down's syndrome, despite having 3 copies of the AIRE gene, expression of thyroid antigens in the thymus is reduced, and this is thought to cause the elevated incidence of autoimmunity in these patients (87). Clearly the thymic selection process is imperfect, in a developmental process designed to provide the maximum repertoire of lymphocytes, some lymphocytes which weakly

recognize autologous thyroid antigens do persist in the circulation, and can be found in normal patients and those with AITD (Table 1) (85).

REGULATORY T CELL ABNORMALITIES

Every T cell-mediated response is tempered by the interaction of effector and regulatory cells (88). Thus, a disproportionately low number or diminished function of regulatory T cells is, in part, responsible for the development of autoimmunity (89, 90). Several studies have demonstrated abnormalities in T cell regulation in GD with conflicting results. Some groups have proposed that patients with GD have a lower proportion of regulatory T cells (91-95), while others report a normal or high number of T regulatory cells but with impaired immune suppressive function (91, 96-100). In addition, Marazuela *et al.* reported a high proportion of defective intrathyroidal regulatory T cells in patients with autoimmune thyroiditis (101). Gangi *et al.* found that administration of GM-CSF induced development of regulatory T cells capable of suppressing immunity to Tg in mice (102). Molteni *et al.* reported that CD8 T cells can induce anergy in TSH-R specific CD4 T cell clones to prevent thyroid

related auto reactivity (103) and, ultimately, Vaidya *et al.* reported higher numbers of naïve activated T cells and lower memory T cells in patients with TED (104). Overall, while there remains some uncertainty, decreased T regulation due to low cell counts or impaired function is involved in the development of GD.

EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) CLASS II

Exposure of thyroid epithelial cells to interferon, presumably secreted from infiltrating lymphocytes or other immune cells, can lead to the expression of MHC class II molecules on the thyroid cell surface (105, 106). Expression of these molecules allows the thyroid epithelial cell to function as a weak antigen presenting cell (APC) (107, 108). Culture of human thyroid cells from patients with GD in vitro shows that the expression of MHC class II molecules expression disappears (109), as it does when the cells are transplanted into nude mice (110). This is a compelling argument indicating that MHC class II expression on GD thyroid cells is secondary rather than primary event.

Table 1. Possible Factors in the Immunological Etiology of Graves' Disease

<p>Persistence of some autoreactive T cells and B cells (failure of negative selection)</p> <p>Genetic polymorphisms</p> <p>Re-exposure to antigens secondary to thyroid cell damage</p> <p>Reduced or dysfunctional regulatory T cells</p> <p>Cross-reacting epitopes on environmental and thyroid antigens</p> <p>Inappropriate HLA-DR expression</p> <p>Mutated T or B cell clones</p> <p>Activation of T cells by polyclonal stimuli</p> <p>Stimulation of the thyroid by cytokines</p>

HLA: Human leukocyte antigen; **CTLA:** Cytotoxic T-lymphocyte-associated protein

Genetic Factors

The increased incidence of GD in certain families and in identical twins has for decades indicated a powerful

genetic influence on disease development (111-113). Studies of large samples of pairs of twins suggest that the genetic factors account for 73-79% of the liability to have positive TSH-R antibodies and to develop GD,

whereas environmental factors account presumably for the remainder (113, 114). Adjusting for covariates (age, TSH and others), the estimate for genetic influence on serum anti-TPO and anti TG antibodies was also found to be between 60 – 80%. This inheritance turns out to be polygenic. Rather than inheriting one gene which, in a dominant fashion, would induce GD, individuals inherit many different genetic polymorphisms which are conducive to the development of AITD (115-117).

HUMAN LEUKOCYTE ANTIGEN (HLA) MOLECULES

HLA molecules are expressed in different isotypes. There are between 50 and 100 different HLA-DR molecules, and a much smaller number of HLA-DQ and HLA-DP molecules, all coded on chromosome 6, in the human genome (118). Of these, the HLA-DR are most abundantly expressed and most important. These molecules exist as dimers on the surface of antigen presenting cells. In the initiation of an immune response, the antigen presenting cell displays a specific epitope complexed in an HLA-DR. Recognition of this bi-molecular complex by the T cell receptor leads to stimulation of T cells. The amino acid sequences of the HLA-DR molecule determine the shape and affinity to the antigen presenting cleft (119). Thus, certain HLA-DR molecules are more efficient to present certain epitopes during the lymphocyte selection and maturation process in the thymus (84). Therefore, the inheritance of certain HLA genes, and the matching of the HLA-DR molecules with the structure of the TSH-R epitopes, or other thyroid related epitopes, plays a significant role in determining the development of AITD.

The first genetic factor to be associated with GD was HLA-B8 (120), a class I major histocompatibility component (MHC). Subsequently, this relation was found to be more specifically significant with an MHC class II molecule, HLA-DR3 (117). Inheritance of this gene, expressed on the surface of antigen presenting cells, was found to confer up to 5.7-fold increased risk

of developing GD (121-123). Additional data demonstrated that the HLA molecules DQA1*0501, DRB1*0301, DQB1*0202, DQB1*0603, DQB1*0609, DQB1*0302, DQB1*0303 were also closely associated with higher risk of developing GD (124-128). In contrast, inheritance of HLA-DR beta 1*07, DQB1*0201, DQB1*0502, and DQB1*0602 appear to be protective (128, 129).

CYTOTOXIC T LYMPHOCYTE ASSOCIATED PROTEIN (CTLA)

When an immune reaction begins, the “first signal” is the recognition by the T cell receptor of an HLA molecule. If only one signal occurs, the T cell tends to be turned off or “anergized.” In order for a progressive immune response to occur, there must be a “second signal” provided by one of several adhesion molecules which exist on the antigen presenting cells (APCs) and T cells, and which tend to augment the affinity of the interaction (130). Of these, one of the most important is “B7”, which exists in two forms, B7.1 and B7.2, present on the surface of APCs. These molecules interact with their cognate receptors on the T cell, CD28 for B7.1 and CTLA-4 for B7.2. In many situations interaction between B7.1 and CD28 give a positive stimulus to growth of the T cell, whereas interaction of B7.1 with CTLA-4 provides a negative signal, suppressing autoimmunity (131). CTLA-4 exists as a gene with several isoforms, and the inheritance of some of them is associated with a higher incidence of GD (132-137), and increased production of anti-TPO and anti-Tg antibodies (138).

Interestingly, the HLA association suggests a relationship to GD specifically, since it has to do with the presentation of specific antigen epitopes, whereas the CTLA-4 polymorphism appears to be a general phenomenon, allowing one population group to have augmented lymphocyte proliferation, but is not specifically related to thyroid disease. These observations also fit with the concept that development of GD is mediated by a set of genes rather than one specific gene.

NON-CODING RNAs

The RNA transcripts that regulate genetic transcription and protein translation, but do not encode a specific protein themselves, are denominated non-coding RNAs (139). These regulators play a key role in immune activation, cellular proliferation, and cytokine production. Thus, their abnormal expression can halt the normal immune response, leading to autoimmunity. In the case of AITD, the understanding of non-coding RNAs associated with development of disease is still limited. Several transcripts have been proposed to play a role in the development of GD but their exact mechanism of action, and their utility for clinical care are unclear (140-142). Ongoing and future efforts aim to clarify the role of non-coding RNAs as well as their potential use as diagnostic biomarkers or therapeutic targets (143).

EXOSOMES

Exosomes are cell-secreted extracellular vesicles that function as biological carriers, and contain a series of molecules (i.e., cytokines, transduction factors, nucleic acids, proteins, and lipids) involved in processes of cellular communication such as antigen presentation and immune response activation. As in other autoimmune conditions, exosomes are presumed to play a role in AITD but research on their pathophysiologic role is still in the early stages (144, 145). Some authors have previously reported the presence of thyroid follicular cell derived exosomes containing TSH-R which are involved in the development of GD (146, 147). In addition, exosomes from patients with GD have been found to stimulate the production of proinflammatory cytokines such as IL-1, IL-6, and TNF- α (148). Furthermore, exosomes containing metalloproteinases and non-coding RNAs have been found in high proportions in patients with AITD and TED (149, 150).

OTHER FACTORS

Numerous other gene polymorphisms have been reported to be associated with GD. It is highly likely that these individual variants contribute a real but small increment in the risk of developing the disease. The initial genetic studies on the TSH-R showed mixed results on a potential association between specific polymorphisms and susceptibility to GD (151, 152). However, more recent studies have endorsed this association (153, 154). Certain genetic variants in TPO and Tg have also been associated with TED and AITD but their role in the development of disease is unclear (155-159). In addition, a vitamin D receptor polymorphisms have been associated with GD and other autoimmune conditions (160). Inheritance of specific genes coding for immunoglobulins may carry the same kind of risk. Additionally, several possible genes linked to GD or AITD have been found by linkage studies, including one recently described at a locus on chromosome 18q21 that is also associated with type 1 diabetes (161).

Other gene polymorphisms can lead to increased susceptibility to GD including CD40, CD25, and ZFAT (required for the correct functioning of B cells and other immune cells) (117, 162-164), CYP27B1 (involved in the activation of vitamin D) (165), IL-6 (166), IL-13 (167), IL-1 (168), IL-23R (169), TNF- α (170), protein tyrosine phosphatase-22 (PTPN22) (involved in inhibition of T cell activation) (171-174), Fc receptor-like protein 3 (FCRL3)(175-177), transforming growth factor beta1 (TGF- β 1) (178), interferon inducible helicase 1 (IFIH-1)(179). Other proposed genes associated with AITD include FOXP3, TBX21, HLX, BTNL2, NOTCH4, and CXCR4 (158, 180).

In conclusion, there are several genes harboring polymorphisms that appear to augment the possibility of developing immunity to thyroid gland protein components. These genetic alterations are likely to interplay with epigenetic aspects of DNA methylation and histone modifications (a phenomenon referred to as epistasis), along with environmental interventions, leading to the overall individual susceptibility to GD.

PATHOGENESIS

GD and Hashimoto's thyroiditis are strongly associated and, in fact, overlapping syndromes. They share immunological abnormalities, histological thyroid changes, and genetic predisposition. Patients can switch from one category to the other, depending upon the stage of their illness. For example, an individual might first present with hypothyroidism, thyroid enlargement and positive anti-thyroperoxidase (TPO) antibodies, and thus qualify as having Hashimoto's thyroiditis. At a later stage, this individual might become hyperthyroid with positive TSH-R autoantibodies and fit in the category of GD. Conversely, a patient with hyperthyroidism might have progressive destruction of the thyroid, or develop blocking antibodies to the TSH-R, and become hypothyroid. The aspects explaining the autoimmunity and pathologic changes at the thyroid level are explained in this section. Additional thyroidal pathophysiologic changes are explained later in the chapter.

The common feature of AITD is the immune reactivity, both humoral and cell-mediated, to specific thyroid antigens such as the TSH-R, TPO, and Tg (21, 181). Antibodies also exist, among others, to megalin (the thyroid cell Tg receptor) (182), to the thyroidal iodide symporter (183), and to components of eye muscle and fibroblasts in patients with thyroid eye disease (184) (Table 2). Up to 90% of patients with GD have anti-TPO antibodies, and up to 50% have anti-Tg antibodies (185-189). Rarely patients have antibodies directed against T4 or T3 (187). Peripheral blood mononuclear cells (190), thyroid lymphocytes (191), and lymph node lymphocytes demonstrated cell-mediated immunity to TPO, Tg and TSH-R (192, 193), and to specific epitopes of these molecules (194-199). Anti-TPO antibodies are not known to play a role in GD, but they could cause a certain degree of cytotoxicity, as noted in couple in vitro studies using serum from AITD patients (200, 201). The functional consequence of having anti-Tg antibodies is uncertain, but they do not appear to cause thyroid cell destruction. Tg and anti-Tg antibody immune complexes are rarely deposited in the kidney basement membrane of the glomeruli and can, in extremely rare circumstances, produce nephritis (200, 202, 203).

Table 2. Antibodies in Graves' Disease			
Antibody	Graves' disease	Hashimoto's thyroiditis	Healthy controls
TSH-receptor antibodies (TRab) (204-209) Thyroid stimulating antibodies (TSAb) TSH- blocking antibody (TBAb) Neutral antibodies	99%	10%	2%
Anti-thyroperoxidase antibodies (Anti-TPOAb) (204, 205)	80%	90-95%	10-15%
Anti-thyroglobulin antibodies (Anti-TgAb) (205, 210, 211)	30-60%	60-80%	8-11.5%

In addition, patients with AITD often develop other organ-specific antibodies, and have higher risk of developing associated conditions such as Addison's disease, premature ovarian failure, chronic hepatitis, celiac disease, primary biliary cirrhosis, pernicious anemia, type 1 diabetes, multiple sclerosis, myasthenia gravis, vitiligo, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, idiopathic thrombocytopenic purpura, urticaria, alopecia, and angioedema (212-220). The most frequent extrathyroidal antibodies include antibodies directed to gastric parietal cells, found in 50% of patients with Hashimoto's thyroiditis (221), to adrenal steroidogenic enzymes, ovarian steroidogenic enzymes, components of the pituitary gland (222), DNA (223), liver mitochondria GD(224), and to cardiolipin (225). Further evidence of ongoing inflammation in GD is the elevation of ICAM-1, IL-6 and IL-8 cytokines seen in hyperthyroid patients (217, 226).

TSH Receptor Antibodies

These antibodies can be classified into three major categories:

1. Thyroid stimulating antibodies (TSab) interact with the TSH-R and stimulate adenylyl cyclase and the protein kinase A pathway, as well as the phospholipase C pathway, thereby triggering thyroid hormone synthesis and cell proliferation (227-229). Functionally, this is identical to the effects induced by TSH itself. When TSab reaches a certain level of function, they cause an increase in thyroid hormone synthesis and secretion, as well as growth of the gland, and cause hyperthyroidism.
2. Thyroid blocking antibodies (TBAb) interact with the TSH-R by binding to different epitopes on the receptor, and they can block the binding of TSH to the receptor without stimulating function themselves (230-233).

3. Thyroid neutral antibodies (TNAb) bind mostly to the hinge region of the TSH-R. While these antibodies neither stimulate nor inhibit its function, they appear to be involved in signaling activity leading to apoptosis of the thyroid follicular cells (234-236).

All these antibodies are commonly recognized by assays which detect their ability to interfere with the binding of TSH to the receptor and are identified as thyrotropin receptor antibody (TRAb), or Thyrotropin binding inhibiting immunoglobulins (TBII) (231). Probably all patients with GD have a mixture of all these three subtypes of antibodies.

TRAb/TBII can be measured with enzyme linked immunosorbent assays (ELISA) that measure the ability of the patient's serum antibodies to inhibit binding of labeled TSH-R ligands (human monoclonal thyroid antibodies) to the TSH-R (209). In addition, TSab can be identified by a bioassay which quantifies the ability of the antibodies to stimulate the adenylyl cyclase function of the TSH-R. Either thyroid cells or thyroid cell membranes can be used, and the cyclic AMP produced by this stimulation is quantitated by a luciferase-based assay (209, 227). A cyclic AMP responsive luciferase construct introduced into Chinese hamster ovary (CHO) cells, allows a sensitive luminescent assay for thyroid stimulating antibodies with the capability of high throughput suitable for use in general laboratories (228).

The TSH-R is initially formed as a single polypeptide inserted into the thyroid cell membrane. After processing, it becomes a two-peptide structure, one extracellular and one transmembrane, with the chains held together by disulfide bonds. Subsequently, reduction of the disulfide bonds by a disulfide isomerase may separate the two molecules and lead to shedding of the "alpha" subunit, which can be augmented by TSH stimulation of thyroid cells (237). The amino-terminal ectodomain of the human TSH-R

has been expressed on the surface of CHO cells as a glycosylphosphatidylinositol-anchored molecule. This material can be released from the cells and is biologically active by binding immunoglobulins from serum of patients with GD, and displaying saturable binding of TSH (8), indicating that all of the "immunologic information" related to production of antibodies resides in the extracellular portion of TSH-R.

The initial bioassay developed by Adams et al. (5), and then by McKenzie (238), could quantitate TSAb (or LATS as it was then known) in up to 60% of patients with active GD. Newer assays measuring cyclic-AMP formation can detect TSAb in over 99% of patients with GD and thyrotoxicosis (239), with a sensitivity of 97% to identify patients with GD, and 93% for patients with TED (240). The presence of TSAb is characteristic of active GD, and if the thyroid can respond (e.g., has not been ablated with RAI), hyperthyroidism ensues. If untreated, the thyroid may be destroyed by the ongoing immune process, or blocking antibodies can develop, and the patient may become hypothyroid. In addition, the coexistence of TSAb and TAb can cause a pull-push effect leading to shifting between hypo- and hyperthyroidism (241, 242).

During antithyroid therapy, TSAb tends to decline. If their titer becomes undetectable there is a high likelihood of disease remission. However, if present in significant concentration, remission is very unlikely, explaining the failure of safely discontinuing antithyroid drug therapy (ATD) in more than 50% of patients after 12-18 months of treatment (243, 244). Similarly, TSAb tends to decline after thyroidectomy (245). After radioactive iodide therapy, TSAb titer increases for up to a year, probably because of the release of thyroidal antigens (246-248). Antibody levels gradually decrease during the subsequent years, reaching pretherapy values around the third year. During ATD, it is speculated that some immune modulation might occur, and the predominant TSAb are replaced by TAb or TAb.

The specific epitopes to which the TSAb bind are in the amino terminal portion of the extracellular domain of the TSH-R and have been better characterized (249, 250). This has led to therapeutic efforts to induce tolerance to these epitopes (251, 252). The blocking antibodies tend to bind to sequences at the carboxy terminal portion of the receptor, closer to the plasma membrane, probably preventing the activation of the receptor through inhibition of signal-transmission required conformational changes (253). Details of these actions are revealed by cryo-electron microscopy analysis of the full-length TSH-R structure complexed with the inhibitory antibody K1-70™. This approach revealed key interactions between the receptor's transmembrane and extracellular domains, suggesting that K1-70™ inhibits TSHR by binding without activating it, while the stimulatory autoantibody M22™ likely induces activation through conformational changes in the hinge region (254).

The Role of Cellular Immunity

Lymphocytes of patients with GD are reactive to the TSH-R (Figure 4), TPO, and synthetic TPO-derived peptides (190, 199, 200, 255). The interaction between antigen presenting cells (APCs) and T cells triggers a multimodal cellular and humoral response. T helper 1 (Th1) cell derived cytokines such as interferon gamma (INF-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL) 1β, IL-6, IL-9, IL-10, and IL-11 play a dominant role in the early phase of AITD (256). Later, there is a predominant T helper 2 (Th2) cell response with its derived IL-4, IL-10, IL-17, and IL-23 (257-260). TSH-R peptides that have aspartic or glutamic acid in the fourth position of their binding motif are particularly susceptible at inducing immune responses in GD and animal T cells (190, 261). Immunoreactivity towards the TSH-R has been reported in samples of orbital fat and preadipocytes, and differentiation of preadipocytes into adipocytes with high TSH-R reactivity has been induced by TSH stimulation (262-264). In addition, immunity to the

TSH-R plays a direct role in the development of TED, through the secretion of proinflammatory cytokines by T cells.

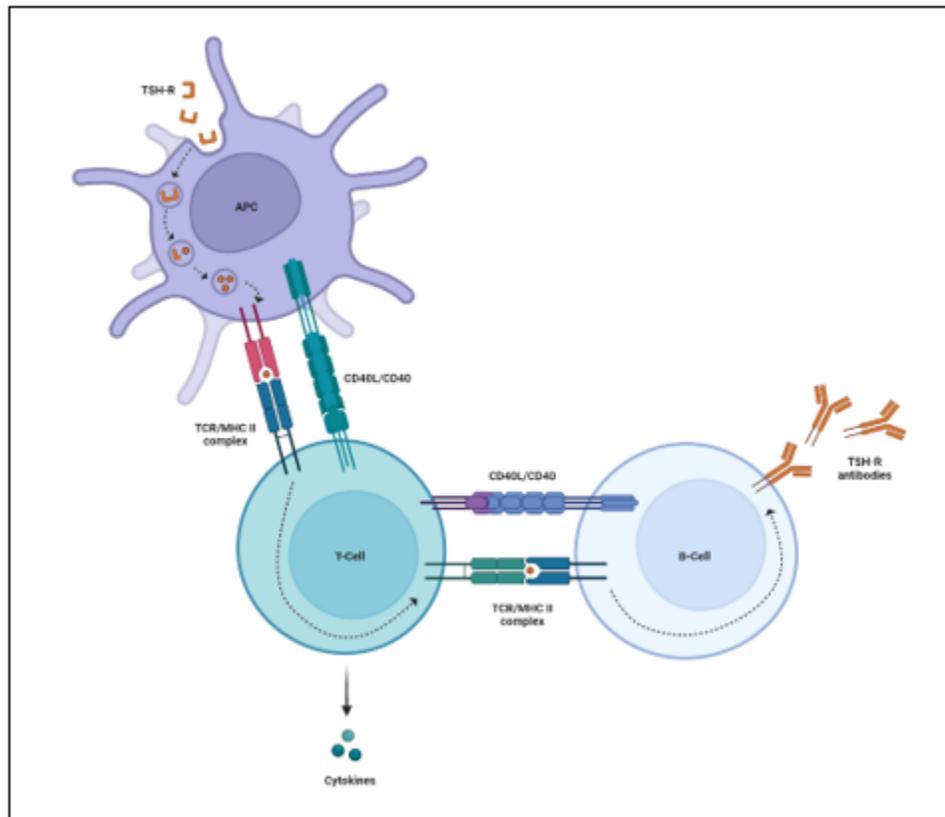


Figure 4. The role of cellular immunity. Schematic representation of TSH-R endocytosis by antigen presenting cells (APC), subsequent proteolysis and presentation to T cells, and stimulation of thyroid stimulating antibody production by B cells. (Created with Biorender.com).

PATHOPHYSIOLOGY

Thyroid Function

In GD, the thyroid gland is functioning at an accelerated rate. Serum TSAb stimulate the TSH-R, as evidenced by the higher activity of the cell membrane adenylyl cyclase activity in the thyroid tissue of patients with GD, compared to normal thyroids (265). The plasma iodine clearance, a reflection of the thyroid iodine uptake, is increased from the normal rate of 10-20 ml/min to 40-2000 ml/minute. For this reason, the percentage of a tracer dose of radioactive iodine (RAI, I^{123}) found in the thyroid gland at 12 hours

is elevated and distributed in a homogeneous fashion (266). Thyroid hormones, Tg, and iodotyrosine - normally secreted in minute amounts - are released into the blood rapidly and at increased rates (73, 267, 268). Furthermore, the rate of turnover of plasma thyroid hormones is also increased. Accelerated degradation is probably secondary to hypermetabolism and is not a primary event (269), although it has been reported that accelerated T4 turnover can persist after treatment of thyrotoxicosis (270). Finally, after anti-thyroid drugs (ATD) the thyroid hormones tend to fall and that response, along

with the required dose of ATD drug required to achieve that response, can be used as predictors of GD remission (271).

An interesting historical observation regarding thyroid function during GD is that the uptake of RAI by the thyroid is not suppressed by the administration of exogenous T4 or T3 (272, 273), even if large amounts of hormone were given (old studies performed before the autoimmune basis for GD was fully understood). Non-suppressibility is caused by stimulation of the thyroid by TSab, and independence of feedback control via TSH.

Iodine Effect on the Thyrotoxic Gland

Iodine affects the metabolism of the diffusely hyperplastic thyrotoxic gland in a way radically different from its action on the normal gland. Years ago, Plummer demonstrated that GD can be temporarily or permanently controlled by the administration of iodide (70). Administration of large doses of iodine to laboratory animals causes a temporary inhibition of iodine organification, the Wolff-Chaikoff effect (274). The same phenomenon occurs in humans, and thyrotoxic patients are especially sensitive to this effect. The thyroid uptake of I^{131} is acutely depressed in thyrotoxic patients by administration of 2 mg potassium iodine, whereas more than 5 mg is needed to depress uptake in normal subjects. Concentrations of serum iodine above 5 $\mu\text{g}/\text{dl}$ block iodine uptake and binding in the thyrotoxic gland (70, 71, 73, 272, 275). The Wolff-Chaikoff effect is transient. With continuous iodine administration, I^{131} uptake and binding recommences. The adaptation to excess iodine in animals involves a reduction of iodine transport into the thyroid which lowers intrathyroidal iodine content and escape from the Wolff-Chaikoff block. This adaptation occurs independently of TSH action.

The biochemical mechanism of the Wolff-Chaikoff effect has not been fully elucidated, but it is partially mediated by the downregulation of the sodium-iodide

symporter (NIS) (276). Iodine does not prevent TSH or TSab from binding to the TSH-R but inhibits both the TSH-stimulated adenylyl cyclase production of cAMP and its derived actions. In addition, iodine also causes a marked reduction in the release of previously formed hormones from the thyrotoxic gland but does not completely prevent further hormone synthesis. This phenomenon has been repeatedly observed and helps explain the beneficial therapeutic effect of iodide in GD (73). Ochi et al. demonstrated that chronic administration of iodine in GD blocks the stimulating effect on hormone release from both TSH and TSab (277). The block of hormone release that occurs in the thyroid of GD can be observed, although not uniformly, in the normal gland and in the normal gland made hyperactive by repeated administration of exogenous TSH. While early laboratory studies on the effect of iodine on the thyroid gland suggested that methimazole can inhibit somewhat the Wolff-Chaikoff effect (278-280), more recent clinical data indicates their ultimate impact on systemic thyroid hormone levels to be additive (281, 282). Clinical practice therefore favors this combination for treatment of severe cases of hyperthyroidism (278-280).

Extrathyroidal Processes

The pathogenesis of extrathyroidal complications of GD such as TED and dermopathy is described in detail in another chapter. Recent evidence demonstrates that stimulation of the TSab on the TSH-R in the orbital fibroblasts can lead to a crosstalk of this receptor with the insulin growth factor 1 receptor (IGF-1R) which stimulates hyaluronan accumulation in the orbital muscles and transformation of orbital fibroblasts into adipocytes (283, 284). This mechanism is believed to play a key role in the pathogenesis of TED and is the basis for emergent therapeutic alternatives in patients with TED and, maybe, dermopathy. Antibodies binding to and directly stimulating the IGF-1R have also been proposed to play a role in this process. However, IGF-1R antibodies exist in sera from about 10% of normal subjects, and in a similar percentage of GD patients,

and are stable over time, strongly suggesting they have no unique role in GD (285).

PATHOLOGY

The ophthalmic and dermatologic changes seen in TED and dermopathy are described in the chapter on the Complications of GD. The thyroid gland changes seen in GD and changes in extrathyroidal organs that can be seen with any case of thyrotoxicosis are described below.

Thyroid Gland

The essential lesion of GD is parenchymatous hypertrophy and hyperplasia (Figure 5). The central features are increased height of the epithelium from

cuboidal to columnar, and varying sizes and shapes of the follicles with reduced colloid content (286, 287). Papillary infoldings, cytologic evidence of increased activity, hypertrophy of the Golgi apparatus, increased number of mitochondria, and increased vacuolization of colloid are also seen. In addition, between the follicles, there is a large array of capillaries, together with a characteristic lymphocyte and plasma cell infiltrate. This infiltrate may be mild and diffuse throughout the gland, but more typically occurs as aggregates of mononuclear cells and even lymphoid germinal centers, referred to as focal thyroiditis. Occasionally the histologic pattern completely overlaps that of Hashimoto's thyroiditis. All pathological changes tend to regress when euthyroidism is achieved.

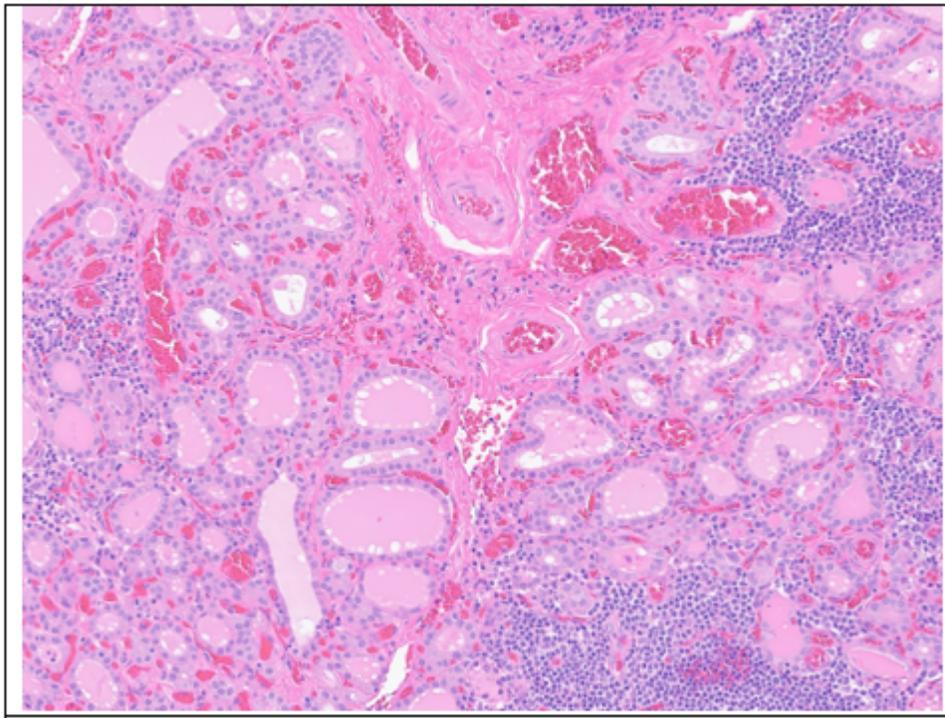


Figure 5. Histology of a thyroid gland of a patient with Graves' disease. Columnar epithelium, vacuolization of colloid, and significant lymphocytic infiltrate are present in the setting of diffuse parenchymal hypertrophy.

Extrathyroidal Changes

MUSCLE

Patients with Graves's disease can have diffuse degenerative atrophy, fatty infiltration, loss of striation, vacuolization, and proliferation or degeneration of nuclei in striated muscles (288-290). Skeletal muscles can also experience interstitial myositis characterized by plasma cells, tissue macrophages, and atrophy of fibers (291). This partly explains the sense of persistent weakness that patients describe after the normalization of thyroid hormone levels. While cardiac and smooth muscles tend to be spared in most patients, myocardial degenerative lesions have been reported in thyrotoxicosis, with foci of cell necrosis, mononuclear infiltrates, and mucopolysaccharide deposits similar to those described in extraocular and skeletal muscles (290).

The extraocular muscle changes are specific for TED, whereas the remainder of the abnormalities may reflect the action of excess hormone.

PITUITARY

The anterior pituitary demonstrates a dramatic decrease in identifiable thyrotropin containing cells, based on data from patients who died from thyroid storm (292, 293). This is entirely reversed in patients who achieve euthyroidism after treatment.

LIVER

Initial studies based on autopsies of patients with GD suggested focal and even diffuse liver cell necrosis, atrophy, and cirrhosis (269). In more contemporary series of liver biopsy specimens obtained from thyrotoxic persons, the deviations from normal were minimal (294, 295). Moderate decrease in glycogen content and increase in fat and round cell infiltrates were noted. The differences among these studies could be explained by a lesser severity and duration of

the disease in more recent series with patients diagnosed earlier and treated effectively, as the disease has now an extremely low mortality rate (296). Recent studies have documented that thyroid hormone analogs specific for the thyroid hormone receptor b such as resmetirom may be a novel therapeutic approach for the therapy of metabolic dysfunction associated steatotic liver disease (MASLD) (297).

BONE

Prolonged hyperthyroidism is known to produce the histologic picture of osteoporosis (298), but osteitis fibrosa also occurs (299). Histomorphometry studies show unmistakable evidence of excess bone formation and resorption.

NATURAL COURSE OF GD AND CLINICAL MANIFESTATIONS OF THYROTOXICOSIS

In the classic presentation, the most common onset is the simultaneous and gradual development, over a period of weeks or months, of thyrotoxicosis-related signs and symptoms, goiter, and exophthalmos. However, GD displays an array of possible clinical patterns. It is possible for GD to develop in a patient with preceding nontoxic multinodular goiter, toxic multinodular goiter (Marine-Lenhart syndrome), to experience thyrotoxicosis without TED, or to have TED preceding the development of thyrotoxicosis. Due to the coexistence of TSAb and TBAbs some patients can first develop hypothyroidism and later thyrotoxicosis, or vice versa (232). In addition, during pregnancy GD tends to be partially suppressed, only to have a rapid recurrence in the post-partum period (300). Sometimes, human chorionic gonadotrophin (hCG) induced thyrotoxicosis, seen in the first part of pregnancy, can also coexist with GD and mask its presentation (301).

Before the general availability of current therapies, hyperthyroidism tended to evolve through periods of exacerbation and remission. In the mild forms, the active disease was self-limited to one year or more, and the patients returned spontaneously to a euthyroid state. In untreated moderate to severe forms, mortality could be observed in 11% of patients (302, 303). Mortality was most frequently attributed to cardiovascular complications (such as myocardial infarction, arrhythmia, or heart failure), or infections, and occurred within the first 4 years after diagnosis. Fortunately, death due to hyperthyroidism is now rare with an excess mortality of 1.2% compared to controls (296). Nowadays, after a period of anti-thyroid drug therapy (ATD) there is re-establishment of normal thyroid homeostasis and over time a sizable proportion of patients can achieve disease remission, allowing them to discontinue ATD and remain euthyroid off therapy.

The most common presenting symptoms are weight loss, weakness, dyspnea, palpitations, increased thirst or appetite, diarrhea, irritability, profuse diaphoresis, heat intolerance and increased tolerance to cold, or tremor. Occasionally, exophthalmos or diplopia is the index symptom, but goiter may antedate all other manifestations. The nutritional state varies greatly. In the past, patients were severely emaciated, but these days, on average, the weight loss is 5 - 20 lbs. (2.3 – 9 kg). Facial expressions of flushing, fright, or extreme anxiousness are common. Notably, in elderly patients the disease can manifest as *apathetic thyrotoxicosis*, in which there is absence of hyperkinetic neuromuscular symptoms, and predominance of cardiac (e.g. arrhythmia), psychiatric (e.g. apathy, depression) and nutritional (e.g., weight loss) symptoms (304).

In patients with GD, the ocular changes of TED, lymphoid hyperplasia, localized abnormalities of skin and connective tissue (e.g., dermatopathy and acropachy) and the goiter itself are direct results of the autoimmune processes of GD. The remainder of the

changes are entirely attributable to an excess of thyroid hormone.

The natural course and manifestations of thyroid storm, TED, and dermatopathy are primarily discussed in the chapter on Complications of GD. The clinical manifestations of thyrotoxicosis are described below.

Thyroid

The diffuse toxic goiter is usually more or less symmetric. The size is related, but not closely, to the severity of the disease. It varies from the barely palpable normal (10- 15 g) to a three-to-six times enlargement (45-100 g) or, rarely, even more. The gland might not be palpable in 1% of cases, either because the thyroid is smaller than usual at baseline or because it is beneath the manubrium. The thyroid may be smooth, lobulated, or rarely nodular. In thyrotoxicosis associated with nodular goiters, the hyperfunctioning tissue may reside between the nodules (305). Usually, the consistency is firm but elastic, or very firm if iodide has been given. The borders are easily demarcated by palpation. Thrills and bruits, usually denote the hypervascularity associated with increased function. Bruits may be continuous or systolic and are usually audible over the entire thyroid. Local pressure symptoms, including dysphagia and the sensation of a lump in the neck, are produced by the enlarged goiter. Vocal cord palsy is only rarely seen in GD (306). In addition, the supraclavicular lymph nodes could become enlarged and, rarely, tender (307). Most thyroid related manifestations tend to regress or disappear with restoration of euthyroidism.

Skin

Cutaneous manifestations are nearly always present when vasomotor overactivity is significant. Heat intolerance and profuse diaphoresis occur under circumstances that would provoke no response in normal people. On palpation, hands are usually erythematous, hot, and moist (hyperhidrosis). There

may be continuous erythema of the face and neck, with superimposed transient blushing after palpation of the thyroid. Occasionally diffuse pruritus or urticaria occur (308). Patchy vitiligo is an associated manifestation of autoimmunity directed toward melanocytes that can be found in 7% of patients with GD.

Fingernails can experience onycholysis characterized by ragged appearance, thinning and posterior erosion of the hyponychium. The free margin of the nail leaves the nail bed, producing a concave or wavy margin at the line of contact. Temporary thinning of the hair is common, but alopecia is rare. Hair loss can occur due to marked changes in metabolism throughout the course of the disease.

Myxedema can be seen in 0.5-4.3% of patients with GD, and 13% of patients with TED (309, 310). The clinical characteristics of thyroid dermopathy are described in the chapter on Complications of GD.

Nervous System

Neural and mental findings are diverse. Nervousness, irritability, anxiety, and restlessness are common (Table 3) (311). The behavioral reactions to all sorts of stimuli are typically exaggerated. When asked to sit up, the patient might jump into an upright position. They may simply wish to cooperate but appear to overdo it. Often emotional instability is combined with this pattern, to the point of a notable change in personality. In some patients, the emotional pattern is that of mania or euphoria. In others, hyperactivity produces a state of exhaustion, and profound fatigue or asthenia. The mind is often highly active, and the patient is troubled with insomnia. Rarely, patients develop visual or auditory hallucinations or a frank

psychosis. The latter is probably the result on an exacerbation of a baseline psychiatric condition rather than a *de novo* process (312). Furthermore, impairment of intellectual function has been found in patients with untreated hyperthyroidism. A recent study has documented that in patients over 65 years, a low TSH level from either endogenous or exogenous thyrotoxicosis is associated with higher risk of incident cognitive disorders (313).

A fine, rapid tremor of the outstretched fingers is classically found, and a generalized tremulousness, also involving the tongue, may be evident. The speed of muscle contraction and relaxation is increased, tendon reflexes tend to be brisk, and the reflex relaxation time is shortened (314). The tremor of Parkinsonism is intensified during thyrotoxicosis, and manifestations of cerebellar disease or pyramidal tract lesions can be seen (315, 316). Muscle fibrillations are not a usual part of the syndrome, but they may occur in chronic thyrotoxic myopathy. Polyneuropathy has also been reported (317). Rarely, patients manifest disorientation, aphasia, grimacing, choreoathetoid movements, symptoms suggestive of encephalitis, episodes of hemiparesis or bulbar paralysis (318). These symptoms clear up completely after restoration of an euthyroid state.

Other possible, although rare, severe neurologic manifestation consist of the new onset, exacerbation, or refractoriness of seizure disorders (319). Electroencephalography reveals increased fast wave activity, and occasionally bursts of tall spike waves. In addition, several reports describe a severe, steroid-responsive encephalopathy in some patients with GD (320).

Table 3. Neurologic Manifestations in Graves' Disease

<p>Common:</p> <p>Nervousness Irritability Restlessness Anxiety Emotional lability including hypomania or euphoria, and fatigue or asthenia). Insomnia Tremors Brisk tendon reflexes with short relaxation time</p> <p>Uncommon:</p> <p>Visual or auditory hallucinations Psychosis Impairment of intellectual function Disorientation Aphasia Choreoathetoid movements Hemiparesis or bulbar paralysis Seizures Encephalopathy Neuropathy</p>
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Muscular System

The muscular symptoms vary from mild myasthenia to profound muscular weakness and atrophy, especially of the proximal muscle groups. Wasting of the temporals and interossei used to be noted in a considerable number of patients while a few had generalized muscle wasting in the decades prior to current diagnostic and therapeutic abilities. Occasionally the myopathy may shade into the picture of polymyositis. Muscle cell necrosis and lymphocyte infiltration may be visible histologically, but usually are not found even when the symptoms of weakness are severe (321, 322). The electromyogram is normal in most instances but may occasionally resemble that of muscular dystrophy (323).

Work efficiency, measured in terms of the calories of heat produced while performing a given amount of work, has been reported to be either normal or decreased (324, 325). The muscles have decreased ability to incorporate creatine from the blood (326, 327). Creatinine excretion is initially increased by the general catabolism of hyperthyroidism, but as muscle mass diminishes, creatinine excretion in the urine decreases.

Myasthenia gravis may simulate thyrotoxicosis, and vice versa (328). The close relationship between these two diseases is apparent in the observation that thyrotoxicosis occurs in 3% of patients with myasthenia gravis. The pathogenic anti-acetylcholine receptor antibodies that occur in myasthenia gravis

are clearly comparable to the TSH-R antibodies found in GD.

Periodic paralysis is precipitated and worsened by thyrotoxicosis (329). It has been more commonly reported in Southeast Asian males who have a higher frequency of certain genetic susceptibilities associated with higher risk of thyrotoxic periodic paralysis (330-333). Paralysis is usually associated with hypokalemia. Inactivating mutations in the inwardly rectifying potassium channel 2.6 encoded by the KCNJ18 gene (in about 30%) have, among other candidates, been associated with susceptibility for developing thyrotoxic periodic paralysis (334, 335). Beta adrenergic stimulation mediated by thyrotoxicosis augments sodium-potassium ATPase activity in the skeletal muscle leading to increased potassium uptake into the cells (336). The episodes of paralysis tend to be infrequent and sporadic, but most commonly occur after a meal, following exercise, or during sleep, and can be induced by administration of glucose and insulin. Episodes last from minutes to hours, usually involving peripheral muscles, but can cause paralysis of the diaphragm and affect the heart. Serious episodes can be associated with extensive muscle cell damage and necrosis, and electrocardiographic (EKG) abnormalities associated with hypokalemia, such as ST and T wave changes, premature ventricular complexes (PVCs), first degree heart block, prolonged QT intervals, and even ventricular fibrillation (337).

Pulmonary System

Except for dyspnea on exertion, symptoms deriving from the lungs are not prominent. Nevertheless, pulmonary function tests can show some reduction in vital capacity, expiratory reserve volume, pulmonary compliance, and airway resistance (338, 339). Minute volume response to exercise is excessive for the amount of oxygen consumed (340).

Cardiovascular System

The first and most common manifestations deriving from the cardiovascular system are palpitations and tachycardia (341, 342). The pulse on palpation is rapid and bounding. When present, it can be effectively controlled with beta- adrenergic blockers (343, 344). PVCs, paroxysmal atrial tachycardia, atrial fibrillation, and shorter P wave duration occur in 6-12% of patients (345-347). When present, atrial fibrillation should be treated with anticoagulation to prevent risk of thromboembolic complications. The systolic blood pressure is frequently elevated. The diastolic blood pressure is characteristically decreased, making the pulse pressure elevated to between 50-80 mm Hg (348). A systolic murmur can sometimes be heard over the precordium due to development of mitral valve prolapse following papillary muscle dysfunction during thyrotoxicosis (349). However, mitral valve insufficiency is usually not clinically relevant and can revert to normal with treatment of thyrotoxicosis.

In thyrotoxicosis, the heart rate, stroke volume, left ventricular mass index, and cardiac output are all increased. The pre-ejection period is shortened, and the left ventricular ejection time remains relatively normal. The interval from initiation of the QRS complex to arrival of the arterial pulse in the brachial artery is reduced (350). Circulation time is decreased. There is dilatation of superficial capillaries and decline in systemic vascular resistance (351). Coronary blood flow and myocardial oxygen consumption in each stroke are increased. Circulating plasma volume is increased (352). Long-term mild excess of thyroid hormone causes impaired cardiac reserve and exercise capacity (353). Cardiac enlargement and heart failure may occur with or without prior heart disease (354). These effects tend to normalize when euthyroidism is restored (355).

Patients with coronary artery disease often develop angina during thyrotoxicosis. However, angina could also develop *de novo* in patients with normal coronary arteries, especially young females. This condition has been ascribed to an imbalance between increased cardiac work and blood supply, even with a patent

vessel (356). Severe coronary vasospasm has been observed during angiography in patients with GD (357). Myocardial damage can occur in thyrotoxic patients with congestive heart failure (358), even when coronary vessels are normal at baseline (359).

It has been suggested that the changes in the cardiovascular system are secondary to increased demand for metabolites and to increased heat production. Dilatation of superficial capillaries for the dissipation of heat does cause increased blood flow and cardiac output (360). However, the direct action of thyroid hormone on the heart is also increased, since the sinus node has higher intrinsic activity, the isolated thyrotoxic heart beats faster than normal, and isolated papillary muscle from a thyrotoxic heart has a shortened contraction time (361-363).

Historically, the cardiovascular effects of triiodothyronine have primarily been attributed to its modulatory influence on nuclear adrenergic receptor genes, among others (364, 365). However, more recent evidence has demonstrated a significant physiological role for the non-genomic effects of

thyroid hormone, particularly in energy homeostasis (366-368). Cardiac muscle contractility is enhanced by a reduction in alpha-adrenergic and cholinergic receptors within the heart. This effect is coupled with an increase in beta-adrenergic receptors, heightened adenosine transport, and enhanced phosphorylation within myocardial cells. Additionally, there is an augmentation in cardiac Na⁺-K⁺ activated membrane ATPase activity, as well as an elevation in sarcoplasmic reticulum Ca⁺⁺-activated ATPase activity. Finally, the increased synthesis of alpha-myosin heavy chains with increased ATPase activity also contributes to this heightened contractility (363, 369-371).

Fatourehchi and Edwards used myocardial biopsy to investigate the presence of an autoimmune process in eleven cases of GD with low output cardiac dysfunction. Two patients had lymphocytic infiltrates suggestive of an autoimmune process, whereas the others did not, indicating that myocardial autoimmunity may occur but would not be the usual cause of cardiac dysfunction in thyrotoxicosis (372).

Table 4. Cardiovascular Manifestations in Graves' Disease

<p>Common:</p> <p>Palpitations Tachycardia Paroxysmal atrial tachycardia Atrial fibrillation Increased stroke volume and cardiac output. Increased coronary blood flow and myocardial oxygen consumption Decreased exercise capacity</p> <p>Uncommon:</p> <p>Impaired cardiac reserve Heart failure Myocardial infarction</p>

Hematologic and Lymphatic Systems

In most patients the hemoglobin and hematocrit are in the normal or low-normal range (373). The glucose-6-phosphate dehydrogenase activity of red cells is increased in thyrotoxicosis (374), while blood volume and the red cell mass are also increased in some patients. In the past, severe thyrotoxicosis used to be associated with normocytic anemia with hemoglobin concentrations as low as 8 g/dl, likely related to iron deficiency and malnutrition (375, 376). However, the presence of anemia in a thyrotoxic patient these days requires a search for an additional explanation, other than thyrotoxicosis.

The reticuloendothelial and lymphocytic systems undergo hyperplasia. There may be generalized lymphadenopathy, and the thymus may be enlarged (377). The thymus enlargement should be considered when mediastinal abnormalities are noted on chest imaging; thymus enlargement resolves with resolution of thyrotoxicosis and that should inform the decision about possible biopsy (378). Relative lymphocytosis and neutropenia with a normal or slightly low total white cell count, constitute the characteristic blood findings of GD (379). A relative and an absolute increase in the number of monocytes has also been

reported (380). Significant pancytopenia with leukocyte counts under $3 \times 10^9/l$ and neutrophils under $2 \times 10^9/l$ rarely occur, and if unrelated to drug therapy, tend to recover with restoration of euthyroidism (381).

GD is often associated with mild thrombocytopenia, and occasionally with idiopathic thrombocytopenic purpura (382). This co-occurrence is thought to reflect the autoimmune pathogenesis of both diseases. Fourteen percent of patients with immune thrombocytopenic purpura are reported to have coincident GD. Mild thrombocytopenia may disappear spontaneously or with treatment of hyperthyroidism, or if severe, may respond to glucocorticoid therapy (383). Bone marrow examination may show normal or increased megakaryocytes. In addition, platelet life span can be shortened due to a more rapid clearing by the activated reticulo-endothelial system.

Usually, thyrotoxicosis results in a mild hypercoagulable state. Although rare, cerebral venous thrombosis has been reported in association with thyrotoxicosis, suggesting that occasionally the propensity for coagulation can lead to profound consequences (384). Mild prolongation of the prothrombin time and elevation of several coagulation factors (Factors VIII, XIII, IX, XI, Von Willebrand,

fibrinogen, and plasminogen activator inhibitor 1, among others) are often seen with thyrotoxicosis, and return to normal with treatment. In addition, recent studies emphasize the role of thyroid hormones in promoting coagulation through non-genomic mechanisms involving platelet activation with subsequent endothelial interactions (385).

Gastrointestinal System

The appetite and the gastrointestinal track absorption are characteristically increased to try to offset nutritional requirements from the increase in catabolism seen in patients with thyrotoxicosis. Despite this, weight loss is usually predominant. In severe thyrotoxicosis, nausea, emesis, and abdominal pain can be present while intestinal transit time is decreased, and occasionally diarrhea occurs (386). Steatorrhea can be seen if fat intake is excessive. Achlorhydria can be as prevalent as 40% (387, 388). Gastric enzymes production is decreased, and a mild gastritis can be present (389). Fasting serum gastrin levels, and their responses to arginine, are increased (390).

Around 55% of patients with thyrotoxicosis can experience at least one abnormality in their liver blood tests. Alkaline phosphatase elevation is the most common, but other common abnormalities include hypoalbuminemia, mild prothrombin time elevation, elevated aminotransferases, hyperbilirubinemia, and elevated lactate dehydrogenase (LDH) (391). Mild to severe liver disease may be found, and the liver is frequently palpable regardless of the coexistence of heart failure (392). Jaundice is possible but often seen when there is significant cholestasis from severe thyrotoxicosis (393, 394). The cause of hepatic disease has been thought to be multifactorial in the setting of congestive hepatopathy from heart failure, malnutrition, previous or concomitant liver disease (i.e., infectious or autoimmune disease), and drug related liver injury, and possible liver ischemia from a mismatch between oxygen consumption and oxygen delivery to the liver (395-399). All gastrointestinal

manifestations tend to improve with restoration of the euthyroid state.

Renal System

Polyuria and occasionally glucosuria are seen in uncomplicated thyrotoxicosis. Polyuria does not indicate insensitivity to vasopressin, for the kidney responds normally to vasopressin with an increase in concentration of urine (400). Glucosuria may reflect accelerated absorption of sugar from the intestine and glucose intolerance. The glomerular filtration rate and renal blood flow are on average increased, probably secondary to increased cardiac output and a direct effect of thyroid hormone on renal function (401). Hyperuricemia with hypercalcemia can be seen in severe thyrotoxicosis, but it rarely injures the kidneys. In addition, occasionally hyposthenuria and uremia occur (402, 403).

Female Reproductive System

Menstruation is characteristically decreased in volume, and rarely amenorrhea with a proliferative endometrium can happen. The menstrual cycle may be either shortened or prolonged. The relative importance of a primary action of excess thyroid hormone on the gonadotroph function is unclear. However, an alteration in pituitary LH production and subsequent ovulation is suggested (404). Hyperprolactinemia is more common in patients with hyperthyroidism than in healthy controls (405). Premature ovarian failure can occur in association with GD in patients with polyglandular autoimmune syndrome type 3 (222).

Fertility is decreased, but pregnancy can develop. The incidence of miscarriage, premature delivery, pre-eclampsia, and gestational heart failure are increased by maternal thyrotoxicosis (406-408). Reduced fertility and increased miscarriage rates are associated with autoimmune thyroid disease (AITD) and positive antibodies. High maternal thyroid hormone levels and/or high titer of TSab (by crossing the placenta in

the 3rd trimester) can lead to fetal thyrotoxicosis with suppressed fetal TSH, lower fetal weight, and fetal death (409). However, pregnancy often ameliorates the biochemistry and the symptoms of thyrotoxicosis due to GD. Unfortunately, relapse is prone to occur in the 3-4 months following delivery.

Male Reproductive System

Peripheral conversion of testosterone and androstenedione to estrone and estradiol is increased in both sexes during hyperthyroidism (293, 410). Thus, men can have elevated circulating levels of free estradiol (411, 412), and some might experience gynecomastia with ductal elongation and epithelial hyperplasia (413, 414). In addition, the slightly elevated LH in men with gynecomastia suggests hypothalamic insensitivity to feedback control and some peripheral unresponsiveness to LH (411).

Both Leydig cell and spermatogenic abnormalities may be present. Previous small series have described a 71% rate of loss of libido, 56% rate of erectile dysfunction, and 80% rate of low sperm counts (<40 millions) in thyrotoxic men (415, 416). In these patients, the total testosterone level was elevated, but because the sex hormone binding globulin level was also high, the free testosterone level was reduced and the response to hCG was blunted. The abnormalities normalize when the patients become euthyroid (417). In addition, RAI therapy can cause transient reductions in both sperm count and motility but do not seem to cause permanent effects with ordinary treatment doses (under 14 mCi, equivalent to around 500 MBq) (417).

Adrenal Function

There are no obvious clinical signs or symptoms of altered adrenal cortical function in thyrotoxicosis, but distinct biochemical changes have been detected. In thyrotoxicosis the adrenal cortex is often hyperplastic and exogenous glucocorticoids are cleared from the

plasma and metabolized at an accelerated rate (418). Since plasma glucocorticoid levels are normal and their rate of metabolism is increased, total daily metabolism and excretion of 17-ketosteroids and 17 hydroxy-corticoids are usually increased (419, 420). Furthermore, there is a relatively increased excretion of 11-oxycorticoid metabolites (421), which are biologically inactive compounds. There is increased secretion of adrenocorticotrophic hormone (ACTH) by the pituitary, and subsequently increased production of steroids by the adrenal gland in order to maintain a normal concentration of active steroids in the peripheral blood and in the tissues (422, 423). However, a reduced response to exogenous ACTH suggests that adrenal reserve is reduced (424), and it has been hypothesized that in severe thyrotoxicosis and in thyroid storm there may be an element of adrenal insufficiency.

An increase in the 5-alpha metabolite of testosterone (androsterone) and a relative decrease in the 5-beta metabolite (etiocholanolone) are seen in the urine of thyrotoxic patients (425, 426). Because administration of substantial amounts of androsterone depresses the level of serum lipids, Hellman et al. have hypothesized that this change in steroid metabolism may be a way in which thyroid hormone affects lipid metabolism.

Skeletal System

Patients with mild thyrotoxicosis can experience some degree of bone mass loss and increased fracture risk, irrespective of age or sex (427-429). Those with thyrotoxicosis extending over several years may develop severe osteoporosis (430, 431). Skeletal mass is augmented after restoration of euthyroidism (428, 429).

The thyroid hormone receptors $\alpha 1$ (TR $\alpha 1$), TR $\beta 1$, and TR $\beta 2$ are expressed in human osteoblasts and bone marrow stromal cells. Histomorphometry evaluations with tetracycline labelling demonstrates accelerated turnover of bone, calcium, and collagen, both in spontaneous hyperthyroidism and in female treated

with excess thyroid hormone (298, 432, 433). Serum osteocalcin, carboxy-terminal-1-telopeptide, and alkaline phosphatase may increase in parallel with hormone levels (434-437). These tend to normalize with restoration of euthyroidism.

The serum calcium level is usually normal but may be sufficiently elevated to produce nausea and emesis (402), and rarely, renal injury (403, 438). Fecal and urinary calcium excretion is greatly augmented, but kidney stones are infrequent since there is a concomitant polyuria with increase in excretion of colloids that stabilize the calcium (433). Intestinal absorption of calcium is usually reduced (439). The hypercalcemia appears to be a direct manifestation of thyroid hormone action on bone metabolism and can lead to secondary hypoparathyroidism with reduced 1,25-dihydroxyvitamin D (440, 441), and elevated serum phosphorus secondary to increased renal resorption (438, 442). It has been proposed that the hypercalcemia can usually be corrected partially or totally by the administration of glucocorticoids, but data is inconclusive (442, 443). Treatment of thyrotoxicosis is certainly able to normalize these abnormalities (444).

Metabolism

METABOLIC RATE

The basal oxygen consumption in thyrotoxicosis, as measured by the basal metabolic rate (BMR), is elevated compared to a euthyroid person. In extreme thyrotoxicosis, the BMR may be double the standard (445-447). In addition, the total metabolic rate, which is the BMR plus the increments from work, food, or stress, is elevated.

Observations regarding energy expenditure are mixed. An increased cost of muscular work with less efficient coupling of oxidation and energy use in patients with thyrotoxicosis was reported many years ago by Plummer and Boothby (448) and Briard et al. (449) among others. However, recent studies suggest

that the increase in energy expenditure caused by work is not altered in thyrotoxicosis (450).

CARBOHYDRATE METABOLISM

Intestinal carbohydrate absorption is accelerated, as is its removal from the plasma. After a standard oral glucose load is given, the thyrotoxic patient characteristically has an early and rapid rise in blood glucose concentration in 30 - 60 minutes followed by a rapid fall, so that by two hours the concentration is normal (451-453). In non-diabetic thyrotoxic patients there is increased insulin demand and there could be some resistance to the action of insulin. Fasting blood glucose levels are associated with double the normal insulin concentration (454), and insulin resistance has been found *in vitro* utilizing adipocytes from patients with untreated hyperthyroidism (455).

Diabetes may develop (in patients with prediabetes) or worsen with the development of thyrotoxicosis and is ameliorated or may disappear when thyrotoxicosis is treated (456). In these patients, there is increased basal hepatic glucose production and reduced ability of insulin and glucose to suppress hepatic glucose production, another marker of insulin resistance (457, 458).

LIPID METABOLISM

Hypocholesterolemia is associated with thyrotoxicosis. It may be produced without a distinct decrease in total body or liver cholesterol. Part of the cholesterol-lowering action of thyroid hormone relates to malnutrition and weight loss, and part may be simply a manifestation of hypermetabolism. There is an increase both in synthesis and degradation of cholesterol, but the balance results in lower steady-state concentrations in the serum (459-469). Thyroid hormone directly enhances conversion of cholesterol to bile acids and their excretion in the bile, disposing of 70-90% of the cholesterol formed in the body (462). They may also affect cholesterol metabolism by directly increasing the number of membrane surface

low-density lipoprotein (LDL) receptors (463). Furthermore, hepatic lipogenesis is also strikingly increased, both by direct action of thyroid hormones and in response to increased insulin levels. Overall, the levels of LDL, HDL, and apolipoproteins are lowered (461, 465-470). Triglyceride levels tend to be normal or slightly elevated (464), and the clearance rate of infused triglycerides might be elevated (461, 465-470). Plasma leptin levels are normal (468), and non-esterified fatty acids are elevated (471).

PROTEIN METABOLISM

In thyrotoxicosis, protein formation and breakdown are both accelerated. Despite the increased protein turnover, there is an overall protein deficit (472, 473). Nitrogen excretion is increased, and nitrogen balance may be normal or negative, depending on whether intake meets the demands of increased catabolism.

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REFERENCES

1. Graves RJ. Clinical Lectures: Newly Observed Affection of the Thyroid Gland in Females. London Medical and Surgical Journal. 1835;7.
2. der KP, Houtstra-Lanz M, Schwarz F. Exophthalmos-producing substance in human serum. J Clin Endocrinol Metab. 1960;20:712-8.
3. Dobyns BM, Steelman SL. The thyroid-stimulating hormone of the anterior pituitary as distinct from the exophthalmos-producing substance. Endocrinology. 1953;52(6):705-11.
4. Adams DD. The presence of an abnormal thyroid-stimulating hormone in the serum of some thyrotoxic patients. J Clin Endocrinol Metab. 1958;18(7):699-712.
5. Adams DD, Fastier FN, Howie JB, Kennedy TH, Kilpatrick JA, Stewart RD. Stimulation of the human thyroid by infusions of plasma containing LATS protector. J Clin Endocrinol Metab. 1974;39(5):826-32.
6. Smith BR, Hall R. Thyroid-stimulating immunoglobulins in Graves' disease. Lancet. 1974;2(7878):427-31.
7. Huber GK, Safirstein R, Neufeld D, Davies TF. Thyrotropin receptor autoantibodies induce human thyroid cell growth and c-fos activation. J Clin Endocrinol Metab. 1991;72(5):1142-7.
8. Cornelis S, Uttenweiler-Joseph S, Panneels V, Vassart G, Costagliola S. Purification and characterization of a soluble bioactive amino-terminal extracellular domain of the human thyrotropin receptor. Biochemistry. 2001;40(33):9860-9.
9. Rees Smith B, McLachlan SM, Furmaniak J. Autoantibodies to the thyrotropin receptor. Endocr Rev. 1988;9(1):106-21.

Catabolism of collagen is increased, and urinary hydroxyproline excretion is characteristically increased (474). While the exact mechanism behind the effect of thyroid hormone on protein metabolism is not fully elucidated, it is believed to be mediated by a combination of mitochondria-dependent cytoplasmic mechanisms, and modulation of nuclear genetic transcription of genes involved in protein metabolism (475-477).

VITAMIN METABOLISM

The absorption of vitamin A is increased and conversion of carotene to vitamin A is accelerated in thyrotoxicosis (478). The requirements of the body are likewise increased, and low blood concentrations of vitamin A may be found. In addition, requirements for thiamine and vitamin B6 are increased (479).

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10. Ludgate ME, Vassart G. The thyrotropin receptor as a model to illustrate receptor and receptor antibody diseases. *Baillieres Clin Endocrinol Metab.* 1995;9(1):95-113.
 11. Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. *Journal of Autoimmunity.* 2010;34(3):J168-J77.
 12. McGrogan A, Seaman HE, Wright JW, De Vries CS. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clinical Endocrinology.* 2008;69(5):687-96.
 13. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol.* 2018;14(5):301-16.
 14. Vos XG, Smit N, Endert E, Brosschot JF, Tijssen JG, Wiersinga WM. Age and stress as determinants of the severity of hyperthyroidism caused by Graves' disease in newly diagnosed patients. *Eur J Endocrinol.* 2009;160(2):193-9.
 15. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older Subjects with Hyperthyroidism Present with a Paucity of Symptoms and Signs: A Large Cross-Sectional Study. *The Journal of Clinical Endocrinology & Metabolism.* 2010;95(6):2715-26.
 16. Smith TJ, Hegedüs L. Graves' Disease. *New England Journal of Medicine.* 2016;375(16):1552-65.
 17. Furszyfer J, Kurland LT, McConahey WM, Elveback LR. Graves' disease in Olmsted County, Minnesota, 1935 through 1967. *Mayo Clin Proc.* 1970;45(9):636-44.
 18. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf).* 1977;7(6):481-93.
 19. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf).* 1995;43(1):55-68.
 20. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and Thyroid Antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology & Metabolism.* 2002;87(2):489-99.
 21. Degroot LJ, Quintans J. The Causes of Autoimmune Thyroid Disease*. *Endocrine Reviews.* 1989;10(4):537-62.
 22. Desai MK, Brinton RD. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. *Frontiers in Endocrinology.* 2019;10.
 23. Kisiel B, Bednarczuk T, Kostrzewa G, Kosińska J, Miśkiewicz P, Płazińska MT, et al. Polymorphism of the oestrogen receptor beta gene (ESR2) is associated with susceptibility to Graves' disease. *Clin Endocrinol (Oxf).* 2008;68(3):429-34.
 24. Merrill SJ, Mu Y. Thyroid autoimmunity as a window to autoimmunity: An explanation for sex differences in the prevalence of thyroid autoimmunity. *J Theor Biol.* 2015;375:95-100.
 25. Struja T, Kutz A, Fischli S, Meier C, Mueller B, Recher M, et al. Is Graves' disease a primary immunodeficiency? New immunological perspectives on an endocrine disease. *BMC Med.* 2017;15(1):174.
 26. Ando T, Imaizumi M, Graves PN, Unger P, Davies TF. Intrathyroidal fetal microchimerism in Graves' disease. *J Clin Endocrinol Metab.* 2002;87(7):3315-20.
 27. Vestergaard P. Smoking and thyroid disorders--a meta-analysis. *Eur J Endocrinol.* 2002;146(2):153-61.
 28. Wiersinga WM. Smoking and thyroid. *Clin Endocrinol (Oxf).* 2013;79(2):145-51.
 29. Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. *Eur J Endocrinol.* 2004;150(5):605-18.
 30. Rodríguez-Paredes M, Esteller M. Cancer epigenetics reaches mainstream oncology. *Nat Med.* 2011;17(3):330-9.
 31. Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, et al. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med.* 2004;10(11):1216-21.
 32. Effraimidis G, Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. *Eur J Endocrinol.* 2014;170(6):R241-52.
 33. Holm IA, Manson JE, Michels KB, Alexander EK, Willett WC, Utiger RD. Smoking and other lifestyle factors and the risk of Graves' hyperthyroidism. *Arch Intern Med.* 2005;165(14):1606-11.
 34. Wenzel BE, Franke TF, Heufelder AE, Heesemann J. Autoimmune thyroid diseases and enteropathogenic *Yersinia enterocolitica*. *Autoimmunity.* 1990;7(4):295-303.
-

35. Wolf MW, Misaki T, Bech K, Tvede M, Silva JE, Ingbar SH. Immunoglobulins of patients recovering from *Yersinia enterocolitica* infections exhibit Graves' disease-like activity in human thyroid membranes. *Thyroid*. 1991;1(4):315-20.
36. Wenzel BE, Heesemann J, Wenzel KW, Scriba PC. Antibodies to plasmid-encoded proteins of enteropathogenic *Yersinia* in patients with autoimmune thyroid disease. *Lancet*. 1988;1(8575-6):56.
37. Akamine H, Takasu N, Komiya I, Ishikawa K, Shinjyo T, Nakachi K, et al. Association of HTLV-I with autoimmune thyroiditis in patients with adult T-cell leukaemia (ATL) and in HTLV-I carriers. *Clin Endocrinol (Oxf)*. 1996;45(4):461-6.
38. de Luis DA, Varela C, de La Calle H, Cantón R, de Argila CM, San Roman AL, et al. *Helicobacter pylori* infection is markedly increased in patients with autoimmune atrophic thyroiditis. *J Clin Gastroenterol*. 1998;26(4):259-63.
39. Rochman H, deGroot LJ, Rieger CH, Varnavides LA, Refetoff S, Joung JI, et al. Carcinoembryonic antigen and humoral antibody response in patients with thyroid carcinoma. *Cancer Res*. 1975;35(10):2689-92.
40. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med*. 1991;325(9):599-605.
41. Vermiglio F, Castagna MG, Volnova E, Lo Presti VP, Moleti M, Violi MA, et al. Post-Chernobyl increased prevalence of humoral thyroid autoimmunity in children and adolescents from a moderately iodine-deficient area in Russia. *Thyroid*. 1999;9(8):781-6.
42. Monzani F, Del Guerra P, Caraccio N, Casolaro A, Lippolis PV, Goletti O. Appearance of Graves' disease after percutaneous ethanol injection for the treatment of hyperfunctioning thyroid adenoma. *J Endocrinol Invest*. 1997;20(5):294-8.
43. Nygaard B, Knudsen JH, Hegedüs L, Scient AV, Hansen JE. Thyrotropin receptor antibodies and Graves' disease, a side-effect of ¹³¹I treatment in patients with nontoxic goiter. *J Clin Endocrinol Metab*. 1997;82(9):2926-30.
44. Schmidt M, Gorbauch E, Dietlein M, Faust M, Stützer H, Eschner W, et al. Incidence of postradioiodine immunogenic hyperthyroidism/Graves' disease in relation to a temporary increase in thyrotropin receptor antibodies after radioiodine therapy for autonomous thyroid disease. *Thyroid*. 2006;16(3):281-8.
45. Peng K, Li X, Yang D, Chan SCW, Zhou J, Wan EYF, et al. Risk of autoimmune diseases following COVID-19 and the potential protective effect from vaccination: a population-based cohort study. *EClinicalMedicine*. 2023;63:102154.
46. Muller I, Consonni D, Crivicich E, Di Marco F, Currò N, Salvi M. Increased risk of Thyroid Eye Disease following Covid-19 Vaccination. *J Clin Endocrinol Metab*. 2023.
47. Rönblom LE, Alm GV, Oberg KE. Autoimmunity after alpha-interferon therapy for malignant carcinoid tumors. *Ann Intern Med*. 1991;115(3):178-83.
48. Berthaud P, Schlumberger M, Comoy E, Avril MF, Le Chevalier T, Spielmann M, et al. Hypothyroidism and goiter during interleukin-2 therapy. *J Endocrinol Invest*. 1990;13(8):689-90.
49. Hoekman K, von Blomberg-van der Flier BM, Wagstaff J, Drexhage HA, Pinedo HM. Reversible thyroid dysfunction during treatment with GM-CSF. *Lancet*. 1991;338(8766):541-2.
50. Pariani N, Willis M, Muller I, Healy S, Nasser T, McGowan A, et al. Alemtuzumab-Induced Thyroid Dysfunction Exhibits Distinctive Clinical and Immunological Features. *The Journal of Clinical Endocrinology & Metabolism*. 2018;103(8):3010-8.
51. Brix TH, Christensen K, Holm NV, Harvald B, Hegedüs L. A population-based study of Graves' disease in Danish twins. *Clin Endocrinol (Oxf)*. 1998;48(4):397-400.
52. Coles AJ, Wing M, Smith S, Coraddu F, Greer S, Taylor C, et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet*. 1999;354(9191):1691-5.
53. Figueroa-Vega N, Alfonso-Pérez M, Benedicto I, Sánchez-Madrid F, González-Amaro R, Marazuela M. Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 2010;95(2):953-62.
54. Chen Q. The expression of interleukin-15 and interleukin-17 in tears and orbital tissues of Graves ophthalmopathy patients. *Journal of Cellular Biochemistry*. 2019;120(4):6299-303.
55. Yao Q, Wang B, Jia X, Li Q, Yao W, Zhang J-a. Increased Human Interleukin-32 Expression Is Related to Disease Activity of Graves' Disease. *Frontiers in Endocrinology*. 2019;10.
56. Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid*. 2003;13(6):547-51.

57. Durelli L, Ferrero B, Oggero A, Verdun E, Ghezzi A, Montanari E, et al. Thyroid function and autoimmunity during interferon beta-1b treatment: a multicenter prospective study. *J Clin Endocrinol Metab.* 2001;86(8):3525-32.
58. Kristan MM, Toro-Tobon D, Francis N, Desale S, Bikas A, Jonklaas J, et al. Immunotherapy-Associated Hypothyroidism: Comparison of the Pre-Existing With De-Novo Hypothyroidism. *Frontiers in Endocrinology.* 2022;13.
59. Borodic G, Hinkle DM, Cia Y. Drug-induced graves disease from CTLA-4 receptor suppression. *Ophthalmic Plast Reconstr Surg.* 2011;27(4):e87-8.
60. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. *Endocr Relat Cancer.* 2014;21(2):371-81.
61. Vagenakis AG, Wang CA, Burger A, Maloof F, Braverman LE, Ingbar SH. Iodide-induced thyrotoxicosis in Boston. *N Engl J Med.* 1972;287(11):523-7.
62. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid.* 1998;8(1):83-100.
63. Vidor GI, Stewart JC, Wall JR, Wangel A, Hetzel BS. Pathogenesis of iodine-induced thyrotoxicosis: studies in northern Tasmania. *J Clin Endocrinol Metab.* 1973;37(6):901-9.
64. Stewart JC, Vidor GI, Buttifield IH, Hetzel BS. Epidemic thyrotoxicosis in northern Tasmania: studies of clinical features and iodine nutrition. *Aust N Z J Med.* 1971;1(3):203-11.
65. Chandrasekaran M, Ramadevi K. Thyromegaly and iodine nutritional status in a tertiary care hospital in South India. *Indian J Endocrinol Metab.* 2013;17(2):260-4.
66. Laurberg P, Jørgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB, et al. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol.* 2006;155(2):219-28.
67. Boukis MA, Koutras DA, Souvatzoglou A, Evangelopoulou A, Vrontakis M, Mouloupoulos SD. Thyroid hormone and immunological studies in endemic goiter. *J Clin Endocrinol Metab.* 1983;57(4):859-62.
68. Rasooly L, Burek CL, Rose NR. Iodine-induced autoimmune thyroiditis in NOD-H-2h4 mice. *Clin Immunol Immunopathol.* 1996;81(3):287-92.
69. Allen EM, Appel MC, Braverman LE. The effect of iodide ingestion on the development of spontaneous lymphocytic thyroiditis in the diabetes-prone BB/W rat. *Endocrinology.* 1986;118(5):1977-81.
70. Kopp PA. Iodine in the Therapy of Graves' Disease: A Century After Henry S. Plummer. *Thyroid.* 2023;33(3):273-5.
71. Feinberg WD, Hoffman DL, Owen CAJ. THE EFFECTS OF VARYING AMOUNTS OF STABLE IODIDE ON THE FUNCTION OF THE HUMAN THYROID*. *The Journal of Clinical Endocrinology & Metabolism.* 1959;19(5):567-82.
72. Degroot LJ, Greer MA. The effect of stable iodide on thyroid secretion in man. *Metabolism.* 1956;5(6 Part 1):682-96.
73. Buhler UK, DeGroot LJ. Effect of stable iodine on thyroid iodine release. *J Clin Endocrinol Metab.* 1969;29(12):1546-52.
74. Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. *Eur J Endocrinol.* 2011;164(5):801-9.
75. Paunkovic N, Paunkovic J, Pavlovic O, Paunovic Z. The significant increase in incidence of Graves' disease in eastern Serbia during the civil war in the former Yugoslavia (1992 to 1995). *Thyroid.* 1998;8(1):37-41.
76. Wang J, Chen Z, Carru C, Capobianco G, Sedda S, Li Z. What is the impact of stress on the onset and anti-thyroid drug therapy in patients with graves' disease: a systematic review and meta-analysis. *BMC Endocr Disord.* 2023;23(1):194.
77. Chiovato L, Pinchera A. Stressful life events and Graves' disease. *Eur J Endocrinol.* 1996;134(6):680-2.
78. Radosavljević VR, Janković SM, Marinković JM. Stressful life events in the pathogenesis of Graves' disease. *Eur J Endocrinol.* 1996;134(6):699-701.
79. Winsa B, Adami HO, Bergström R, Gamstedt A, Dahlberg PA, Adamson U, et al. Stressful life events and Graves' disease. *Lancet.* 1991;338(8781):1475-9.
80. Matos-Santos A, Nobre EL, Costa JG, Nogueira PJ, Macedo A, Galvão-Teles A, et al. Relationship between the number and impact of stressful life events and the onset of Graves' disease and toxic nodular goitre. *Clin Endocrinol (Oxf).* 2001;55(1):15-9.
81. Landsberg L. Catecholamines and hyperthyroidism. *Clin Endocrinol Metab.* 1977;6(3):697-718.

82. Bruun E. Exophthalmic goiter developing after treatment with thyroid preparations. *Acta Med Scand.* 1945;122:13-29.
83. Takaba H, Takayanagi H. The Mechanisms of T Cell Selection in the Thymus. *Trends Immunol.* 2017;38(11):805-16.
84. Strominger JL. Developmental biology of T cell receptors. *Science.* 1989;244(4907):943-50.
85. Spitzweg C, Joba W, Heufelder AE. Expression of thyroid-related genes in human thymus. *Thyroid.* 1999;9(2):133-41.
86. Sospedra M, Ferrer-Francesch X, Domínguez O, Juan M, Foz-Sala M, Pujol-Borrell R. Transcription of a broad range of self-antigens in human thymus suggests a role for central mechanisms in tolerance toward peripheral antigens. *J Immunol.* 1998;161(11):5918-29.
87. Giménez-Barcons M, Casteràs A, Armengol Mdel P, Porta E, Correa PA, Marín A, et al. Autoimmune predisposition in Down syndrome may result from a partial central tolerance failure due to insufficient intrathymic expression of AIRE and peripheral antigens. *J Immunol.* 2014;193(8):3872-9.
88. Miyara M, Sakaguchi S. Natural regulatory T cells: mechanisms of suppression. *Trends Mol Med.* 2007;13(3):108-16.
89. Lahl K, Loddenkemper C, Drouin C, Freyer J, Arnason J, Eberl G, et al. Selective depletion of Foxp3⁺ regulatory T cells induces a scurfy-like disease. *J Exp Med.* 2007;204(1):57-63.
90. Li Q, Wang B, Mu K, Zhang JA. The pathogenesis of thyroid autoimmune diseases: New T lymphocytes - Cytokines circuits beyond the Th1-Th2 paradigm. *J Cell Physiol.* 2019;234(3):2204-16.
91. Nakano A, Watanabe M, Iida T, Kuroda S, Matsuzuka F, Miyauchi A, et al. Apoptosis-induced decrease of intrathyroidal CD4⁺CD25⁺ regulatory T cells in autoimmune thyroid diseases. *Thyroid.* 2007;17(1):25-31.
92. Klatka M, Grywalska E, Partyka M, Charytanowicz M, Kiszczak-Bochynska E, Rolinski J. Th17 and Treg cells in adolescents with Graves' disease. Impact of treatment with methimazole on these cell subsets. *Autoimmunity.* 2014;47(3):201-11.
93. Mao C, Wang S, Xiao Y, Xu J, Jiang Q, Jin M, et al. Impairment of regulatory capacity of CD4⁺CD25⁺ regulatory T cells mediated by dendritic cell polarization and hyperthyroidism in Graves' disease. *J Immunol.* 2011;186(8):4734-43.
94. Sridama V, Pacini F, DeGroot LJ. Decreased suppressor T-lymphocytes in autoimmune thyroid diseases detected by monoclonal antibodies. *J Clin Endocrinol Metab.* 1982;54(2):316-9.
95. Wang Y, Fang S, Zhou H. Pathogenic role of Th17 cells in autoimmune thyroid disease and their underlying mechanisms. *Best Pract Res Clin Endocrinol Metab.* 2023;37(2):101743.
96. Glick AB, Wodzinski A, Fu P, Levine AD, Wald DN. Impairment of regulatory T-cell function in autoimmune thyroid disease. *Thyroid.* 2013;23(7):871-8.
97. Pan D, Shin YH, Gopalakrishnan G, Hennessey J, De Groot LJ. Regulatory T cells in Graves' disease. *Clin Endocrinol (Oxf).* 2009;71(4):587-93.
98. Pacini F, DeGroot LJ. Studies of immunoglobulin synthesis in cultures of peripheral T and B lymphocytes: reduced T-suppressor cell activity in Graves' disease. *Clin Endocrinol (Oxf).* 1983;18(3):219-32.
99. Topliss DJ, Okita N, Lewis M, Row VV, Volpé R. Allosuppressor T lymphocytes abolish migration inhibition factor production in autoimmune thyroid disease: evidence from radiosensitivity experiments. *Clin Endocrinol (Oxf).* 1981;15(4):335-41.
100. Topliss D, How J, Lewis M, Row V, Volpé R. Evidence for cell-mediated immunity and specific suppressor T lymphocyte dysfunction in Graves' disease and diabetes mellitus. *J Clin Endocrinol Metab.* 1983;57(4):700-5.
101. Marazuela M, García-López MA, Figueroa-Vega N, de la Fuente H, Alvarado-Sánchez B, Monsiváis-Urenda A, et al. Regulatory T cells in human autoimmune thyroid disease. *J Clin Endocrinol Metab.* 2006;91(9):3639-46.
102. Gangi E, Vasu C, Cheatem D, Prabhakar BS. IL-10-producing CD4⁺CD25⁺ regulatory T cells play a critical role in granulocyte-macrophage colony-stimulating factor-induced suppression of experimental autoimmune thyroiditis. *J Immunol.* 2005;174(11):7006-13.
103. Molteni M, Rossetti C, Scrofani S, Bonara P, Scorza R, Kohn LD. Regulatory CD8⁺ T cells control thyrotropin receptor-specific CD4⁺ clones in healthy subjects. *Cancer Detect Prev.* 2003;27(3):167-74.
104. Vaidya B, Shenton BK, Stamp S, Miller M, Baister E, Andrews CD, et al. Analysis of peripheral blood T-cell subsets in active thyroid-associated ophthalmopathy:

- absence of effect of octreotide-LAR on T-cell subsets in patients with thyroid-associated ophthalmopathy. *Thyroid*. 2005;15(9):1073-8.
105. Migita K, Eguchi K, Tezuka H, Otsubo T, Kawakami A, Nakao H, et al. Cytotoxic activity of interleukin-2 (IL-2) activated killer cells toward thyroid epithelial cells. *Clin Exp Immunol*. 1989;77(2):196-201.
106. Piccinini LA, Mackenzie WA, Platzer M, Davies TF. Lymphokine regulation of HLA-DR gene expression in human thyroid cell monolayers. *J Clin Endocrinol Metab*. 1987;64(3):543-8.
107. Eguchi K, Otsubo T, Kawabe Y, Shimomura C, Ueki Y, Nakao H, et al. Synergy in antigen presentation by thyroid epithelial cells and monocytes from patients with Graves' disease. *Clin Exp Immunol*. 1988;72(1):84-90.
108. Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet*. 1983;2(8359):1115-9.
109. Mukuta T, Arreaza G, Nishikawa M, Resetkova E, Jamieson C, Tamai H, et al. Thyroid xenografts from patients with Graves' disease in severe combined immunodeficient mice and NIH-beige-nude-xid mice. *Clin Invest Med*. 1997;20(1):5-15.
110. Leclere J, Bene MC, Duprez A, Faure G, Thomas JL, Vignaud JM, et al. Behaviour of thyroid tissue from patients with Graves' disease in nude mice. *J Clin Endocrinol Metab*. 1984;59(1):175-7.
111. Martin L. The hereditary and familial aspects of exophthalmic goitre and nodular goitre. *Q J Med*. 1945;14:207-19.
112. Harvald B, Hauge M. A catamnestic investigation of Danish twins; a preliminary report. *Dan Med Bull*. 1956;3(5):150-8.
113. Brix TH, Kyvik KO, Christensen K, Hegedüs L. Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. *J Clin Endocrinol Metab*. 2001;86(2):930-4.
114. Hansen PS, Brix TH, Iachine I, Kyvik KO, Hegedüs L. The relative importance of genetic and environmental effects for the early stages of thyroid autoimmunity: a study of healthy Danish twins. *Eur J Endocrinol*. 2006;154(1):29-38.
115. Berisso GA, van Lint MT, Bacigalupo A, Marmont AM. Adoptive autoimmune hyperthyroidism following allogeneic stem cell transplantation from an HLA-identical sibling with Graves' disease. *Bone Marrow Transplant*. 1999;23(10):1091-2.
116. Taylor JC, Gough SC, Hunt PJ, Brix TH, Chatterjee K, Connell JM, et al. A genome-wide screen in 1119 relative pairs with autoimmune thyroid disease. *J Clin Endocrinol Metab*. 2006;91(2):646-53.
117. Lee HJ, Stefan-Lifshitz M, Li CW, Tomer Y. Genetics and epigenetics of autoimmune thyroid diseases: Translational implications. *Best Pract Res Clin Endocrinol Metab*. 2023;37(2):101661.
118. Campbell RD, Trowsdale J. Map of the human MHC. *Immunol Today*. 1993;14(7):349-52.
119. Geluk A, Van Meijgaarden KE, Janson AA, Drijfhout JW, Meloen RH, De Vries RR, et al. Functional analysis of DR17(DR3)-restricted mycobacterial T cell epitopes reveals DR17-binding motif and enables the design of allele-specific competitor peptides. *J Immunol*. 1992;149(9):2864-71.
120. Grumet FC, Payne RO, Konishi J, Kriss JP. HL-A antigens as markers for disease susceptibility and autoimmunity in Graves' disease. *J Clin Endocrinol Metab*. 1974;39(6):1115-9.
121. Farid NR, Stone E, Johnson G. Graves' disease and HLA: clinical and epidemiologic associations. *Clin Endocrinol (Oxf)*. 1980;13(6):535-44.
122. Manglabruks A, Cox N, DeGroot LJ. Genetic factors in autoimmune thyroid disease analyzed by restriction fragment length polymorphisms of candidate genes. *J Clin Endocrinol Metab*. 1991;73(2):236-44.
123. Pichurin P, Chen CR, Pichurina O, David C, Rapoport B, McLachlan SM. Thyrotropin receptor-DNA vaccination of transgenic mice expressing HLA-DR3 or HLA-DQ6b. *Thyroid*. 2003;13(10):911-7.
124. Yanagawa T, Manglabruks A, Chang YB, Okamoto Y, Fisfalen ME, Curran PG, et al. Human histocompatibility leukocyte antigen-DQA1*0501 allele associated with genetic susceptibility to Graves' disease in a Caucasian population. *J Clin Endocrinol Metab*. 1993;76(6):1569-74.
125. Yanagawa T, Manglabruks A, DeGroot LJ. Strong association between HLA-DQA1*0501 and Graves' disease in a male Caucasian population. *J Clin Endocrinol Metab*. 1994;79(1):227-9.
126. Sawai Y, DeGroot LJ. Binding of human thyrotropin receptor peptides to a Graves' disease-predisposing

- human leukocyte antigen class II molecule. *J Clin Endocrinol Metab.* 2000;85(3):1176-9.
127. Kong YC, Lomo LC, Motte RW, Giraldo AA, Baisch J, Strauss G, et al. HLA-DRB1 polymorphism determines susceptibility to autoimmune thyroiditis in transgenic mice: definitive association with HLA-DRB1*0301 (DR3) gene. *J Exp Med.* 1996;184(3):1167-72.
128. Ramgopal S, Rathika C, Padma MR, Murali V, Arun K, Kamaludeen MN, et al. Interaction of HLA-DRB1* alleles and CTLA4 (+49 AG) gene polymorphism in Autoimmune Thyroid Disease. *Gene.* 2018;642:430-8.
129. Chen QY, Huang W, She JX, Baxter F, Volpe R, Maclaren NK. HLA-DRB1*08, DRB1*03/DRB3*0101, and DRB3*0202 are susceptibility genes for Graves' disease in North American Caucasians, whereas DRB1*07 is protective. *J Clin Endocrinol Metab.* 1999;84(9):3182-6.
130. Thompson CB. Distinct roles for the costimulatory ligands B7-1 and B7-2 in T helper cell differentiation? *Cell.* 1995;81(7):979-82.
131. Karandikar NJ, Vanderlugt CL, Walunas TL, Miller SD, Bluestone JA. CTLA-4: a negative regulator of autoimmune disease. *J Exp Med.* 1996;184(2):783-8.
132. Donner H, Rau H, Walfish PG, Braun J, Siegmund T, Finke R, et al. CTLA4 alanine-17 confers genetic susceptibility to Graves' disease and to type 1 diabetes mellitus. *J Clin Endocrinol Metab.* 1997;82(1):143-6.
133. Yanagawa T, Hidaka Y, Guimaraes V, Soliman M, DeGroot LJ. CTLA-4 gene polymorphism associated with Graves' disease in a Caucasian population. *J Clin Endocrinol Metab.* 1995;80(1):41-5.
134. Yanagawa T, Taniyama M, Enomoto S, Gomi K, Maruyama H, Ban Y, et al. CTLA4 gene polymorphism confers susceptibility to Graves' disease in Japanese. *Thyroid.* 1997;7(6):843-6.
135. Heward JM, Allahabadia A, Armitage M, Hattersley A, Dodson PM, Macleod K, et al. The development of Graves' disease and the CTLA-4 gene on chromosome 2q33. *J Clin Endocrinol Metab.* 1999;84(7):2398-401.
136. Vaidya B, Imrie H, Perros P, Young ET, Kelly WF, Carr D, et al. The Cytotoxic T Lymphocyte Antigen-4 is a Major Graves' Disease Locus. *Human Molecular Genetics.* 1999;8(7):1195-9.
137. Kouki T, Sawai Y, Gardine CA, Fisfalen ME, Alegre ML, DeGroot LJ. CTLA-4 gene polymorphism at position 49 in exon 1 reduces the inhibitory function of CTLA-4 and contributes to the pathogenesis of Graves' disease. *J Immunol.* 2000;165(11):6606-11.
138. Zaletel K, Krhin B, Gaberscek S, Pirnat E, Hojker S. The influence of the exon 1 polymorphism of the cytotoxic T lymphocyte antigen 4 gene on thyroid antibody production in patients with newly diagnosed Graves' disease. *Thyroid.* 2002;12(5):373-6.
139. Adams BD, Parsons C, Walker L, Zhang WC, Slack FJ. Targeting noncoding RNAs in disease. *J Clin Invest.* 2017;127(3):761-71.
140. Chen X, Huang F, Qi Y, Zhou M, Yin Q, Peng Y, et al. Serum and thyroid tissue level of let-7b and their correlation with TRAB in Graves' disease. *Journal of Translational Medicine.* 2018;16(1):188.
141. Al-Heety RA, Al-Hadithi HS, Turki KM. Correlation of circulating miRNA-146a-5p and let-7b expression with thyroid-stimulating hormone receptor antibody in patients with graves disease. *Gene Reports.* 2020;19:100608.
142. Martínez-Hernández R, Sampedro-Núñez M, Serrano-Somavilla A, Ramos-Leví AM, de la Fuente H, Triviño JC, et al. A MicroRNA Signature for Evaluation of Risk and Severity of Autoimmune Thyroid Diseases. *The Journal of Clinical Endocrinology & Metabolism.* 2018;103(3):1139-50.
143. Yin L, Zeng C, Yao J, Shen J. Emerging Roles for Noncoding RNAs in Autoimmune Thyroid Disease. *Endocrinology.* 2020;161(8).
144. Zou J, Peng H, Liu Y. The Roles of Exosomes in Immunoregulation and Autoimmune Thyroid Diseases. *Front Immunol.* 2021;12:757674.
145. Wang Y, Xu F, Zhong JY, Lin X, Shan SK, Guo B, et al. Exosomes as Mediators of Cell-to-Cell Communication in Thyroid Disease. *Int J Endocrinol.* 2020;2020:4378345.
146. Rossi M, Taddei AR, Fasciani I, Maggio R, Giorgi F. The cell biology of the thyroid-disrupting mechanism of dichlorodiphenyltrichloroethane (DDT). *J Endocrinol Invest.* 2018;41(1):67-73.
147. Edo N, Kawakami K, Fujita Y, Morita K, Uno K, Tsukamoto K, et al. Exosomes Expressing Thyrotropin Receptor Attenuate Autoantibody-Mediated Stimulation of Cyclic Adenosine Monophosphate Production. *Thyroid.* 2019;29(7):1012-7.
148. Hiratsuka I, Yamada H, Munetsuna E, Hashimoto S, Itoh M. Circulating MicroRNAs in Graves' Disease in Relation to Clinical Activity. *Thyroid.* 2016;26(10):1431-40.

149. Hodgson NM, Rajaii F. Current Understanding of the Progression and Management of Thyroid Associated Orbitopathy: A Systematic Review. *Ophthalmol Ther.* 2020;9(1):21-33.
150. Han J-S, Kim SE, Jin J-Q, Park NR, Lee J-Y, Kim HL, et al. Tear-Derived Exosome Proteins Are Increased in Patients with Thyroid Eye Disease. *International Journal of Molecular Sciences.* 2021;22(3):1115.
151. Cuddihy RM, Dutton CM, Bahn RS. A polymorphism in the extracellular domain of the thyrotropin receptor is highly associated with autoimmune thyroid disease in females. *Thyroid.* 1995;5(2):89-95.
152. Kotsa KD, Watson PF, Weetman AP. No association between a thyrotropin receptor gene polymorphism and Graves' disease in the female population. *Thyroid.* 1997;7(1):31-3.
153. Tomer Y. Genetic susceptibility to autoimmune thyroid disease: past, present, and future. *Thyroid.* 2010;20(7):715-25.
154. Hiratani H, Bowden DW, Ikegami S, Shirasawa S, Shimizu A, Iwatani Y, et al. Multiple SNPs in intron 7 of thyrotropin receptor are associated with Graves' disease. *J Clin Endocrinol Metab.* 2005;90(5):2898-903.
155. Kuś A, Szymański K, Jurecka-Lubieniecka B, Pawlak-Adamska E, Kula D, Miśkiewicz P, et al. Gender-dependent and age-of-onset-specific association of the rs11675434 single-nucleotide polymorphism near TPO with susceptibility to Graves' ophthalmopathy. *Journal of Human Genetics.* 2017;62(3):373-7.
156. Huang C-J, Jap T-S. A systematic review of genetic studies of thyroid disorders in Taiwan. *Journal of the Chinese Medical Association.* 2015;78(3).
157. Begum MN, Islam MT, Hossain SR, Bhuyan GS, Halim MA, Shahriar I, et al. Mutation Spectrum in TPO Gene of Bangladeshi Patients with Thyroid Dysmorphogenesis and Analysis of the Effects of Different Mutations on the Structural Features and Functions of TPO Protein through *In Silico* Approach. *BioMed Research International.* 2019;2019:9218903.
158. Razmara E, Salehi M, Aslani S, Bitaraf A, Yousefi H, Colón JR, et al. Graves' disease: introducing new genetic and epigenetic contributors. *J Mol Endocrinol.* 2021;66(2):R33-r55.
159. Citterio CE, Rivolta CM, Targovnik HM. Structure and genetic variants of thyroglobulin: Pathophysiological implications. *Molecular and Cellular Endocrinology.* 2021;528:111227.
160. Ban Y, Taniyama M, Ban Y. Vitamin D receptor gene polymorphism is associated with Graves' disease in the Japanese population. *J Clin Endocrinol Metab.* 2000;85(12):4639-43.
161. Vaidya B, Imrie H, Perros P, Young ET, Kelly WF, Carr D, et al. Evidence for a new Graves disease susceptibility locus at chromosome 18q21. *Am J Hum Genet.* 2000;66(5):1710-4.
162. Tomer Y, Concepcion E, Greenberg DA. A C/T single-nucleotide polymorphism in the region of the CD40 gene is associated with Graves' disease. *Thyroid.* 2002;12(12):1129-35.
163. Kurylowicz A, Kula D, Ploski R, Skorka A, Jurecka-Lubieniecka B, Zebracka J, et al. Association of CD40 gene polymorphism (C-1T) with susceptibility and phenotype of Graves' disease. *Thyroid.* 2005;15(10):1119-24.
164. Shirasawa S, Harada H, Furugaki K, Akamizu T, Ishikawa N, Ito K, et al. SNPs in the promoter of a B cell-specific antisense transcript, SAS-ZFAT, determine susceptibility to autoimmune thyroid disease. *Hum Mol Genet.* 2004;13(19):2221-31.
165. Lopez ER, Zwermann O, Segni M, Meyer G, Reincke M, Seissler J, et al. A promoter polymorphism of the CYP27B1 gene is associated with Addison's disease, Hashimoto's thyroiditis, Graves' disease and type 1 diabetes mellitus in Germans. *Eur J Endocrinol.* 2004;151(2):193-7.
166. Imani D, Rezaei R, Razi B, Alizadeh S, Mahmoudi M. Association Between IL6-174 G/C Polymorphism and Graves' Disease: A Systematic Review and Meta-Analysis. *Acta Med Iran.* 2017;55(11):665-71.
167. Hiromatsu Y, Fukutani T, Ichimura M, Mukai T, Kaku H, Nakayama H, et al. Interleukin-13 gene polymorphisms confer the susceptibility of Japanese populations to Graves' disease. *J Clin Endocrinol Metab.* 2005;90(1):296-301.
168. Liu N, Li X, Liu C, Zhao Y, Cui B, Ning G. The association of interleukin-1alpha and interleukin-1beta polymorphisms with the risk of Graves' disease in a case-control study and meta-analysis. *Hum Immunol.* 2010;71(4):397-401.
169. Zeitlin AA, Simmonds MJ, Gough SC. Genetic developments in autoimmune thyroid disease: an evolutionary process. *Clin Endocrinol (Oxf).* 2008;68(5):671-82.

170. Tu Y, Fan G, Zeng T, Cai X, Kong W. Association of TNF- α promoter polymorphism and Graves' disease: an updated systematic review and meta-analysis. *Biosci Rep.* 2018;38(2).
171. Ban Y, Tozaki T, Taniyama M, Tomita M, Ban Y. The codon 620 single nucleotide polymorphism of the protein tyrosine phosphatase-22 gene does not contribute to autoimmune thyroid disease susceptibility in the Japanese. *Thyroid.* 2005;15(10):1115-8.
172. Zhang Q, Liu S, Guan Y, Chen Q, Zhang Q, Min X. RNASET2, GPR174, and PTPN22 gene polymorphisms are related to the risk of liver damage associated with the hyperthyroidism in patients with Graves' disease. *Journal of Clinical Laboratory Analysis.* 2018;32(2):e22258.
173. Wawrusiewicz-Kurylonek N, Koper-Lenkiewicz OM, Gościk J, Myśliwiec J, Pawłowski P, Krętowski AJ. Association of PTPN22 polymorphism and its correlation with Graves' disease susceptibility in Polish adult population—A preliminary study. *Molecular Genetics & Genomic Medicine.* 2019;7(6):e661.
174. Valta M, Gazali AM, Viisanen T, Ihantola E-L, Ekman I, Toppari J, et al. Type 1 diabetes linked PTPN22 gene polymorphism is associated with the frequency of circulating regulatory T cells. *European Journal of Immunology.* 2020;50(4):581-8.
175. Yuan M, Wei L, Zhou R, Bai Q, Wei Y, Zhang W, et al. Four FCRL3 Gene Polymorphisms (FCRL3_3, _5, _6, _8) Confer Susceptibility to Multiple Sclerosis: Results from a Case-Control Study. *Molecular Neurobiology.* 2016;53(3):2029-35.
176. Fang Y, Li Y, Zeng J, Wang J, Liu R, Cao C. Genetic association of Fc receptor-like glycoprotein with susceptibility to Graves' disease in a Chinese Han population. *Immunobiology.* 2016;221(1):56-62.
177. Schoenmakers EFPM, Wanschura S, Mols R, Bullerdiek J, Van den Berghe H, Van de Ven WJM. Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumours. *Nature Genetics.* 1995;10(4):436-44.
178. Yamada H, Watanabe M, Nanba T, Akamizu T, Iwatani Y. The +869T/C polymorphism in the transforming growth factor-beta1 gene is associated with the severity and intractability of autoimmune thyroid disease. *Clin Exp Immunol.* 2008;151(3):379-82.
179. Sutherland A, Davies J, Owen CJ, Vaikkakara S, Walker C, Cheetham TD, et al. Genomic polymorphism at the interferon-induced helicase (IFIH1) locus contributes to Graves' disease susceptibility. *J Clin Endocrinol Metab.* 2007;92(8):3338-41.
180. Vejrazkova D, Vcelak J, Vaclavikova E, Vankova M, Zajickova K, Duskova M, et al. Genetic predictors of the development and recurrence of Graves' disease. *Physiol Res.* 2018;67(Suppl 3):S431-s9.
181. Calder EA, Penhale WJ, Barnes EW, Irvine WJ. Evidence for circulating immune complexes in thyroid disease. *Br Med J.* 1974;2(5909):30-1.
182. Marinò M, Chiovato L, Friedlander JA, Latrofa F, Pinchera A, McCluskey RT. Serum antibodies against megalin (GP330) in patients with autoimmune thyroiditis. *J Clin Endocrinol Metab.* 1999;84(7):2468-74.
183. Morris JC, Bergert ER, Bryant WP. Binding of immunoglobulin G from patients with autoimmune thyroid disease to rat sodium-iodide symporter peptides: evidence for the iodide transporter as an autoantigen. *Thyroid.* 1997;7(4):527-34.
184. Kubota S, Gunji K, Stolarski C, Kennerdell JS, Wall J. Reevaluation of the prevalences of serum autoantibodies reactive with "64-kd eye muscle proteins" in patients with thyroid-associated ophthalmopathy. *Thyroid.* 1998;8(2):175-9.
185. Mori T, Kriss JP. Measurements by competitive binding radioassay of serum anti-microsomal and anti-thyroglobulin antibodies in Graves' disease and other thyroid disorders. *J Clin Endocrinol Metab.* 1971;33(4):688-98.
186. Wang PW, Huang MJ, Liu RT, Chen CD. Triiodothyronine autoantibodies in Graves' disease: their changes after antithyroid therapy and relationship with the thyroglobulin antibodies. *Acta Endocrinol (Copenh).* 1990;122(1):22-8.
187. Nakamura S, Sakata S, Shima H, Komaki T, Kojima N, Kamikubo K, et al. Thyroid hormone autoantibodies (THAA) in two cases of Graves' disease: effects of antithyroid drugs, prednisolone, and subtotal thyroidectomy. *Endocrinol Jpn.* 1986;33(6):751-9.
188. Kasagi K, Kousaka T, Higuchi K, Iida Y, Misaki T, Alam MS, et al. Clinical significance of measurements of antithyroid antibodies in the diagnosis of Hashimoto's thyroiditis: comparison with histological findings. *Thyroid.* 1996;6(5):445-50.
189. Amino N, Hagen SR, Yamada N, Refetoff S. Measurement of circulating thyroid microsomal antibodies by the tanned red cell haemagglutination technique: its usefulness in the

- diagnosis of autoimmune thyroid diseases. *Clin Endocrinol (Oxf)*. 1976;5(2):115-25.
190. Mullins RJ, Cohen SB, Webb LM, Chernajovsky Y, Dayan CM, Londei M, et al. Identification of thyroid stimulating hormone receptor-specific T cells in Graves' disease thyroid using autoantigen-transfected Epstein-Barr virus-transformed B cell lines. *J Clin Invest*. 1995;96(1):30-7.
191. Weetman AP, Gunn C, Hall R, McGregor AM. Thyroid autoantigen-induced lymphocyte proliferation in Graves' disease and Hashimoto's thyroiditis. *J Clin Lab Immunol*. 1985;17(1):1-6.
192. Fisfalen ME, DeGroot LJ, Quintans J, Franklin WA, Soltani K. Microsomal antigen-reactive lymphocyte lines and clones derived from thyroid tissue of patients with Graves' disease. *J Clin Endocrinol Metab*. 1988;66(4):776-84.
193. Soliman M, Kaplan E, Fisfalen ME, Okamoto Y, DeGroot LJ. T-cell reactivity to recombinant human thyrotropin receptor extracellular domain and thyroglobulin in patients with autoimmune and nonautoimmune thyroid diseases. *J Clin Endocrinol Metab*. 1995;80(1):206-13.
194. Aoki N, DeGroot J. Lymphocyte blastogenic response to human thyroglobulin in Graves' disease, Hashimoto's thyroiditis, and metastatic thyroid cancer. *Clin Exp Immunol*. 1979;38(3):523-30.
195. Inaba H, De Groot LJ, Akamizu T. Thyrotropin Receptor Epitope and Human Leukocyte Antigen in Graves' Disease. *Front Endocrinol (Lausanne)*. 2016;7:120.
196. Soliman M, Kaplan E, Yanagawa T, Hidaka Y, Fisfalen ME, DeGroot LJ. T-cells recognize multiple epitopes in the human thyrotropin receptor extracellular domain. *J Clin Endocrinol Metab*. 1995;80(3):905-14.
197. Kula D, Bednarczuk T, Jurecka-Lubieniecka B, Polanska J, Hasse-Lazar K, Jarzab M, et al. Interaction of HLA-DRB1 alleles with CTLA-4 in the predisposition to Graves' disease: the impact of DRB1*07. *Thyroid*. 2006;16(5):447-53.
198. Tandon N, Freeman M, Weetman AP. T cell responses to synthetic thyroid peroxidase peptides in autoimmune thyroid disease. *Clin Exp Immunol*. 1991;86(1):56-60.
199. Fisfalen ME, Soliman M, Okamoto Y, Soltani K, DeGroot LJ. Proliferative responses of T-cells to thyroid antigens and synthetic thyroid peroxidase peptides in autoimmune thyroid disease. *J Clin Endocrinol Metab*. 1995;80(5):1597-604.
200. Chiovato L, Bassi P, Santini F, Mammoli C, Lapi P, Carayon P, et al. Antibodies producing complement-mediated thyroid cytotoxicity in patients with atrophic or goitrous autoimmune thyroiditis. *J Clin Endocrinol Metab*. 1993;77(6):1700-5.
201. Rebuffat SA, Nguyen B, Robert B, Castex F, Peraldi-Roux S. Anti-thyroperoxidase antibody-dependent cytotoxicity in autoimmune thyroid disease. *J Clin Endocrinol Metab*. 2008;93(3):929-34.
202. Ploth DW, Fitz A, Schnetzler D, Seidenfeld J, Wilson CB. Thyroglobulin-anti-thyroglobulin immune complex glomerulonephritis complicating radioiodine therapy. *Clin Immunol Immunopathol*. 1978;9(3):327-34.
203. Matsuura M, Kikkawa Y, Akashi K, Kitagawa T, Inage Z, Iwamori M, et al. Thyroid antigen-antibody nephritis: possible involvement of fucosyl-GM1 as the antigen. *Endocrinol Jpn*. 1987;34(4):587-93.
204. Carvalho GAd, Perez CLS, Ward LS. Utilização dos testes de função tireoidiana na prática clínica. *Arquivos Brasileiros de Endocrinologia & Metabologia*. 2013;57.
205. Fröhlich E, Wahl R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. *Front Immunol*. 2017;8:521.
206. Tada H, Izumi Y, Watanabe Y, Takano T, Fukata S, Kuma K, et al. Blocking Type Anti-TSH Receptor Antibodies Detected by Radioreceptor Assay in Graves' Disease. *Endocrine Journal*. 2001;48(6):703-10.
207. Kim WB, Chung HK, Park YJ, Park DJ, Tahara K, Kohn LD, et al. The Prevalence and Clinical Significance of Blocking Thyrotropin Receptor Antibodies in Untreated Hyperthyroid Graves' Disease. *Thyroid*. 2000;10(7):579-86.
208. Roti E, Braverman LE, DeGroot LJ. TSH Receptor Antibody Measurement in the Diagnosis and Management of Graves' Disease Is Rarely Necessary. *The Journal of Clinical Endocrinology & Metabolism*. 1998;83(11):3781-4.
209. Kotwal A, Stan M. Thyrotropin Receptor Antibodies-An Overview. *Ophthalmic Plast Reconstr Surg*. 2018;34(4S Suppl 1):S20-s7.
210. Cárdenas Roldán J, Amaya-Amaya J, Castellanos-de la Hoz J, Giraldo-Villamil J, Montoya-Ortiz G, Cruz-Tapias P, et al. Autoimmune thyroid disease in rheumatoid arthritis: a global perspective. *Arthritis*. 2012;2012:864907.
211. Yavasoglu I, Senturk T, Coskun A, Bolaman Z. Rheumatoid arthritis and anti-thyroid antibodies. *Autoimmunity*. 2009;42(2):168-9.

212. Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. *Thyroid*. 2002;12(11):977-88.
213. Ochi Y, DeGroot LJ. Vitiligo in Graves' disease. *Ann Intern Med*. 1969;71(5):935-40.
214. Welti H. [Skin manifestations associated with severe forms of Basedow's disease]. *Bull Schweiz Akad Med Wiss*. 1968;23(5):476-82.
215. Amoroso A, Garzia P, Pasquarelli C, Sportelli G, Afeltra A. Hashimoto's thyroiditis associated with urticaria and angio-oedema: disappearance of cutaneous and mucosal manifestations after thyroidectomy. *J Clin Pathol*. 1997;50(3):254-6.
216. Marinó M, Ricciardi R, Pinchera A, Barbesino G, Manetti L, Chiovato L, et al. Mild clinical expression of myasthenia gravis associated with autoimmune thyroid diseases. *J Clin Endocrinol Metab*. 1997;82(2):438-43.
217. Sonnet E, Massart C, Gibassier J, Allannic H, Maugendre D. Longitudinal study of soluble intercellular adhesion molecule-1 (ICAM-1) in sera of patients with Graves' disease. *J Endocrinol Invest*. 1999;22(6):430-5.
218. Marshall JS, Weisberger AS, Levy RP, Breckenridge RT. Coexistent Idiopathic Thrombocytopenic Purpura and Hyperthyroidism. *Annals of Internal Medicine*. 1967;67(2):411-4.
219. White RG, Bass BH, Williams E. Lymphadenoid goitre and the syndrome of systemic lupus erythematosus. *Lancet*. 1961;1(7173):368-73.
220. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. *Ann Rheum Dis*. 2004;63(9):1159-61.
221. Irvine WJ, Davies SH, Teitelbaum S, Delamore IW, Williams AW. The clinical and pathological significance of gastric parietal cell antibody. *Ann N Y Acad Sci*. 1965;124(2):657-91.
222. Dittmar M, Kahaly GJ. Polyglandular Autoimmune Syndromes: Immunogenetics and Long-Term Follow-Up. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(7):2983-92.
223. Katakura M, Yamada T, Aizawa T, Hiramatsu K, Yukimura Y, Ishihara M, et al. Presence of antideoxyribonucleic acid antibody in patients with hyperthyroidism of Graves' disease. *J Clin Endocrinol Metab*. 1987;64(3):405-8.
224. Cowling DC, Mackay IR, Taft LI. Lupoid hepatitis. *Lancet*. 1956;271(6957):1323-6.
225. Paggi A, Caccavo D, Ferri GM, Di Prima MA, Amoroso A, Vaccaro F, et al. Anti-cardiolipin antibodies in autoimmune thyroid diseases. *Clin Endocrinol (Oxf)*. 1994;40(3):329-33.
226. Siddiqi A, Monson JP, Wood DF, Besser GM, Burrin JM. Serum cytokines in thyrotoxicosis. *J Clin Endocrinol Metab*. 1999;84(2):435-9.
227. Orgiazzi J, Williams DE, Chopra IJ, Solomon DH. Human thyroid adenyl cyclase-stimulating activity in immunoglobulin G of patients with Graves' disease. *J Clin Endocrinol Metab*. 1976;42(2):341-54.
228. Evans C, Morgenthaler NG, Lee S, Llewellyn DH, Clifton-Bligh R, John R, et al. Development of a luminescent bioassay for thyroid stimulating antibodies. *J Clin Endocrinol Metab*. 1999;84(1):374-7.
229. Di Cerbo A, Di Paola R, Menzaghi C, De Filippis V, Tahara K, Corda D, et al. Graves' immunoglobulins activate phospholipase A2 by recognizing specific epitopes on thyrotropin receptor. *J Clin Endocrinol Metab*. 1999;84(9):3283-92.
230. Smyth PP, McMullan NM, Grubeck-Loebenstien B, O'Donovan DK. Thyroid growth-stimulating immunoglobulins in goitrous disease: relationship to thyroid-stimulating immunoglobulins. *Acta Endocrinol (Copenh)*. 1986;111(3):321-30.
231. Endo K, Kasagi K, Konishi J, Ikekubo K, Okuno T, Takeda Y, et al. Detection and properties of TSH-binding inhibitor immunoglobulins in patients with Graves' disease and Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 1978;46(5):734-9.
232. Irvine WJ, Lamberg BA, Cullen DR, Gordin R. Primary hypothyroidism preceding thyrotoxicosis: a report of 2 cases and a review of the literature. *J Clin Lab Immunol*. 1979;2(4):349-52.
233. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab*. 2006;91(9):3464-70.
234. Morshed SA, Davies TF. Graves' Disease Mechanisms: The Role of Stimulating, Blocking, and Cleavage Region TSH Receptor Antibodies. *Horm Metab Res*. 2015;47(10):727-34.

-
235. Morshed SA, Ando T, Latif R, Davies TF. Neutral Antibodies to the TSH Receptor Are Present in Graves' Disease and Regulate Selective Signaling Cascades. *Endocrinology*. 2010;151(11):5537-49.
236. Ando T, Latif R, Daniel S, Eguchi K, Davies TF. Dissecting linear and conformational epitopes on the native thyrotropin receptor. *Endocrinology*. 2004;145(11):5185-93.
237. Misrahi M, Milgrom E. Cleavage and shedding of the TSH receptor. *Eur J Endocrinol*. 1997;137(6):599-602.
238. McKenzie JM. FURTHER EVIDENCE FOR A THYROID ACTIVATOR IN HYPERTHYROIDISM*. *The Journal of Clinical Endocrinology & Metabolism*. 1960;20(3):380-8.
239. Takasu N, Oshiro C, Akamine H, Komiya I, Nagata A, Sato Y, et al. Thyroid-stimulating antibody and TSH-binding inhibitor immunoglobulin in 277 Graves' patients and in 686 normal subjects. *J Endocrinol Invest*. 1997;20(8):452-61.
240. Stan MN, Algeciras-Schimmich A, Murthy V, Thapa P, Araki N. Diagnostic Utility of a New Assay for Thyroid Stimulating Immunoglobulins in Graves' Disease and Thyroid Eye Disease. *Thyroid*. 2021;32(2):170-6.
241. McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. *Thyroid*. 2013;23(1):14-24.
242. Ahmad E, Hafeez K, Arshad MF, Isuga J, Vrettos A. Hypothyroidism conversion to hyperthyroidism: it's never too late. *Endocrinol Diabetes Metab Case Rep*. 2018;2018.
243. Kuzuya N, Chiu SC, Ikeda H, Uchimura H, Ito K, Nagataki S. Correlation between thyroid stimulators and 3,5,3'-triiodothyronine suppressibility in patients during treatment for hyperthyroidism with thionamide drugs: comparison of assays by thyroid-stimulating and thyrotropin-displacing activities. *J Clin Endocrinol Metab*. 1979;48(4):706-11.
244. Visscher SL, Naessens JM, Yawn BP, Reinalda MS, Anderson SS, Borah BJ. Developing a standardized healthcare cost data warehouse. *BMC Health Serv Res*. 2017;17(1):396.
245. Soliman M, Kaplan E, Abdel-Latif A, Scherberg N, DeGroot LJ. Does thyroidectomy, radioactive iodine therapy, or antithyroid drug treatment alter reactivity of patients' T cells to epitopes of thyrotropin receptor in autoimmune thyroid diseases? *J Clin Endocrinol Metab*. 1995;80(8):2312-21.
246. Fenzi G, Hashizume K, Roudebush CP, DeGroot LJ. Changes in thyroid-stimulating immunoglobulins during antithyroid therapy. *J Clin Endocrinol Metab*. 1979;48(4):572-6.
247. Mukhtar ED, Smith BR, Pyle GA, Hall R, Vice P. Relation of thyroid-stimulating immunoglobulins to thyroid function and effects of surgery, radioiodine, and antithyroid drugs. *Lancet*. 1975;1(7909):713-5.
248. Nygaard B, Metcalfe RA, Phipps J, Weetman AP, Hegedüs L. Graves' disease and thyroid associated ophthalmopathy triggered by 131I treatment of non-toxic goiter. *J Endocrinol Invest*. 1999;22(6):481-5.
249. Pichurin P, Pham N, David CS, Rapoport B, McLachlan SM. HLA-DR3 transgenic mice immunized with adenovirus encoding the thyrotropin receptor: T cell epitopes and functional analysis of the CD40 Graves' polymorphism. *Thyroid*. 2006;16(12):1221-7.
250. Inaba H, Pan D, Shin YH, Martin W, Buchman G, De Groot LJ. Immune response of mice transgenic for human histocompatibility leukocyte Antigen-DR to human thyrotropin receptor-extracellular domain. *Thyroid*. 2009;19(11):1271-80.
251. Pearce SHS, Dayan C, Wraith DC, Barrell K, Olive N, Jansson L, et al. Antigen-Specific Immunotherapy with Thyrotropin Receptor Peptides in Graves' Hyperthyroidism: A Phase I Study. *Thyroid*. 2019;29(7):1003-11.
252. Jansson L, Vrolix K, Jahraus A, Martin KF, Wraith DC. Immunotherapy With Apitopes Blocks the Immune Response to TSH Receptor in HLA-DR Transgenic Mice. *Endocrinology*. 2018;159(9):3446-57.
253. Diana T, Olivo PD, Kahaly GJ. Thyrotropin Receptor Blocking Antibodies. *Horm Metab Res*. 2018;50(12):853-62.
254. Núñez Miguel R, Sanders P, Allen L, Evans M, Holly M, Johnson W, et al. Structure of full-length TSH receptor in complex with antibody K1-70™. *J Mol Endocrinol*. 2023;70(1).
255. Fisfalen ME, Palmer EM, Van Seventer GA, Soltani K, Sawai Y, Kaplan E, et al. Thyrotropin-receptor and thyroid peroxidase-specific T cell clones and their cytokine profile in autoimmune thyroid disease. *J Clin Endocrinol Metab*. 1997;82(11):3655-63.
256. Ferrari SM, Paparo SR, Ragusa F, Elia G, Mazzi V, Patrizio A, et al. Chemokines in thyroid autoimmunity. *Best Pract Res Clin Endocrinol Metab*. 2023;37(2):101773.
-

-
257. Hiromatsu Y, Yang D, Bednarczuk T, Miyake I, Nonaka K, Inoue Y. Cytokine Profiles in Eye Muscle Tissue and Orbital Fat Tissue from Patients with Thyroid-Associated Ophthalmopathy*. *The Journal of Clinical Endocrinology & Metabolism*. 2000;85(3):1194-9.
258. Wakelkamp IM, Gerding MN, Van Der Meer JW, Prummel MF, Wiersinga WM. Both Th1- and Th2-derived cytokines in serum are elevated in Graves' ophthalmopathy. *Clin Exp Immunol*. 2000;121(3):453-7.
259. Zheng L, Ye P, Liu C. The role of the IL-23/IL-17 axis in the pathogenesis of Graves' disease. *Endocr J*. 2013;60(5):591-7.
260. Kościuszko M, Popławska-Kita A, Pawłowski P, Lipińska D, Hryniewicka J, Jankowska D, et al. Clinical relevance of estimating circulating interleukin-17 and interleukin-23 during methylprednisolone therapy in Graves' orbitopathy: A preliminary study. *Advances in Medical Sciences*. 2021;66(2):315-20.
261. Inaba H, Martin W, Ardito M, De Groot AS, De Groot LJ. The role of glutamic or aspartic acid in position four of the epitope binding motif and thyrotropin receptor-extracellular domain epitope selection in Graves' disease. *J Clin Endocrinol Metab*. 2010;95(6):2909-16.
262. Crisp M, Starkey KJ, Lane C, Ham J, Ludgate M. Adipogenesis in thyroid eye disease. *Invest Ophthalmol Vis Sci*. 2000;41(11):3249-55.
263. Bell A, Gagnon A, Grunder L, Parikh SJ, Smith TJ, Sorisky A. Functional TSH receptor in human abdominal preadipocytes and orbital fibroblasts. *Am J Physiol Cell Physiol*. 2000;279(2):C335-40.
264. Haraguchi K, Shimura H, Kawaguchi A, Ikeda M, Endo T, Onaya T. Effects of thyrotropin on the proliferation and differentiation of cultured rat preadipocytes. *Thyroid*. 1999;9(6):613-9.
265. Kasagi K, Konishi J, Endo K, Mori T, Nagahara K, Makimoto K, et al. Adenylate cyclase activity in thyroid tissue from patients with untreated Graves' disease. *J Clin Endocrinol Metab*. 1980;51(3):492-9.
266. Intenzo CM, dePapp AE, Jabbour S, Miller JL, Kim SM, Capuzzi DM. Scintigraphic manifestations of thyrotoxicosis. *Radiographics*. 2003;23(4):857-69.
267. Acland JD. The interpretation of the serum protein-bound iodine: A review. *J Clin Pathol*. 1971;24(3):187-218.
268. Farran HE, Shalom ES. Effect of L-tyrosine upon the protein bound iodine in thyrotoxicosis. *J Clin Endocrinol Metab*. 1966;26(8):918-20.
269. Sterling K, Chodos RB. Radiothyroxine turnover studies in myxedema, thyrotoxicosis, and hypermetabolism without endocrine disease. *J Clin Invest*. 1956;35(7):806-13.
270. Ingbar SH, Freinkel N. Studies of thyroid function and the peripheral metabolism of I 131-labeled thyroxine in patients with treated Graves disease. *J Clin Invest*. 1958;37(11):1603-14.
271. Uller RP, Van Herle AJ. Effect of therapy on serum thyroglobulin levels in patients with Graves' disease. *J Clin Endocrinol Metab*. 1978;46(5):747-55.
272. Greer MA, Smith GE. Method for increasing the accuracy of the radioiodine uptake as a test for thyroid function by the use of desiccated thyroid. *J Clin Endocrinol Metab*. 1954;14(11):1374-84.
273. Werner SC, Spooner M. A new and simple test for hyperthyroidism employing L-triiodothyronine and the twenty-four hour I-131 uptake method. *Bull N Y Acad Med*. 1955;31(2):137-45.
274. Raben MS. The paradoxical effects of thiocyanate and of thyrotropin on the organic binding of iodine by the thyroid in the presence of large amounts of iodide. *Endocrinology*. 1949;45(3):296-304.
275. Suzuki H, Mashimo K. Significance of the iodide-perchlorate discharge test in patients with 131 I-treated and untreated hyperthyroidism. *J Clin Endocrinol Metab*. 1972;34(2):332-8.
276. Uchida T, Shimamura M, Taka H, Kaga N, Miura Y, Nishida Y, et al. The Effect of Long-Term Inorganic Iodine on Intrathyroidal Iodothyronine Content and Gene Expression in Mice with Graves' Hyperthyroidism. *Thyroid*. 2023;33(3):330-7.
277. Ochi Y, DeGroot LJ. TSH- or LATS-stimulated thyroid hormone release is inhibited by iodide. *Endocrinology*. 1969;84(6):1305-9.
278. Grollman EF, Smolar A, Ommaya A, Tombaccini D, Santisteban P. Iodine Suppression of Iodide Uptake in FRTL-5 Thyroid Cells. *Endocrinology*. 1986;118(6):2477-82.
279. Granner DK, Scranton JR, Curtis SJ. Kinetic analysis of thyroidal iodide concentration in hypophysectomized rats fed high or low iodine diets. *Endocrinology*. 1963;72:503-4.
-

280. Sherwin JR, Tong W. The actions of iodide and TSH on thyroid cells showing a dual control system for the iodide pump. *Endocrinology*. 1974;94(5):1465-74.
281. Sato S, Noh JY, Sato S, Suzuki M, Yasuda S, Matsumoto M, et al. Comparison of efficacy and adverse effects between methimazole 15 mg+inorganic iodine 38 mg/day and methimazole 30 mg/day as initial therapy for Graves' disease patients with moderate to severe hyperthyroidism. *Thyroid*. 2015;25(1):43-50.
282. Takata K, Amino N, Kubota S, Sasaki I, Nishihara E, Kudo T, et al. Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease. *Clin Endocrinol (Oxf)*. 2010;72(6):845-50.
283. Krieger CC, Neumann S, Place RF, Marcus-Samuels B, Gershengorn MC. Bidirectional TSH and IGF-1 receptor cross talk mediates stimulation of hyaluronan secretion by Graves' disease immunoglobins. *J Clin Endocrinol Metab*. 2015;100(3):1071-7.
284. Neumann S, Krieger Christine C, Gershengorn Marvin C. Targeting TSH and IGF-1 Receptors to Treat Thyroid Eye Disease. *European Thyroid Journal*. 2020;9(Suppl. 1):59-65.
285. Minich WB, Dehina N, Welsink T, Schwiebert C, Morgenthaler NG, Köhrle J, et al. Autoantibodies to the IGF1 receptor in Graves' orbitopathy. *J Clin Endocrinol Metab*. 2013;98(2):752-60.
286. Heimann P. ULTRASTRUCTURE OF HUMAN THYROID. *Acta Endocrinologica (Norway)*. 1966;53(2_Supplement):S6-S102.
287. LiVolsi VA, Baloch ZW. The Pathology of Hyperthyroidism. *Frontiers in Endocrinology*. 2018;9.
288. Bostrom H, Hed R. Thyrotoxic myopathy and polymyositis in elderly patients; differential-diagnostic viewpoints. *Acta Med Scand*. 1958;162(3):225-30.
289. McEachern D, Ross WD. CHRONIC THYROTOXIC MYOPATHY: A REPORT OF THREE CASES WITH A REVIEW OF PREVIOUSLY REPORTED CASES. *Brain*. 1942;65(2):181-92.
290. Rundle FF, Finlay-Jones LR, Noad KB. MALIGNANT EXOPHTHALMOS: A QUANTITATIVE ANALYSIS OF THE ORBITAL TISSUES. *Australasian Annals of Medicine*. 1953;2(2):128-35.
291. Dudgeon LS, Urquhart AL. LYMPHORRHAGES IN THE MUSCLES IN EXOPHTHALMIC GOITRE. *Brain*. 1926;49(2):182-6.
292. Ezrin C, Swanson HE, Humphrey JG, Dawson JW, Hill FM. THE CELLS OF THE HUMAN ADENOHYPHYSIS IN THYROID DISORDERS*. *The Journal of Clinical Endocrinology & Metabolism*. 1959;19(8):958-66.
293. Scheithauer BW, Kovacs KT, Young WF, Jr., Randall RV. The pituitary gland in hyperthyroidism. *Mayo Clin Proc*. 1992;67(1):22-6.
294. Movitt ER, Gerstl B, Davis AE. NEEDLE LIVER BIOPSY IN THYROTOXICOSIS. *AMA Archives of Internal Medicine*. 1953;91(6):729-39.
295. Piper J, Poulsen E. Liver biopsy in thyrotoxicosis. *Acta Med Scand*. 1947;127(4):439-47.
296. Okosieme OE, Taylor PN, Evans C, Thayer D, Chai A, Khan I, et al. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. *Lancet Diabetes Endocrinol*. 2019;7(4):278-87.
297. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med*. 2024;390(6):497-509.
298. Fallon MD, Perry HM, 3rd, Bergfeld M, Droke D, Teitelbaum SL, Avioli LV. Exogenous hyperthyroidism with osteoporosis. *Arch Intern Med*. 1983;143(3):442-4.
299. Follis RH, Jr. Skeletal changes associated with hyperthyroidism. *Bull Johns Hopkins Hosp*. 1953;92(6):405-21.
300. Hershman JM. Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. *Thyroid*. 1999;9(7):653-7.
301. Nguyen CT, Sasso EB, Barton L, Mestman JH. Graves' hyperthyroidism in pregnancy: a clinical review. *Clin Diabetes Endocrinol*. 2018;4:4.
302. White WH. On the Prognosis of Secondary Symptoms and Conditions of Exophthalmic Goitre. *Br Med J*. 1886;2(1334):151-3.
303. Sattler H. Basedow's disease. New York: Grune & Stratton; 1952.
304. Arnold BM, Casal G, Higgins HP. Apathetic thyrotoxicosis. *Can Med Assoc J*. 1974;111(9):957-8.
305. Leblond CP, Fertman MB, et al. Radio-iodine autography in studies of human goitrous thyroid glands. *Arch Pathol (Chic)*. 1946;41:510-5.

-
306. Collazo-Clavell ML, Gharib H, Maragos NE. Relationship between vocal cord paralysis and benign thyroid disease. *Head Neck*. 1995;17(1):24-30.
307. Mahaux JE, Chamla-Soumenkoff J, Delcourt R, Levin S. Painful enlargement of left subtrapezoid lymph nodes in Graves's disease. *Br Med J*. 1971;1(5745):384.
308. Rumblyrt JS, Schocket AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin North Am*. 2004;24(2):215-23, vi.
309. Fatourechi V, Garrity JA, Bartley GB, Bergstralh EJ, Gorman CA. Orbital decompression in Graves' ophthalmopathy associated with pretibial myxedema. *J Endocrinol Invest*. 1993;16(6):433-7.
310. Bartley GB, Fatourechi V, Kadmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. The incidence of Graves' ophthalmopathy in Olmsted County, Minnesota. *Am J Ophthalmol*. 1995;120(4):511-7.
311. Swanson JW, Kelly JJ, Jr., McConahey WM. Neurologic aspects of thyroid dysfunction. *Mayo Clin Proc*. 1981;56(8):504-12.
312. Brownlie BE, Rae AM, Walshe JW, Wells JE. Psychoses associated with thyrotoxicosis - 'thyrotoxic psychosis.' A report of 18 cases, with statistical analysis of incidence. *Eur J Endocrinol*. 2000;142(5):438-44.
313. Adams R, Oh ES, Yasar S, Lyketsos CG, Mammen JS. Endogenous and Exogenous Thyrotoxicosis and Risk of Incident Cognitive Disorders in Older Adults. *JAMA Intern Med*. 2023;183(12):1324-31.
314. Gold HK, Spann JF, Jr., Braunwald E. Effect of alterations in the thyroid state on the intrinsic contractile properties of isolated rat skeletal muscle. *J Clin Invest*. 1970;49(4):849-54.
315. Woodbury DM, Hurley RE, Lewis NG, McArthur MW, Copeland WW, Kirschvink JF, et al. Effect of thyroxin, thyroidectomy and 6-n-propyl-2-thiouracil on brain function. *J Pharmacol Exp Ther*. 1952;106(3):331-40.
316. Ravera JJ, Cervino JM, Fernandez G, Ferrari Forcade A, Malosetti H, Muxi F, et al. Two cases of Graves' disease with signs of a pyramidal lesion. Improvement in neurologic signs during treatment with antithyroid drugs. *J Clin Endocrinol Metab*. 1960;20:876-80.
317. Feibel JH, Campa JF. Thyrotoxic neuropathy (Basedow's paraplegia). *J Neurol Neurosurg Psychiatry*. 1976;39(5):491-7.
318. Waldenström JAN. Acute Thyrotoxic Encephalo- or Myopathy, its cause and treatment. *Acta Medica Scandinavica*. 1945;121(2-3):251-94.
319. Condon JV, Becka DR, Gibbs FA. Electroencephalographic abnormalities in hyperthyroidism. *J Clin Endocrinol Metab*. 1954;14(12):1511-8.
320. Cantón A, de Fàbregas O, Tintoré M, Mesa J, Codina A, Simó R. Encephalopathy associated to autoimmune thyroid disease: a more appropriate term for an underestimated condition? *J Neurol Sci*. 2000;176(1):65-9.
321. Priest WM. Chronic thyrotoxic myopathy. *Br Med J*. 1967;4(5574):295-6.
322. Whitfield AGW, Hudson WA. CHRONIC THYROTOXIC MYOPATHY. *QJM: An International Journal of Medicine*. 1961;30(3):257-67.
323. Sanderson KV, Adey WR. Electromyographic and endocrine studies in chronic thyrotoxic myopathy. *J Neurol Neurosurg Psychiatry*. 1952;15(3):200-5.
324. Zürcher RM, Horber FF, Grünig BE, Frey FJ. Effect of thyroid dysfunction on thigh muscle efficiency. *J Clin Endocrinol Metab*. 1989;69(5):1082-6.
325. Erkiñtalo M, Bendahan D, Mattéi JP, Fabreguettes C, Vague P, Cozzone PJ. Reduced metabolic efficiency of skeletal muscle energetics in hyperthyroid patients evidenced quantitatively by in vivo phosphorus-31 magnetic resonance spectroscopy. *Metabolism*. 1998;47(7):769-76.
326. Fitch CD, Coker R, Dinning JS. Metabolism of creatine-1-C14 by vitamin E-deficient and hyperthyroid rats. *Am J Physiol*. 1960;198:1232-4.
327. Thorn GW. CREATINE STUDIES IN THYROID DISORDERS. *Endocrinology*. 1936;20:628-34.
328. Drachman DB. Myasthenia gravis. *N Engl J Med*. 1994;330(25):1797-810.
329. Engel AG. Thyroid function and periodic paralysis. *Am J Med*. 1961;30:327-33.
330. Ober KP. Thyrotoxic periodic paralysis in the United States. Report of 7 cases and review of the literature. *Medicine (Baltimore)*. 1992;71(3):109-20.
331. Kelley DE, Gharib H, Kennedy FP, Duda RJ, Jr., McManis PG. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. *Arch Intern Med*. 1989;149(11):2597-600.
-

332. Hsieh MJ, Lyu RK, Chang WN, Chang KH, Chen CM, Chang HS, et al. Hypokalemic thyrotoxic periodic paralysis: clinical characteristics and predictors of recurrent paralytic attacks. *Eur J Neurol*. 2008;15(6):559-64.
333. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. *J Am Soc Nephrol*. 2012;23(6):985-8.
334. Gbefon CY, Sobral CPS, Caldas A, Rocha VCC, Azulay RSS, Nascimento GC, et al. Genetic Screening of Patients with Thyrotoxic Hypokalemic Periodic Paralysis: An Experience from a Tertiary Care Hospital in the Northeast of Brazil. *Endocr Metab Immune Disord Drug Targets*. 2021;21(12):2231-7.
335. Brugnoli R, Canioni E, Filosto M, Pini A, Tonin P, Rossi T, et al. Mutations associated with hypokalemic periodic paralysis: from hotspot regions to complete analysis of CACNA1S and SCN4A genes. *Neurogenetics*. 2022;23(1):19-25.
336. Rhee EP, Scott JA, Dighe AS. Case records of the Massachusetts General Hospital. Case 4-2012. A 37-year-old man with muscle pain, weakness, and weight loss. *N Engl J Med*. 2012;366(6):553-60.
337. Fisher J. Thyrotoxic periodic paralysis with ventricular fibrillation. *Arch Intern Med*. 1982;142(7):1362-4.
338. Siafakas NM, Milona I, Salesiotou V, Filaditaki V, Tzanakis N, Bouros D. Respiratory muscle strength in hyperthyroidism before and after treatment. *Am Rev Respir Dis*. 1992;146(4):1025-9.
339. Stein M, Kimbel P, Johnson RL. PULMONARY FUNCTION IN HYPERTHYROIDISM. *J Clin Invest*. 1961;40(2):348-63.
340. Massey DG, Becklake MR, McKenzie JM, Bates DV. Circulatory and ventilatory response to exercise in thyrotoxicosis. *N Engl J Med*. 1967;276(20):1104-12.
341. Sandler G, Wilson GM. The nature and prognosis of heart disease in thyrotoxicosis. A review of 150 patients treated with 131 I. *Q J Med*. 1959;28:347-69.
342. McDevitt DG, Shanks RG, Hadden DR, Montgomery DA, Weaver JA. The role of the thyroid in the control of heart-rate. *Lancet*. 1968;1(7550):998-1000.
343. Pietras RJ, Real MA, Poticha GS, Bronsky D, Waldstein SS. Cardiovascular response in hyperthyroidism. The influence of adrenergic-receptor blockade. *Arch Intern Med*. 1972;129(3):426-9.
344. DeGroot W, Leonard J, Paley H, Johnson J, Warren J. The importance of autonomic integrity in maintaining the hyperkinetic circulatory dynamics of human hyperthyroidism. *J Clin Invest*. 1961;40(June):1033.
345. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J*. 2001;142(5):838-42.
346. Blizzard JJ, Rupp JJ. Prolongation of the P-R interval as a manifestation of thyrotoxicosis. *Jama*. 1960;173:1845.
347. Tayal B, Graff C, Selmer C, Kragholm KH, Kihlstrom M, Nielsen JB, et al. Thyroid dysfunction and electrocardiographic changes in subjects without arrhythmias: a cross-sectional study of primary healthcare subjects from Copenhagen. *BMJ Open*. 2019;9(6):e023854.
348. Buccino RA, Spann JFJ, Sonnenblick EH, Braunwald E. Effect of Thyroid State on Myocardial Contractility. *Endocrinology*. 1968;82(1):191-2.
349. Reynolds JL, Woody HB. Thyrotoxic mitral regurgitation: a probable form of intrinsic papillary muscle dysfunction. *Am J Dis Child*. 1971;122(6):544-8.
350. Rodbard D, Fujita T, Rodbard S. Estimation of thyroid function by timing the arterial sounds. *Jama*. 1967;201(11):884-7.
351. Klein I, Danzi S. Thyroid disease and the heart. *Circulation*. 2007;116(15):1725-35.
352. Rowe GG, Huston JH, Weinstein AB, Tuchman H, Brown JF, Crumpton CW. The hemodynamics of thyrotoxicosis in man with special reference to coronary blood flow and myocardial oxygen metabolism. *J Clin Invest*. 1956;35(3):272-6.
353. Biondi B, Fazio S, Cuocolo A, Sabatini D, Nicolai E, Lombardi G, et al. Impaired cardiac reserve and exercise capacity in patients receiving long-term thyrotropin suppressive therapy with levothyroxine. *J Clin Endocrinol Metab*. 1996;81(12):4224-8.
354. Graettinger JS, Muenster JJ, Selverstone LA, Campbell JA. A correlation of clinical and hemodynamic studies in patients with hyperthyroidism with and without congestive heart failure. *J Clin Invest*. 1959;38(8):1316-27.
355. Smit JW, Eustatia-Rutten CF, Corssmit EP, Pereira AM, Frölich M, Bleeker GB, et al. Reversible diastolic dysfunction after long-term exogenous subclinical hyperthyroidism: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2005;90(11):6041-7.

-
356. Resnekov L, Falicov RE. Thyrotoxicosis and lactate-producing angina pectoris with normal coronary arteries. *Br Heart J*. 1977;39(10):1051-7.
357. Choi YH, Chung JH, Bae SW, Lee WH, Jeong EM, Kang MG, et al. Severe coronary artery spasm can be associated with hyperthyroidism. *Coron Artery Dis*. 2005;16(3):135-9.
358. Martí V, Ballester M, Rigla M, Narula J, Bernà L, Pons-Lladó G, et al. Myocardial damage does not occur in untreated hyperthyroidism unless associated with congestive heart failure. *Am Heart J*. 1997;134(6):1133-7.
359. Kotler MN, Michaelides KM, Bouchard RJ, Warbasse JR. Myocardial infarction associated with thyrotoxicosis. *Arch Intern Med*. 1973;132(5):723-8.
360. Levey GS, Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. *Am J Med*. 1990;88(6):642-6.
361. Mintz G, Pizzarello R, Klein I. Enhanced left ventricular diastolic function in hyperthyroidism: noninvasive assessment and response to treatment. *J Clin Endocrinol Metab*. 1991;73(1):146-50.
362. Valcavi R, Menozzi C, Roti E, Zini M, Lolli G, Roti S, et al. Sinus node function in hyperthyroid patients. *J Clin Endocrinol Metab*. 1992;75(1):239-42.
363. Smolenski RT, Yacoub MH, Seymour A-ML. Hyperthyroidism increases adenosine transport and metabolism in the rat heart. *Molecular and Cellular Biochemistry*. 1995;143(2):143-9.
364. Brent GA. The molecular basis of thyroid hormone action. *N Engl J Med*. 1994;331(13):847-53.
365. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344(7):501-9.
366. Schmidt BM, Martin N, Georgens AC, Tillmann HC, Feuring M, Christ M, et al. Nongenomic cardiovascular effects of triiodothyronine in euthyroid male volunteers. *J Clin Endocrinol Metab*. 2002;87(4):1681-6.
367. Davis PJ, Davis FB. Nongenomic actions of thyroid hormone on the heart. *Thyroid*. 2002;12(6):459-66.
368. Hönes GS, Rakov H, Logan J, Liao XH, Werbenko E, Pollard AS, et al. Noncanonical thyroid hormone signaling mediates cardiometabolic effects in vivo. *Proc Natl Acad Sci U S A*. 2017;114(52):E11323-e32.
369. Dillmann WH. Biochemical basis of thyroid hormone action in the heart. *Am J Med*. 1990;88(6):626-30.
370. Tse J, Wrenn RW, Kuo JF. Thyroxine-induced changes in characteristics and activities of beta-adrenergic receptors and adenosine 3',5'-monophosphate and guanosine 3',5'-monophosphate systems in the heart may be related to reputed catecholamine supersensitivity in hyperthyroidism. *Endocrinology*. 1980;107(1):6-16.
371. Williams LT, Lefkowitz RJ, Watanabe AM, Hathaway DR, Besch HR, Jr. Thyroid hormone regulation of beta-adrenergic receptor number. *J Biol Chem*. 1977;252(8):2787-9.
372. Fatourechi V, Edwards WD. Graves' disease and low-output cardiac dysfunction: implications for autoimmune disease in endomyocardial biopsy tissue from eleven patients. *Thyroid*. 2000;10(7):601-5.
373. Nightingale S, Vitek PJ, Himsworth RL. The haematology of hyperthyroidism. *Q J Med*. 1978;47(185):35-47.
374. Viherkoski M, Lamberg BA. The Glucose-6-Phosphate Dehydrogenase Activity (G-6-PD) of the Red Blood Cells in Hyperthyroidism and Hypothyroidism. *Scandinavian Journal of Clinical and Laboratory Investigation*. 1970;25(2):137-43.
375. Popovic WJ, Brown JE, Adamson JW. The influence of thyroid hormones on in vitro erythropoiesis. Mediation by a receptor with beta adrenergic properties. *J Clin Invest*. 1977;60(4):907-13.
376. Rivlin RS, Wagner HN, Jr. Anemia in hyperthyroidism. *Ann Intern Med*. 1969;70(3):507-16.
377. Bergman TA, Mariash CN, Oppenheimer JH. Anterior mediastinal mass in a patient with Graves' disease. *J Clin Endocrinol Metab*. 1982;55(3):587-8.
378. Huang W, Molitch ME. Enlarged thymus in a patient with dyspnea and weight loss. *Jama*. 2015;313(21):2174-5.
379. Irvine WJ, Wu FC, Urbaniak SJ, Toolis F. Peripheral blood leucocytes in thyrotoxicosis (Graves' disease) as studied by conventional light microscopy. *Clin Exp Immunol*. 1977;27(2):216-21.
380. Hertz S, Lerman J. THE BLOOD PICTURE IN EXOPHTHALMIC GOITRE AND ITS CHANGES RESULTING FROM IODINE AND OPERATION. A STUDY BY MEANS OF THE SUPRAVITAL TECHNIQUE. *J Clin Invest*. 1932;11(6):1179-96.
381. Lima CS, Zantut Wittmann DE, Castro V, Tambascia MA, Lorand-Metze I, Saad ST, et al. Pancytopenia in untreated patients with Graves' disease. *Thyroid*. 2006;16(4):403-9.
-

382. Lamberg BA, Kivikangas V, Pelkonen R, Vuopio P. Thrombocytopenia and decreased life-span of thrombocytes in hyperthyroidism. *Ann Clin Res.* 1971;3(2):98-102.
383. Adrouny A, Sandler RM, Carmel R. Variable presentation of thrombocytopenia in Graves' disease. *Arch Intern Med.* 1982;142(8):1460-4.
384. Verberne HJ, Fliers E, Prummel MF, Stam J, Brandjes DP, Wiersinga WM. Thyrotoxicosis as a predisposing factor for cerebral venous thrombosis. *Thyroid.* 2000;10(7):607-10.
385. Davis PJ, Mousa SA, Schechter GP. New Interfaces of Thyroid Hormone Actions With Blood Coagulation and Thrombosis. *Clinical and Applied Thrombosis/Hemostasis.* 2018;24(7):1014-9.
386. Wegener M, Wedmann B, Langhoff T, Schaffstein J, Adamek R. Effect of hyperthyroidism on the transit of a caloric solid-liquid meal through the stomach, the small intestine, and the colon in man. *J Clin Endocrinol Metab.* 1992;75(3):745-9.
387. Lerman J, Means JH. THE GASTRIC SECRETION IN EXOPHTHALMIC GOITRE AND MYXOEDEMA. *J Clin Invest.* 1932;11(1):167-82.
388. Berryhill WR, Williams HA. A STUDY OF THE GASTRIC SECRETION IN HYPERTHYROIDISM BEFORE AND AFTER OPERATION. *J Clin Invest.* 1932;11(4):753-60.
389. Siurala M, Lamberg BA. Stomach in thyrotoxicosis. *Acta Med Scand.* 1959;165:181-8.
390. Seino Y, Matsukura S, Miyamoto Y, Goto Y, Taminato T, Imura H. Hypergastrinemia in hyperthyroidism. *J Clin Endocrinol Metab.* 1976;43(4):852-5.
391. Scappaticcio L, Longo M, Maiorino MI, Pernice V, Caruso P, Esposito K, et al. Abnormal Liver Blood Tests in Patients with Hyperthyroidism: Systematic Review and Meta-Analysis. *Thyroid.* 2021;31(6):884-94.
392. Lamberg BA, Gordin R. Liver Function in Thyrotoxicosis: Studies on the Cholesterol and Prothrombin Level in the Blood During the Treatment of Thyrotoxicosis. *Acta Endocrinologica (Norway).* 1954;15(1):82-96.
393. Thompson P, Jr., Strum D, Boehm T, Wartofsky L. Abnormalities of liver function tests in tyrotoxicosis. *Mil Med.* 1978;143(8):548-51.
394. Greenberger NJ, Milligan FD, Degroot LJ, Isselbacher KJ. JAUNDICE AND THYROTOXICOSIS IN THE ABSENCE OF CONGESTIVE HEART FAILURE. A STUDY OF FOUR CASES. *Am J Med.* 1964;36:840-6.
395. Kubota S, Amino N, Matsumoto Y, Ikeda N, Morita S, Kudo T, et al. Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis. *Thyroid.* 2008;18(3):283-7.
396. Yorke E. Hyperthyroidism and Liver Dysfunction: A Review of a Common Comorbidity. *Clin Med Insights Endocrinol Diabetes.* 2022;15:11795514221074672.
397. de Campos Mazo DF, de Vasconcelos GB, Pereira MA, de Mello ES, Bacchella T, Carrilho FJ, et al. Clinical spectrum and therapeutic approach to hepatocellular injury in patients with hyperthyroidism. *Clin Exp Gastroenterol.* 2013;6:9-17.
398. Youssef WI, Mullen KD. The liver in other (nondiabetic) endocrine disorders. *Clin Liver Dis.* 2002;6(4):879-89, vii.
399. Piantanida E, Ippolito S, Gallo D, Masiello E, Premoli P, Cusini C, et al. The interplay between thyroid and liver: implications for clinical practice. *J Endocrinol Invest.* 2020;43(7):885-99.
400. Epstein FH, Rivera MJ. Renal concentrating ability in thyrotoxicosis. *J Clin Endocrinol Metab.* 1958;18(10):1135-7.
401. Ford RV, Owens JC, Curd GW, Jr., Moyer JH, Spurr CL. Kidney function in various thyroid states. *J Clin Endocrinol Metab.* 1961;21:548-53.
402. Sataline LR, Powell C, Hamwi GJ. Suppression of the hypercalcemia of thyrotoxicosis by corticosteroids. *N Engl J Med.* 1962;267:646-50.
403. Sallin O. Hypercalcemic Nephropathy in Thyrotoxicosis. *Acta Endocrinologica (Norway).* 1958;29(3):425-34.
404. Goldsmith RE, Sturgis SH, Lerman J, Stanbury JB. The menstrual pattern in thyroid disease. *J Clin Endocrinol Metab.* 1952;12(7):846-55.
405. Sanjari M, Safi Z, Tahroodi KM. HYPERTHYROIDISM AND HYPERPROLACTINEMIA: IS THERE ANY ASSOCIATION? *Endocr Pract.* 2016;22(12):1377-82.
406. Freedberg IM, Hamolsky MW, Freedberg AS. The thyroid gland in pregnancy. *N Engl J Med.* 1957;256(11):505-10; contd.
407. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society

- clinical practice guideline. *J Clin Endocrinol Metab.* 2012;97(8):2543-65.
408. Polak M, Le Gac I, Vuillard E, Guibourdenche J, Leger J, Toubert ME, et al. Fetal and neonatal thyroid function in relation to maternal Graves' disease. *Best Pract Res Clin Endocrinol Metab.* 2004;18(2):289-302.
409. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *Jama.* 2004;292(6):691-5.
410. Southren AL, Olivo J, Gordon GG, Vittek J, Brener J, Raffi F. The conversion of androgens to estrogens in hyperthyroidism. *J Clin Endocrinol Metab.* 1974;38(2):207-14.
411. Chopra IJ, Tulchinsky DAN. Status of Estrogen-Androgen Balance in Hyperthyroid Men with Graves' Disease. *The Journal of Clinical Endocrinology & Metabolism.* 1974;38(2):269-77.
412. Chopra IJ, Abraham GE, Chopra U, Solomon DH, Odell WD. Alterations in circulating estradiol-17-beta in male patients with Graves's disease. *N Engl J Med.* 1972;286(3):124-9.
413. Becker KL, Winnacker JL, Matthews MJ, Higgins GA, Jr. Gynecomastia and hyperthyroidism. An endocrine and histological investigation. *J Clin Endocrinol Metab.* 1968;28(2):277-85.
414. Bercovici JP, Mauvais-Jarvis P. Hyperthyroidism and gynecomastia: metabolic studies. *J Clin Endocrinol Metab.* 1972;35(5):671-7.
415. Kidd GS, Glass AR, Vigersky RA. The hypothalamic-pituitary-testicular axis in thyrotoxicosis. *J Clin Endocrinol Metab.* 1979;48(5):798-802.
416. Abalovich M, Levalle O, Hermes R, Scaglia H, Aranda C, Zylbersztein C, et al. Hypothalamic-pituitary-testicular axis and seminal parameters in hyperthyroid males. *Thyroid.* 1999;9(9):857-63.
417. Krassas GE, Perros P. Thyroid disease and male reproductive function. *J Endocrinol Invest.* 2003;26(4):372-80.
418. Peterson RE. The influence of the thyroid on adrenal cortical function. *J Clin Invest.* 1958;37(5):736-43.
419. Kenny FM, Iturzaeta N, Preeyasombat C, Taylor FH, Migeon CJ, Richards C. Cortisol Production Rate. VII. Hypothyroidism and Hyperthyroidism in Infants and Children. *The Journal of Clinical Endocrinology & Metabolism.* 1967;27(11):1616-22.
420. Toro-Tobon D, Bancos I, Brito JP. Abstract #1408256: In Search of New Biomarkers of Thyroid Function: The Association Between Thyroid Dysfunction and 11-beta Hydroxysteroid Dehydrogenase 2 Activity. *Endocrine Practice.* 2023;29(5):S116.
421. Hellman L, Bradlow HL, Zumoff B, Gallagher TF. The influence of thyroid hormone on hydrocortisone production and metabolism. *J Clin Endocrinol Metab.* 1961;21:1231-47.
422. Gallagher TF, Hellman L, Finkelstein J, Yoshida K, Weitzman ED, Roffwarg HD, et al. Hyperthyroidism and cortisol secretion in man. *J Clin Endocrinol Metab.* 1972;34(6):919-27.
423. Hilton JG, Black WC, Athos W, Mc HB, Westermann CD. Increased ACTH-like activity in plasma of patients with thyrotoxicosis. *J Clin Endocrinol Metab.* 1962;22:900-5.
424. Felber J-P, Reddy WJ, Selenkow HA, Thorn GW. ADRENOCORTICAL RESPONSE TO THE 48-HOUR ACTH TEST IN MYXEDEMA AND HYPERTHYROIDISM*. *The Journal of Clinical Endocrinology & Metabolism.* 1959;19(8):895-906.
425. Hellman L, Bradlow HL, Zumoff B, Fukushima DK, Gallagher TF. Thyroid-androgen interrelations and the hypocholesteremic effect of androsterone. *J Clin Endocrinol Metab.* 1959;19:936-48.
426. Hoshiro M, Ohno Y, Masaki H, Iwase H, Aoki N. Comprehensive study of urinary cortisol metabolites in hyperthyroid and hypothyroid patients. *Clinical Endocrinology.* 2006;64(1):37-45.
427. Fraser SA, Anderson JB, Smith DA, Wilson GM. Osteoporosis and fractures following thyrotoxicosis. *Lancet.* 1971;1(7707):981-3.
428. Rosen CJ, Adler RA. Longitudinal changes in lumbar bone density among thyrotoxic patients after attainment of euthyroidism. *J Clin Endocrinol Metab.* 1992;75(6):1531-4.
429. Langdahl BL, Loft AG, Eriksen EF, Mosekilde L, Charles P. Bone mass, bone turnover, body composition, and calcium homeostasis in former hyperthyroid patients treated by combined medical therapy. *Thyroid.* 1996;6(3):161-8.
430. Jódar E, Martínez-Díaz-Guerra G, Azriel S, Hawkins F. Bone mineral density in male patients with L-thyroxine suppressive therapy and Graves disease. *Calcif Tissue Int.* 2001;69(2):84-7.

431. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. *J Clin Endocrinol Metab.* 1996;81(12):4278-89.
432. Krane SM, Brownell GL, Stanbury JB, Corrigan H. The effect of thyroid disease on calcium metabolism in man. *J Clin Invest.* 1956;35(8):874-87.
433. Harvey RD, McHardy KC, Reid IW, Paterson F, Bewsher PD, Duncan A, et al. Measurement of bone collagen degradation in hyperthyroidism and during thyroxine replacement therapy using pyridinium cross-links as specific urinary markers. *J Clin Endocrinol Metab.* 1991;72(6):1189-94.
434. Lukert BP, Higgins JC, Stoskopf MM. Serum osteocalcin is increased in patients with hyperthyroidism and decreased in patients receiving glucocorticoids. *J Clin Endocrinol Metab.* 1986;62(5):1056-8.
435. Cooper DS, Kaplan MM, Ridgway EC, Maloof F, Daniels GH. Alkaline phosphatase isoenzyme patterns in hyperthyroidism. *Ann Intern Med.* 1979;90(2):164-8.
436. Siddiqi A, Burrin JM, Noonan K, James I, Wood DF, Price CP, et al. A longitudinal study of markers of bone turnover in Graves' disease and their value in predicting bone mineral density. *J Clin Endocrinol Metab.* 1997;82(3):753-9.
437. Garrel DR, Delmas PD, Malaval L, Tourniaire J. Serum bone Gla protein: a marker of bone turnover in hyperthyroidism. *J Clin Endocrinol Metab.* 1986;62(5):1052-5.
438. Epstein FH, Freedman LR, Levitin H. Hypercalcemia, nephrocalcinosis and reversible renal insufficiency associated with hyperthyroidism. *N Engl J Med.* 1958;258(16):782-5.
439. Peerenboom H, Keck E, Krüskemper HL, Strohmeyer G. The defect of intestinal calcium transport in hyperthyroidism and its response to therapy. *J Clin Endocrinol Metab.* 1984;59(5):936-40.
440. Bouillon R, De Moor P. Parathyroid function in patients with hyper- or hypothyroidism. *J Clin Endocrinol Metab.* 1974;38(6):999-1004.
441. Bouillon R, Muls E, De Moor P. Influence of thyroid function on the serum concentration of 1,25-dihydroxyvitamin D3. *J Clin Endocrinol Metab.* 1980;51(4):793-7.
442. Bortz W, Eisenberg E, Bowers CY, Pont M. DIFFERENTIATION BETWEEN THYROID AND PARATHYROID CAUSES OF HYPERCALCEMIA. *Annals of Internal Medicine.* 1961;54(4):610-9.
443. David NJ, Verner JV, Engel FL. The diagnostic spectrum of hypercalcemia. Case reports and discussion. *Am J Med.* 1962;33:88-110.
444. Kleeman CR, Tuttle S, Bassett SH. METABOLIC OBSERVATIONS IN A CASE OF THYROTOXICOSIS WITH HYPERCALCEMIA*. *The Journal of Clinical Endocrinology & Metabolism.* 1958;18(5):477-91.
445. Danforth E, Jr., Burger A. The role of thyroid hormones in the control of energy expenditure. *Clin Endocrinol Metab.* 1984;13(3):581-95.
446. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Ann Intern Med.* 2003;139(3):205-13.
447. Yavuz S, Salgado Nunez del Prado S, Celi FS. Thyroid Hormone Action and Energy Expenditure. *Journal of the Endocrine Society.* 2019;3(7):1345-56.
448. Plummer H, Boothby W. The cost of work in exophthalmic goiter. *Am J Physiol.* 1923;63(406):1922-3.
449. Briard SP, McClintock JT, Baldrige CW. COST OF WORK IN PATIENTS WITH HYPERMETABOLISM DUE TO LEUKEMIA AND TO EXOPHTHALMIC GOITER. *Archives of Internal Medicine.* 1935;56(1):30-7.
450. Acheson K, Jéquier E, Burger A, Danforth E, Jr. Thyroid hormones and thermogenesis: the metabolic cost of food and exercise. *Metabolism.* 1984;33(3):262-5.
451. Potenza M, Via MA, Yanagisawa RT. Excess Thyroid Hormone and Carbohydrate Metabolism. *Endocrine Practice.* 2009;15(3):254-62.
452. Eom YS, Wilson JR, Bernet VJ. Links between Thyroid Disorders and Glucose Homeostasis. *Diabetes Metab J.* 2022;46(2):239-56.
453. Mitrou P, Raptis SA, Dimitriadis G. Insulin Action in Hyperthyroidism: A Focus on Muscle and Adipose Tissue. *Endocrine Reviews.* 2010;31(5):663-79.
454. Kabadi UM, Eisenstein AB. Impaired pancreatic alpha-cell response in hyperthyroidism. *J Clin Endocrinol Metab.* 1980;51(3):478-82.
455. Wennlund A, Arner P, Ostman J. Changes in the effects of insulin on human adipose tissue metabolism in hyperthyroidism. *J Clin Endocrinol Metab.* 1981;53(3):631-5.

456. Houssay BA. THYROID AND METATHYROID DIABETES. *Endocrinology*. 1944;35(3):158-72.
457. Bratusch-Marrain PR, Komjati M, Waldhäusl WK. Glucose metabolism in noninsulin-dependent diabetic patients with experimental hyperthyroidism. *J Clin Endocrinol Metab*. 1985;60(6):1063-8.
458. Elrick H, Hlad CJ, Jr., Arai Y. Influence of thyroid function on carbohydrate metabolism and a new method for assessing response to insulin. *J Clin Endocrinol Metab*. 1961;21:387-400.
459. Kritchevsky D. Influence of thyroid hormones and related compounds on cholesterol biosynthesis and degradation: a review. *Metabolism*. 1960;9:984-94.
460. Siperstein MD, Murray AW. Cholesterol metabolism in man. *J Clin Invest*. 1955;34(9):1449-53.
461. O'Brien T, Katz K, Hodge D, Nguyen TT, Kottke BA, Hay ID. The effect of the treatment of hypothyroidism and hyperthyroidism on plasma lipids and apolipoproteins AI, AII and E. *Clin Endocrinol (Oxf)*. 1997;46(1):17-20.
462. Chait A, Bierman EL, Albers JJ. Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. *J Clin Endocrinol Metab*. 1979;48(5):887-9.
463. Tulloch BR, Vydellingum N, Lewis B, Fraser R. Triglyceride metabolism in thyroid disease. *Clin Sci*. 1973;44(2):6P passim.
464. Cachefo A, Boucher P, Vidon C, Dusserre E, Diraison F, Beylot M. Hepatic lipogenesis and cholesterol synthesis in hyperthyroid patients. *J Clin Endocrinol Metab*. 2001;86(11):5353-7.
465. Arons DL, Schreiberman PH, Downs P, Braverman LE, Arky RA. Decreased post-heparin lipases in Graves's disease. *N Engl J Med*. 1972;286(5):233-7.
466. Sachs BA, Danielson E, Isaacs MC, Weston RE. Effect of triiodothyronine on the serum lipids and lipoproteins of euthyroid and hyperthyroid subjects. *J Clin Endocrinol Metab*. 1958;18(5):506-15.
467. Kung AW, Pang RW, Lauder I, Lam KS, Janus ED. Changes in serum lipoprotein(a) and lipids during treatment of hyperthyroidism. *Clin Chem*. 1995;41(2):226-31.
468. Ozata M, Uckaya G, Bolu E, Corapcioglu D, Bingol N, Ozdemir IC. Plasma leptin concentrations in patients with Graves' disease with or without ophthalmopathy. *Med Sci Monit*. 2001;7(4):696-700.
469. Strisower B, Elmlinger P, Gofman JW, Delalla O. The effect of 1-thyroxine on serum lipoprotein and cholesterol concentrations. *J Clin Endocrinol Metab*. 1959;19(1):117-26.
470. Postel S. Total free tocopherols in the serum of patients with thyroid disease. *J Clin Invest*. 1956;35(12):1345-56.
471. Rich C, Bierman EL, Schwartz IL. Plasma nonesterified fatty acids in hyperthyroid states. *J Clin Invest*. 1959;38(2):275-8.
472. Riis AL, Jørgensen JO, Ivarsen P, Frystyk J, Weeke J, Møller N. Increased protein turnover and proteolysis is an early and primary feature of short-term experimental hyperthyroidism in healthy women. *J Clin Endocrinol Metab*. 2008;93(10):3999-4005.
473. Lewallen CG, Rall JE, Berman M. Studies of iodoalbumin metabolism. II. The effects of thyroid hormone. *J Clin Invest*. 1959;38(1, Part 1):88-101.
474. Kivirikko KI, Laitinen O, Aer J, Halme J. Metabolism of collagen in experimental hyperthyroidism and hypothyroidism in the rat. *Endocrinology*. 1967;80(6):1051-61.
475. Crispell KR, Parson W, Hollifield G. A study of the rate of protein synthesis before and during the administration of L-triiodothyronine to patients with myxedema and healthy volunteers using N-15 glycine. *J Clin Invest*. 1956;35(2):164-9.
476. Sokoloff L, Kaufman S. Effects of thyroxin on amino acid incorporation into protein. *Science*. 1959;129(3348):569-70.
477. Sokoloff L, Roberts PA, Januska MM, Kline JE. Mechanisms of stimulation of protein synthesis by thyroid hormones in vivo. *Proc Natl Acad Sci U S A*. 1968;60(2):652-9.
478. Aktuna D, Buchinger W, Langsteger W, Meister E, Sternad H, Lorenz O, et al. [Beta-carotene, vitamin A and carrier proteins in thyroid diseases]. *Acta Med Austriaca*. 1993;20(1-2):17-20.
479. Wohl MG, Levy HA, Szutka A, Maldia G. Pyridoxine deficiency in hyperthyroidism. *Proc Soc Exp Biol Med*. 1960;105:523-7.



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