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, dermopathy. 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 dermopathy. 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 dermopathy 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.

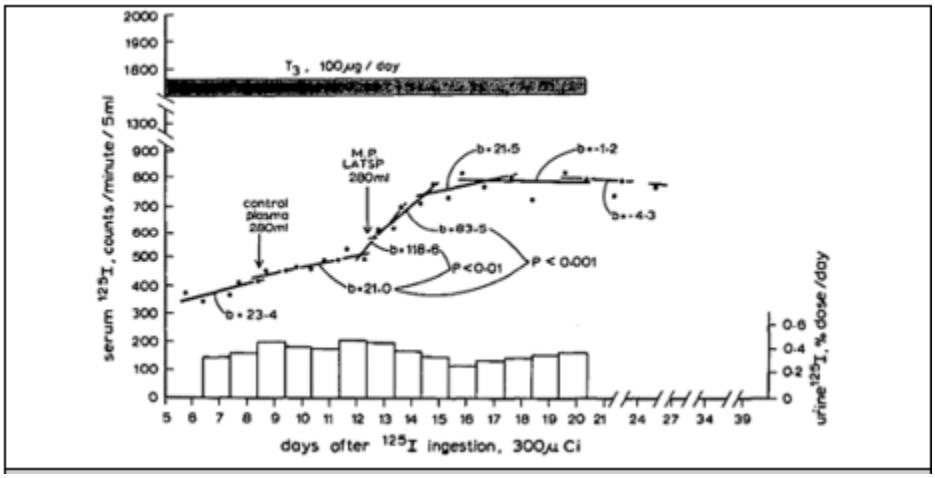

Figure 2. Stimulation of thyroid hormone secretion by LATS-P. The subject's thyroid iodine was labeled by administration of I^{131}, and serial observations were made on the appearance of I^{131}-labeled hormone in blood (Y axis) over one month (X axis). An infusion of 280 ml control plasma had no effect, 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).

EPIDEMIIOLOGY

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.

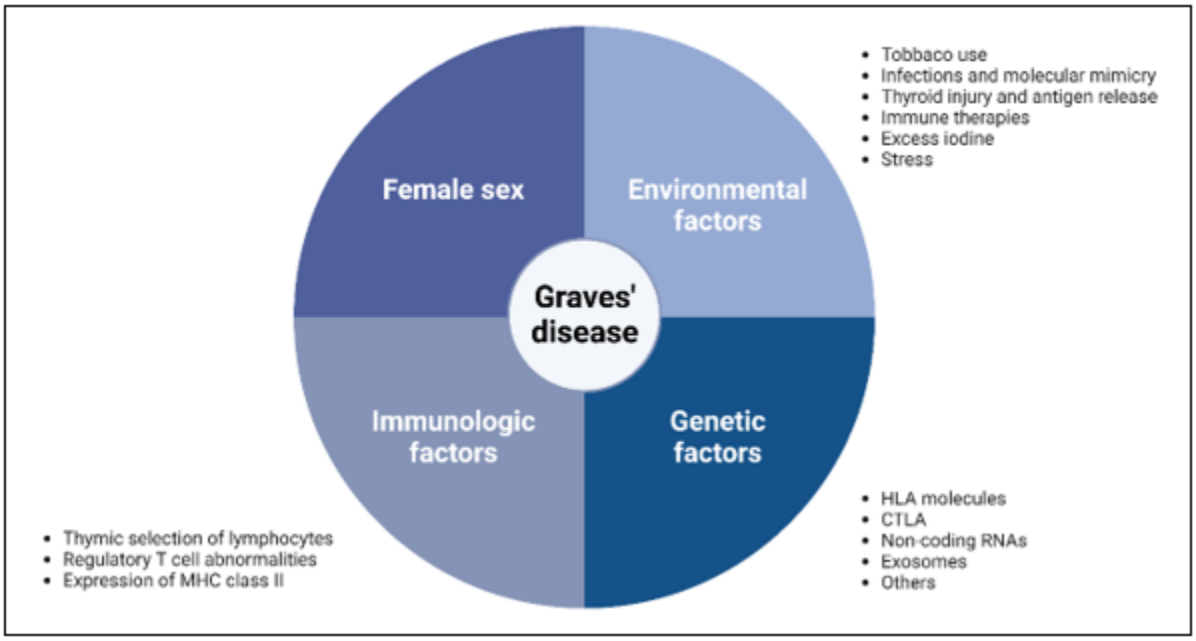

Figure 3. Risk factors for Graves' disease. MHC: Major histocompatibility complex; HLA: Human leukocyte antigen; CTLA: Cytotoxic T-lymphocyte-associated protein; RNA: Ribonucleic acid. (Created with Biorender.com)

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 AIDT (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 muco-candidiasis. 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

Persistence of some autoreactive T cells and B cells (failure of negative selection)
Genetic polymorphisms
Re-exposure to antigens secondary to thyroid cell damage
Reduced or dysfunctional regulatory T cells
Cross-reacting epitopes on environmental and thyroid antigens
Inappropriate HLA-DR expression
Mutated T or B cell clones
Activation of T cells by polyclonal stimuli
Stimulation of the thyroid by cytokines
***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-β1) (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 erythematous, 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 adenyl 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 adenyl 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 TBab 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 TNab or Tbab.

The specific epitopes to which the TSab bind are in the amino terminal portion of the extracellular domain of the TSR-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.

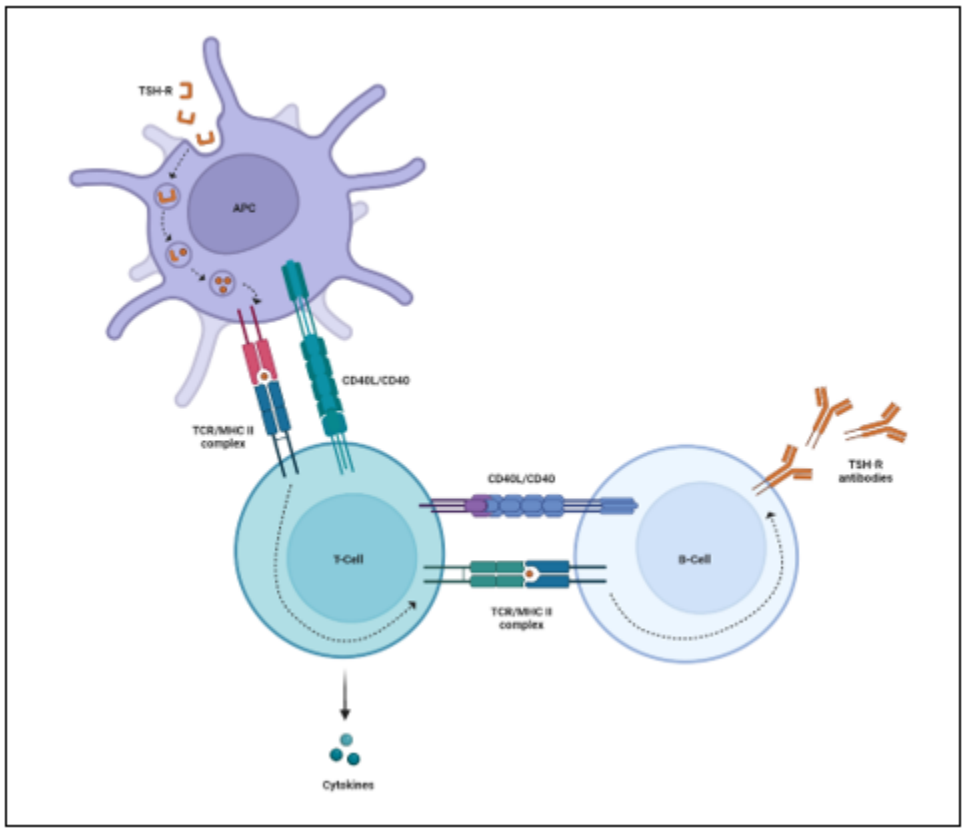

Figure 4. The role of cellular immunity. Schematic representation of TSH-R endocytosis by antigen presenting cells (APC), subsequent proteolysis and presentation to T cells, and stimulation of thyroid stimulating antibody production by B cells. (Created with Biorender.com).

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 adenyl 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 µg/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 adenyl 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.

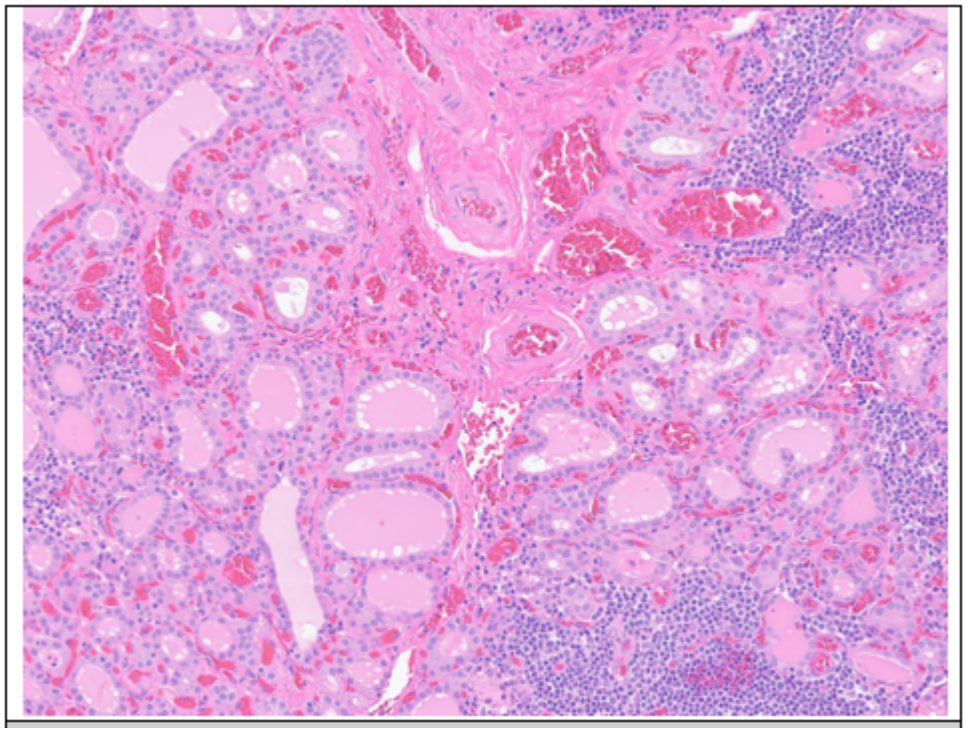

Figure 5. Histology of a thyroid gland of a patient with Graves' disease. Columnar epithelium, vacuolization of colloid, and significant lymphocytic infiltrate are present in the setting of diffuse parenchymal hypertrophy.

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

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).

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

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 $3x10^9$/l and neutrophiles under $2x10^9$/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 restauration 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 adrenocorticotropic 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 restauration of euthyroidism (428, 429).

The thyroid hormone receptors α1 (TRα1), TRβ1, and TRβ2 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 restauration 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. 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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