Chapter

Graves' Disease: Clinical Significance and Management

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Abstract

Graves' Disease is an autoimmune disease characterized by hyperthyroidism due to circulating autoantibodies. Graves' Disease was originally known as "exophthalmic goiter" but is now named after Sir Robert Graves, an Irish doctor who first described the condition in 1835. A number of conditions can cause hyperthyroidism, but Graves' Disease is the most common, affecting around 1 in 200 people. It most often affects women under the age of 40, but it is also found in men. It affects an estimated 2–3 percent of the world's population. Thyroid-stimulating immunoglobulin (TSIs) binds to and activates thyrotropin receptors, causing the thyroid gland to grow and the thyroid follicles to increase synthesis of thyroid hormone. The overproduction of thyroid hormones can have a variety of effects on the body causes exophthalmic goiter, Graves ophthalmopathy, Graves dermopathy etc.,. Thyroid profile including antithyroid antibodies, radioactive iodine uptake study, and thyroid scan are the main diagnostic investigations to rule out Graves' Disease. The major aim of the treatment is to inhibit the overproduction of thyroid hormones by targeting the thyroid gland, to reduce the symptoms, and prevention of complication is also major challenges.

Keywords: anti-thyroid drug, autoimmune thyroid disease, goiter, Graves' Disease, Graves ophthalmopathy, hyperthyroidism, thyroglobulin, thyroidectomy, thyrotropine receptor antibody, radioactive iodine

1. Introduction

Thyroid diseases are one of the most common endocrinopathies globally [1]. The thyroid gland is a small, butterfly-shaped endocrine gland located in the lower front of the neck synthesizes and secretes mainly two hormones i.e., T4 (Thyroxine) and T3 (Triiodothyronine) [2] into the blood and then carried to every tissues in the body. TSH stands for thyroid stimulating hormone, which is produced by the pituitary gland of the brain. This gland stimulates the thyroid to synthesize and release the thyroid hormones into the blood. Thyroid hormones act on almost all nucleated cells and are essential for normal growth and energy metabolism1. It also controls the body temperature, menstrual cycles, the functioning of the lungs, heart & muscle strength and ancillary vital organs [3]. When thyroid gland secretes either too much or too little of the thyroid hormones T4 and T3, it's called a thyroid disease. There are several different types of thyroid disease, including hyperthyroidism, hypothyroidism, thyroid cancer, thyroiditis, and autoimmune thyroid disease.

Graves' Disease is an autoimmune disorder that leads to overactivity of the entire thyroid gland due to circulating autoantibodies. The synonyms of Graves' Disease are Basedow disease, exophthalmic goiter, Graves' hyperthyroidism, Parry disease

and toxic diffuse goiter [4]. Graves' Disease is the commonest cause of hyperthyroidism. Graves' Disease was originally known as exophthalmic goiter but now it is named after Sir Robert Graves, an Irish physician, who described this form of hyperthyroidism in 1830s [5]. Autoimmune thyroid disease ranges from one end of Hashimoto's hypothyroidism (HH) to another end of Graves' hyperthyroidism (GH). Autoimmune diseases are characterized by the activity of autoreactive lymphocytes, which cause tissue or organ damage through the formation of antibodies that react against host tissues, or effector T cells, which are specific for endogenous self-peptides [6]. Thyroid peroxidase (TPO) and thyroglobulin (Tg) are the major autoantigens in Hashimoto's disease whereas in Graves' Disease TPO-Ab and Tg-Ab are also occur in 70% of patients with Graves' Disease [7], but The thyroid-stimulating hormone receptor (TSHR) is the major autoantigen in Graves' Disease. The antibody called thyrotropin receptor antibody (TRAb) and thyroid-stimulating immunoglobulins (TSIs) bind to and activate thyrotropin receptors, causing the thyroid gland to grow and the thyroid follicles to increase synthesis of thyroid hormone.

Graves' Disease is not only affecting the thyroid and often affecting the skin and eyes named as Graves' dermopathy, Graves' orbitopathy and Graves' ophthalmopathy. The overproduction of thyroid hormones can have a variety of effects on the other body systems too. About 3 in every 4 people with an overactive thyroid gland have a condition called Graves' Disease [8]. Graves' Disease is considered to be an autoimmune disorder, but other causes may contribute to its development, including genetic, environmental, and/or other factors. Graves' Disease usually affects people between ages 30 and 50, but can occur at any age [9]. The disease is seven to eight times more common in women than men [10].

2. Epidemiology

Graves' Disease occurs in almost any part of the world. Graves' Disease is the most common causes of spontaneous thyrotoxicosis and it represents 60–90% of all causes of thyrotoxicosis in different regions of the world and it is estimated to affect 2–3 percent of the world's population [4]. Graves' Disease is the most common cause of hyperthyroidism in the United States. The incidence of Graves' Disease in Olmstead County was found to be 30 cases per 100,000 annually [11]. The overall prevalence of hyperthyroidism in the United States is 1.2% with an incidence of 20/100,000 to 50/100,000 in a study conducted in Olmstead County, Minnesota. The incidence of Graves' Disease was 24.8 cases per 100,000 with an adjusted female to male ratio of 3.9:1 [12, 13] but studies specifically on Graves' Disease are rare [14]. In Canada, Graves' Disease is the most common cause of hyperthyroidism affecting one in every 100 people. It appears to becoming even more common. In the Wickham Study in the United Kingdom, the incidence of Graves' Disease was reported to be 100–200 cases per 100,000 population per year which is significantly higher than previous estimates [15] and among women, it has been reported to be 80 cases 100,000 per year [16]. The age adjusted incidence of adult onset Graves' Disease in Sheffield, UK was 24.8 per 100,000 per year. It is more common in women than men and the most common in people with ages 20 to 50 years and the risk for Graves' Disease in women and men are 3% and 0.5%. The 12-year incidence of Graves' Disease among women with 25 to 42 years was as high as 4.6/1000 as per Nurses' Health Study II report. The ratio of 3.9:1 reported in this study is however in keeping with other studies in Iceland and Sweden that reported a gender ratio of 4:1 in hyperthyroidism in general [16]. In Sweden, the reported incidence of Graves' Disease (2003–2005) was 21.4 per 100,000 per year with a Female:Male ratio of 5.6:1 [17].

The prevalence of maternal thyrotoxicosis is approximately 1 case per 500 persons, with maternal Graves' Disease being the most common etiology [10]. Graves' Disease

is observed with a rate of 0.1–0.4% in pregnant women [18]. Aside from the infrequent occurrence of postnatal thyrotoxicosis due to maternal antibodies, the incidence of spontaneous Graves' Disease in children before the age of ten is most unusual, but the incidence climbs with each decade until about age 60 [14–15, 19] . Pediatric Graves' Disease accounts for 10–15% of thyroid disorders in patients less than 18 years of age [20]. Graves' Disease is rare under the age of 5 years and has a peak incidence at 10–15 years of age [21]. The incidence of Graves' Disease is believed to be between 0.1 and 3 per 100,000 children [22] with a prevalence of 1 in 10,000 children in the United States [23]. A study found that out of 57 patients with the average age of the 32.8 years, male:female ratio of 1:3.3, 52 (91%) had subacute thyroiditis as the cause of thyrotoxicosis while Graves' Disease was seen in 9% [24]. The Graves' Disease affecting all countries and races equally across the world and it occurs eight times more common in women than men between 30 to 60 years of age group [14, 15].

3. Causes

Graves' Disease is caused by a malfunction in the body's disease-fighting immune system. The immune system usually produces antibodies against the target specific antigens such as bacteria, virus, or other foreign substance. In Graves' Disease, the immune system produces an antibody against the own cell of the thyroid gland. Normally, thyroid gland function is regulated by a hormone thyroid-releasing hormone (TRH) which is secreted from the posterior lobe of the pituitary gland. The immune system produces antibodies called thyrotropin receptor antibody (TRAb) that trigger the TSH receptor, tricking and dominance over the normal function of the thyroid gland and also causing an oversecretion of thyroid hormones. However the exact cause for Graves' Disease is not well understood. Despite there are risk factors like a combination of genetic and environmental factors which triggered the immune system against the thyroid.

4. Risk factors

Although anyone can develop Graves' Disease, many factors (**Table 1**) can increase the risk of disease, including:

Genetic	Environmental Agents
• Genetic background: family history of thyroid disease	• Infectious agents
• Race	• Dietary Iodine
• Age	• Dietary Selenium
• Gender: Women	• Pregnancy and the Postpartum Period
• Other autoimmune disorders	• Medication: (amiodarone,
○ Type 1 diabetes	• interferon-a (IFN-a), and CD52 MABs)
○ Rheumatoid arthritis	• Smoking
○ Pernicious anemia	• Stress
○ Lupus erthymatosus	• Radiation Exposure
○ Addison's disease	• Toxicants
○ Vitiligo	
○ Crohn's disease	

Table 1.
Risk factors of Graves' Disease.

4.1 Heredity/genetics

Family history of Graves' Disease is a known risk factor; there is likely a gene or genes that can make a person more susceptible to the disorder. 70%–80% of susceptibility to autoimmune thyroid disease is based on genetics; individuals with a personal history of autoimmune disease or family history of autoimmune thyroid disease are the most susceptible. The specific genes involved include human leukocyte antigen-DR3, cytotoxic T lymphocyte-associated factor 4, CD40, protein tyrosine phosphotase-22 gene, thyroglobulin (Tg), and TSH receptor [25]. Graves' Disease include genes encoding thyroglobulin, thyrotropin receptor, HLA-DRβ-Arg74, the protein tyrosine phosphatase nonreceptor type 22 (PTPN22), and proteins involved in T cell signaling [26–28]. HLA-DRB1 and HLA-DQB1 also appear to be associated with Graves' Disease susceptibility. Cytotoxic T lymphocyte-associated molecule-4 (CTLA4) is a major thyroid autoantibody susceptibility gene, [29, 30] and it is a negative regulator of T-cell activation and may play an important role in the pathogenesis of Graves' Disease. Heredity increases genetic susceptibility to environmental triggers.

4.1.1 Race

The loci associated with autoimmune thyroid diseases are AITD1, CTLA4, GD1, GD2, GD3, HT1, and HT2 among white race and also different loci have been linked in persons of other races. The more susceptible to occur autoimmune thyroid disease is influenced by gene in human leukocyte antigen region on chromosome 6 and in *CTLA4* on band 2q33. It is associated with specific HLA haplotypes and vary with ethnicity [10].

4.1.2 Gender

Women are much more likely to develop Graves' Disease than are men. Women develop it seven to eight times more frequently than men [10] and are due to the production of special proteins (called antibodies) that attack the thyroid gland. The ratio of developing Graves' hyperthyroidism between women and men is 7:1 and is often mediated with either more estrogen or less testosterone and also observed that moderate amounts of estrogen enhance immunologic reactivity [31–33]. However, the X-chromosome is the source of the increased susceptibility rather than sex steroid since the susceptibility continues after the menopause and X-chromosome inactivation has been linked with autoimmune thyroid disease [34].

4.1.3 Age

Typically, Graves' Disease is a disease of young women, but it may occur in persons of any age. Graves' Disease is usually occur in people between ages 30 and 50 years but can occur at any age. The typical age range is 20–40 years and the most affected women are aged 30–60 years [35].

4.1.4 Other autoimmune disorders

People with other autoimmune disorders are more likely to develop Graves' Disease than people without these disorders such as type 1 diabetes, rheumatoid arthritis, pernicious anemia, lupus erthymatosus, addison's disease, vitiligo, or crohn's disease.

4.2 Environmental agents

The remaining 20%–30% contribution to the onset of autoimmune thyroid disease is thought to be due to environmental exposures or triggers. Interfere with thyroid function at multiple sites, including thyroid hormone synthesis, thyroid hormone metabolism and excretion, and thyroid hormone action [36–39]. Most of these agents may influence the pituitary and thyrotropin (TSH) secretion, or even be partial thyroid hormone receptor agonists. There are a number of exposures that have been identified and proposed, both from human and animal studies (11–14) [40–43]. These include infections, life stress, iodine intake, smoking, medications such as amiodarone and interferon, radiation, and environmental toxicants. The environmental parameters commonly reported as contributing factors are infectious agents, iodine, drugs (amiodarone, Interferon-a (IFN-a), and CD52 MABs), tobacco, and stress [44].

4.2.1 Infection

Autoimmune thyroiditis can be induced in experimental animals by certain viral infections. Graves' Disease has been associated with a variety of infectious agents such as Yersinia enterocolitica and Borrelia burgdorferi. Homologies have been shown between proteins of these organisms and thyroid autoantigens [45, 46]. Thyroid autoimmune disease is associated with infections in the thyroid gland itself such as subacute thyroiditis, congenital rubella etc., and could initiate class II molecule expression. When Hepatitis C infection is treated with interferon therapy is a well-recognized precipitator of autoimmune thyroid disease, although less commonly a Graves' Disease develops rather than thyroiditis [47].

4.2.2 Stress

Both physical and emotional stressful life events and illness may act as a trigger for the onset of Graves' Disease among people who have genes that increase their risk. A review of the literature including seven case–control studies has highlighted the preexistence of a 'negative' stressful event in patients with Graves' Disease [48–55]. In general, stress suppresses the immune function, possibly mediated by the actions of cortisol on immune cells. Stress-induced suppression may be followed by rebound immunologic hyperactivity which could precipitate autoimmune thyroid disease in genetically susceptible individuals. The major T helper cells involved in Graves' Disease is Th2 and more recently found that Th17 is favor for the production of the pathogenic antibody directed against the TSH receptor by B lymphocytes both in mice and humans. Stress hormones direct stimulate the Th2, and Th17 or Th1 and also induce IL4, IL6, and IL12 by dentritic cells. Stress causes immature DCs which induce apoptosis in Treg cells leads not to act like regulators of Th2 and Th17 effector cells. It has been found that patients with untreated Graves' Disease have low in Treg cells which is inversely correlated with serum concentration of TSH receptor antibodies [56].

4.2.3 Pregnancy and the postpartum period

Pregnancy or recent childbirth may increase the risk of the disorder, particularly among women who have genes that increase their risk. The immune suppression is associated with the onset of autoimmune diseases especially postpartum thyroiditis. Fetal microchimerism, fetal cells in maternal tissue has maternal immune response is recognized as a trigger for thyroid autoimmunity and development of postpartum autoimmune thyroid disease [57]. During pregnancy severe Graves' Disease is

uncommon because hyperthyroidism is associated with increased pregnancy loss pregnancy loss and reduced fertility. Even if pregnancy occurs it can cause complication to mother as well fetus. Both B-cell and T-cell functions are declined during pregnancy, while Tregs increase dampening the disease [44, 58]. After delivery, the slow rebound from immunosuppression results in immune reactivity which contributes to the occurrence of postpartum thyroid disease, including recurrence or the new onset of Graves' Disease [59]. Around 30 percent of young women have a history of pregnancy in the 12 months before the onset of Graves' Disease [60], which shows that postpartum Graves' Disease is a surprisingly common condition and that pregnancy is a major risk factor for susceptible women.

4.2.4 Smoking

Cigarette smoke contains cyanide, which is metabolized to thiocyante, and can interfere with iodine concentration in the thyroid [37]. Cigarette Smoking has been associated with an increased production of T3 and thyroglobulin [61, 62], affect the thyroid hormone action [63], enhanced sympathetic nervous activity, or by affecting thyroid-directed autoimmune responses [49, 62, 64–66]. Cigarette smoking causes complex interactions with the immune system which may increase cytokines in orbit and thyroid causes Graves' Disease and also smokers who have Graves' Disease exacerbating risk of developing Graves' ophthalmopathy [41, 67–68].

4.2.5 Dietary iodine

Iodine is essential for thyroid hormone production, although a number of regulatory factors allow a normal amount of thyroid hormone to be produced across a fairly wide range of iodine intake. Deficient iodine intake is well known to be associated with reduced thyroid hormone production. Excess iodine, however, can also have adverse effects depending on underlying thyroid function, as well as the extent and duration of iodine excess [69]. Patients with multinodular goiter and associated areas of autonomous, TSH-independent, thyroid hormone production can have excess thyroid hormone production in response to iodine, the Jod–Basedow effect. Increased immunogenicity of thyroglobulin, thyroid cell destruction, In response to iodine supplementation in areas of iodine deficiency, there is an increase in thyroid autoantibodies and in some cases autoimmune thyroid disease [42, 43, 70, 71]. The mechanism of stimulation of autoimmune thyroid disease in response to iodine supplementation is not established. Excess iodine intake is associated with highly iodinated Tg, which is thought to be more immunogenic than poorly iodinated Tg [42, 70].

4.2.6 Dietary selenium

Selenium interacts with immune response. Low selenium intake has been associated with an increase in thyroid autoantibodies, and selenium supplementation with a reduction in antibodies [41].

4.2.7 Medications

Medications associated with the onset of autoimmune thyroid disease include lithium, amiodarone, interferon α, interleukin 2, campath-1 h, and highly active anti-retroviral therapy [42]. Some medications, such as lithium, may not trigger

autoimmunity, but accelerate the autoimmune process by interfering with thyroid function. It may stimulate the immune response at multiple sites. Medications differ in their mechanisms of stimulating thyroid autoimmunity, as well as the relative effect on promoting hypothyroidism or Graves' Disease [41].

4.2.8 Radiation Exposure

Radiation exposure especially medical radiation is one of the environmental exposures linked to effects on the thyroid which stimulate thyroid autoantibodies, increases thyroid antigens, inflammation. Autoimmune thyroid disease has been linked to therapeutic medical radiation [72–74]. Patients receiving 131I for thyroid disorder develop Graves' Disease later in their life and, sometimes, it can lead Graves' ophthalmopathy [73]. Radiation therapy with 131I causes low level thyroid autoantibody positivity in a sensitive TSH receptor antibody measurement which was associated with the development of Graves' Disease [73].

4.2.9 Toxicants

The main sources of toxicants are industrial chemicals, pesticides and herbicides, toxins in consumer goods, and heavy metals which may impair the thyroid function by recruiting antibodies to attack the thyroid. Most municipal water sources are now closely monitored for a range of toxicants, including those that affect the thyroid and well water also to be tested regularly for contaminants [75, 76].

5. Pathophysiology

Hypothalamic–pituitary-thyroid axis feedback mechanism is controlled the secretion of thyroid hormone by involving the interaction of stimulatory and inhibitory factors. Hypothalamus secretes Thyrotropin-releasing hormone (TRH) which stimulates the anterior lobe of pituitary gland to release Thyroid Stimulating Hormone (TSH). TSH binds with receptors on the thyroid gland leads to the release of thyroid hormones primarily T4 and to a lesser extent T3. Elevated levels of these hormones act on the hypothalamus to decrease TRH secretion and thus the synthesis of TSH and vice versa. Iodine requires for the synthesis of thyroid hormone. Dietary inorganic iodide is carried to the thyroid gland by iodide transporter. In the presence of thyroid peroxidase enzyme inorganic iodide is converted to iodine and bound to thyroglobulin through a process called organification. This causes the formation of Monoiodotyrosine (MIT) and Diiodotyrosine (DIT) and coupled to form triiodothyronine (T3) and thyroxine (T4) and then stored in the thyroid's follicular lumen with thyroglobulin. These preformed hormones which diffuse into the peripheral circulation form thyroid gland. In the peripheral circulation more than 99.9% of T4 and T3 are in inactive form. However, free T3 is 20–100 times more biologically active than free T4. Free T3 acts by binding to DNA-binding proteins in cell nuclei which regulate the transcription of various cellular proteins [77]. Any causes that alter the process leads to an increase in the peripheral circulation of unbound thyroid hormone can cause hyperthyroidism.

Thyroid Stimulating Hormone – Receptor (TSH-R) is a G-protein coupled receptor with seven transmembrane-spanning domains which primarily seen thyroid gland. It is also present in adipocytes, fibroblasts, bone cells and a variety

of additional sites [78, 79]. TSHR regulates thyroid growth and thyroid hormone production and secretion and TSH also acting via TSHR. Hyperthyroidism in Graves' Disease manifested by the production of autoantibodies against the TSHR. These autoantibodies mimic the effects of the hormone on thyroid cells thereby stimulating autonomous production of T3 and T4. The derangement of immune function also lead to the production of pathologic autoantibodies complex by involving B and T cells which enhance the several autoantigens in addition to TSH-R. In Graves' Disease, B and T lymphocyte-mediated autoimmunity are known to be directed at 4 well-known thyroid antigens: thyroglobulin (Tg), thyroid peroxidase (TPO), sodium-iodide symporter and the thyrotropin receptor. Thyroid stimulating immunoglobulin binds with thyroid-stimulating hormone (TSH) receptor on the thyroid cell membrane and stimulates the action of the thyroid-stimulating hormone. It stimulates both, thyroid hormone synthesis and thyroid gland growth, causing hyperthyroidism and thyromegaly [3] The stimulating activity of thyrotropin receptor antibodies is found in the immunoglobulin G. Circulating autoantibodies against the thyrotropin receptor continuously stimulate the thyroid gland to increase the secretion of thyroid hormone and thyroglobulin that is mediated by 3,'5′-cyclic adenosine monophosphate which suppresses the secretion of pituitary thyrotropin. These autoanitbodies also stimulate iodine uptake, protein synthesis, and thyroid gland growth [80].

Intrathyroidal lymphocytic infiltration observed in initial histologic examination in autoimmune thyroid disease and can be correlated with thyroid antibodies titer. The thyroid cells express molecules due to being the source of autoantigens that mediate T cell adhesion and complement regulation such as Fas and cytokines which interact the immune system and also the proportion of CD4 lymphocytes is lower in the thyroid than in the peripheral blood. Besides being the source of autoantigens, the thyroid cells express molecules that mediate T cell adhesion and complement regulation (Fas and cytokines) that participate and interact with the immune system. In these patients, the proportion of CD4 lymphocytes is lower in the thyroid than in the peripheral blood. The increased Fas expression in intrathyroidal CD4 T lymphocytes causes CD4 lymphocyte reduction. The autoimmune thyroid disease susceptibility genes are CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 [25, 81] which specific either Graves' Disease or Hashimoto thyroiditis. The two new susceptibility loci are RNASET2-FGFR1OP-CCR6 region at 6q27 and an intergenic region at 4p14 [82]. Positive Graves' Disease is strongly associated with thyroid-stimulating hormone receptor and major histocompatibility complex variants with persistently thyroid stimulating hormone receptor autoantibodies. [83]

5.1 Graves' thyroid gland

The thyroid gland is diffusely enlarged but not always. The pathological change of the thyroid gland is follicular hyperplasia, intracellular colloid droplets, cell scalloping, a reduction in follicular colloid, and a patchy (multifocal) lymphocytic infiltration. The majority of intrathyroidal lymphocytes are T cells but plenty of B cells may be present. In some areas, thyroid epithelial cell size correlates with the intensity of the lymphocytic infiltrate, suggesting thyroid-cell stimulation by local B cells secreting stimulating TSHR-Ab [84].

5.2 Autoantibodies of thyroid

Thyroid autoantibodies, including TSHR-Abs secretes spontaneously from lymphocytes of Graves' thyroid tissue in activated state [85]. It may also secretes

activated autoantibodies when decline in serum thyroid autoantibody concentrations after antithyroid drug treatment, after thyroidectomy, and late after radioactive iodine therapy.

5.3 TSH receptor and autoantibodies

Long-acting thyroid stimulator (LATS) was found among patients with Graves' hyperthyroidism [86] and it is proved to be an immunoglobulin which inhibited the binding of radiolabeled thyroid stimulating hormone to thyroid membranes due to the presence of antibodies to the TSH receptor (TSHR-Ab) [87].

5.4 TSHR agonists and antagonists

The characteristics TSHR-Abs are stimulatory or inhibitory or neutral. In case of Hashimoto's thyroiditis, block the binding and action of TSH and, therefore, can cause hypothyroidism. Whereas in Graves' Disease, TSHR-Abs has both stimulating and blocking thereby the clinical presentation may manifest depend upon a balance between these different antibodies. In third category, TSHR-Abs is of the neutral variety which may bind to the receptor but not influencing thyroid stimulating hormone binding. However, these antibodies may not be entirely neutral and can have cell signaling capability of untoward changes [88].

5.5 Similarities with autoimmune thyroiditis

- Lymphocytic infiltration of the thyroid and anti-Tg and anti-TPO antibodies in the serum occur in both Graves' Disease and chronic autoimmune (Hashimoto's) thyroiditis

- The genetic susceptibility of both disorders is HLA

- Areas of cellular apoptosis may be seen even in Graves' thyroid glands [89, 90].

- The presence of antibodies that bind to the TSH receptor in both disorders and differ in biological activities

- Progression from Graves' hyperthyroidism to chronic autoimmune thyroiditis and hypothyroidism is well-recognized [91] and vice versa also occurs [92]. Patients who have hypothyroidism one year, Graves' hyperthyroidism another year, and again hypothyroidism later [93].

- In families of patients, some members may have chronic autoimmune thyroiditis and others may have Graves' Disease [94]

5.6 Immune mechanisms of Graves' Disease

The immune mechanisms involved in the pathogenesis of Graves' hyperthyroidism are molecular mimicry (specificity crossover), thyroid-cell expression of human leukocyte-associated molecules (antigens), and bystander activation [95].

5.7 B cell in Graves' Disease

Monoclonal antibody to the CD 34 antigen on the surface of B cells has demonstrated that changing the B cell repertoire can have profound influences on

Graves' Disease [40]. B cell also plays an important role in TSHR-Ab interaction with retro-orbital TSHRs which expressed on fibroblasts and adipocytes cause Graves Ophthalmology [95].

5.8 T cell in Graves' Disease

T cells are present in the immune repertoire react with appropriate peptides which are derived from thyroid autoantigens in Graves' Disease. Secretion of thyroid-specific autoantibodies from B cells is increase against the activated T cells. The thyroid-specific T cells in Graves' Disease primarily act as helper (CD4+ Th1) cells. However, based on the production of cytokines, subsets of T cells have been distinguished most easily

- CD4+ Th1 cells — Secrete interleukin-2, interferon gamma, and tumor necrosis factor-alpha which in turn activate cytotoxic cells and may induce thyroid cell apoptosis when CD4+ Th1 cells activated
- CD4+ Th2 cells — Secrete interleukin −4 and interleukin −5 and activate antibody production.
- CD4+ Th17 cells — Interleukin −17 is secreted under the influence of interleukin −23 by the CD4+ Th17 cells which is a newly identified pro-inflammatory subset of cells [95].

6. Clinical manifestations

Graves' Disease is a syndrome which consists of hyperthyroidism, goiter, Graves' orbitopathy, and occasionally a Graves' dermopathy referred to as pretibial or localized myxedema (PTM). High amounts of T4, T3, or both can cause an excessively high metabolic rate. Signs and symptoms of Graves' Disease manifested due to the effect of hypermetabolism as well over stimulation of nervous system by T4, T3 or both.

6.1 General

- Muscle weakness
- Fatigue

6.2 Neck

- Enlargement of the thyroid gland (goiter)
- May be palpable thyroid nodules
- Thyroid bruits on auscultation

6.3 Cardiovascular system

- Rapid or irregular heartbeat (palpitations)
- Increased heart rate (Tachycardia)
- High Blood Pressure
- Heart failure

6.4 Respiratory system

- Dyspnea

6.5 Gastro intestinal system

- Diarrhea or increased Frequent bowel movements

6.6 Musculoskeletal

- Proximal muscle weakness
- Easy fatigability
- Back Pain
- Increased risk for fracture

6.7 Neuromuscular system

- A fine tremor of the hands or fingers
- Hyperactive deep tendon reflexes

6.8 Metabolic

- Weight loss, despite normal eating habits
- Worsening diabetes control

6.9 Hematologic

- Easy bruising

6.10 Endocrine/reproductive system

- Change in menstrual cycles
- Erectile dysfunction or reduced libido
- Secondary amenorrhea
- Gynecomastia
- Impotence

6.11 Integumentary

- Heat sensitivity and an increase in perspiration or warm, moist skin,
- Hair loss

- Onycholysis
- Vitiligo
- Thick, red skin usually on the shins or tops of the feet a condition called Graves' dermopathy or Pretibial Myxedema (PTM)

6.12 Extremities

- Edema
- Thyroid Acropachy: is a rare manifestation with characteristic imaging findings. Clinically, it presents as nail clubbing, swelling of digits and toes.
- Onycholysis: Separation of the nail plate starting at the distal free margin and progressing proximally usually starting at the tip and/or sides on the ring finger but can occur on any of the fingernails

6.13 Psychiatric

- Restlessness
- Anxiety
- Irritability
- Insomnia

6.14 Eyes

Bulging eyes (Graves' ophthalmopathy) Graves' ophthalmopathy also called Graves Orbitopathy, Graves Eye Disease, or Thyroid Eye Disease (TED), is an autoimmune inflammatory disorder of the orbit and periorbital tissues, characterized by upper eyelid retraction, lid lag, swelling, redness (erythema), conjunctivitis, and bulging eyes (exophthalmos) It is a problem that develops in people with an overactive thyroid caused by Graves' Disease which increase rate of peripheral blood mononuclear cell conversion into CD34+ fibrocytes. These cells may contribute to the pathophysiology of ophthalmopathy by accumulating in orbital tissues and producing inflammatory cytokines, including TNF-alpha and IL-6. although most cases of thyroid-associated orbitopathy do not result in visual loss, this condition can cause vision-threatening exposure keratopathy, troublesome diplopia, and compressive optic neuropathy.

6.14.1 Early symptom

- Feeling of irritation in the eyes
- Excessive tearing or dry eye
- Forward displacement of the eye
- Sensitivity to light
- Double vision

6.14.2 Late symptoms

- Swelling of the eye
- Inability to move the eye
- Corneal ulceration
- Rarely, loss of vision

7. Complications

7.1 Goiter

An enlarged thyroid gland that has grown big enough to appear as a visible bulge on the neck caused by Graves' Disease is known as a diffuse thyrotoxic goiter. As thyroid enlarges bigger without treatment, goiter gets big enough to make difficulty in swallowing, causes coughing, and sleep disruption.

7.2 Thyroid storm

If Graves' Disease left untreated or treated inadequately, can cause a rare but life-threatening complication called Thyroid Storm also known as thyrotoxic crisis or accelerated hyperthyroidism and requires immediate emergency care. The sudden and drastic raise in thyroid hormones causes fever, sweating, vomiting, diarrhea, delirium, severe weakness, seizures, irregular heartbeat, yellow skin and eyes (jaundice), severe low blood pressure, and coma.

7.3 Heart disorders

Untreated, Graves' Disease can lead to heart rhythm disorders, changes in the structure and function of the heart muscles leads to inability of the heart to pump enough blood to the cells to meet the metabolic demand. Hyper secretion of thyroid hormone causes left ventricular thickening which may lead to heart failure and cardiac-related death. Thyrotoxicosis also has been associated with dilated cardiomyopathy, [96] right sided heart failure with pulmonary hypertension, diastolic dysfunction and atrial fibrillation [97]. An irregular heartbeat that can lead to blood clots, stroke, heart failure, and other heart-related problems such as angina.

7.4 Brittle bones

Untreated hyperthyroidism increase in the rate of bone resorption can lead to weak, brittle bones (osteoporosis). Too much thyroid hormone interferes with body's ability to incorporate calcium into bones. Patients with Graves' Disease have significantly increased in serum calcium and phosphate, plasma FGF-23 compared to healthy individuals and amongst FGF-23 is physiologically related to serum phosphate homeostasis in untreated Graves' Disease [98].

7.5 Maternal/fetal complications

Possible complications of Graves' Disease during pregnancy include miscarriage, preterm birth, fetal thyroid dysfunction, poor fetal growth, maternal heart failure

and preeclampsia. Preeclampsia is a maternal condition that results in high blood pressure and other serious signs and symptoms.

8. Assessment and diagnostic investigations

8.1 History collection

Analysis of medical and family history with associated sign and symptoms.

8.2 Physical examination

From head to toe examination and the findings are diffusely enlarged thyroid gland, thyrotoxic signs and symptoms. The unique findings to Graves' Disease such as Graves ophthalmopathy and dermopathy, Myxedematous changes of the skin (usually in the pretibial areas) are described as resembling an orange peel in color and texture, and Onycholysis can be seen usually in the fourth and fifth fingernails.

8.3 Blood investigations including thyroid profile

In case of Graves' Disease, abnormally high levels of T3 and T4, and a very low level of TSH seen as well elevated TSI and positive Thyroid peroxidase antibody

- Thyroid stimulating hormone (TSH)
- Thyroid hormone Triiodothyronine (T3)
- Free T3 or Free triiodothyronine (FT3)
- Thyroid hormone Thyroxine (T4)
- Antithyroid Antibodies: Thyroid peroxidase (TPO) antibody titers provide an evidence for Graves' Disease. More than 95% of patients have positive assays for TPO (thyroperoxidase or microsomal antigen), and about 50% have positive anti-thyroglobulin antibody assays.
- Thyroid-stimulating Immunoglobulin (TSI): It is measured from drawn blood and increase in the level of TSI antibodies reveals that the thyroid gland is more active and release excess amounts of thyroid hormone into the blood (**Table 2**).

Hormone	Normal range
Thyroid stimulating hormone (TSH)	0.40–4.50 mIU/mL
Thyroxine (T4)	5.0–11.0 ug/dL
Free Thyroxine (T4)	0.9–1.7 ng/dL
Triiodothyronine (T3)	100–200 ng/dL
Free triiodothyronine (FT3)	2.3–4.1 pg./mL

Table 2.
Normal range of thyroid profile.

8.4 Radioactive iodine uptake (RAIU) study

A radioactive iodine uptake test and scan will measure the amount of iodine that thyroid gland absorbs and also determines if the entire or only part of the thyroid is overactive. If thyroid absorbs more iodine from blood stream which indicates Graves' Disease.

8.5 Thyroid scan

It shows how and where iodine is distributed in the thyroid. With Graves' Disease, the entire thyroid is involved, so the iodine shows up throughout the gland. It also may confirm hypoechogenicity or intense vascularity of Graves' Disease if a color Doppler flow exam is done.

8.6 Thyroid ultrasound

High-frequency sound waves to produce images of structures inside the thyroid gland. It's most useful when radioactive iodine uptake study is contraindicated such as pregnant women, iodine hypersensitivity.

8.7 Imaging test

computed tomography (CT) scan or magnetic resonance imaging (MRI) scan is indicated for clear picture of thyroid gland when the clinical assessment is not clear. CT scan and MRI of the eye muscles and eye sockets (called orbital imaging) in order to define the exact impact of Graves' Disease on the eyes and to confirm the Graves ophthalmopathy.

8.8 Other investigations to rule out complications

- Electro cardiogram
- ECHO cardiogram
- Blood sugar
- Blood cholesterol
- Serum calcium
- Serum phosphate
- Bone mineral density Test

9. Treatment approaches

The main aims of the management of Graves' Disease are to inhibit the overproduction of thyroid hormones by targeting thyroid gland and to alleviate the effect of an excess hormones on various system of the body thereby correct the thyrotoxic state.

The management includes

- Radioactive iodine therapy
- Anti-thyroid medications
- Beta blockers
- Thyroid Surgery
- Treating Graves' ophthalmopathy
  - Corticosteroids.
  - Teprotumumab (Tepezza)
  - Prisms.
  - Orbital decompression surgery
  - Orbital radiotherapy

9.1 Radioactive iodine therapy

The most commonly used therapy for Graves' Disease is radioactive iodine (radioiodine) since the 1940s. It is still popular because it is non-invasive and highly effective on thyroid gland and has fewer side effects. Graves' Disease with a large thyroid gland, multiple symptoms of thyrotoxicosis, high levels of thyroxine, and high titers of TSI are indicated for radioactive iodine and women who are pregnant or breastfeeding are contraindicated for this therapy. Commonly used radioactive iodine is iodine-131 (I-131) and can be administered orally in the form of capsule or liquid. The dose is calculated based on the age, weight of the thyroid gland and radioiodine uptake and the usual dose ranges from 5–15 mCi. Iodine is essential for thyroid gland to produce hormones, the thyroid absorbs the radioiodine into the thyroid cells and the radiation destroys the hyperactive thyroid cells. This causes the thyroid gland to shrink, hormones to return normal and gradually alleviate the symptoms. It usually takes several weeks to several months. Follow up the patient and monitoring the thyroid profile is very important because it causes hypothyroidism.

9.2 Anti-thyroid medications

Antithyroid medications are one of the prominent methods to treat hyperthyroidism which interfere with the use of iodine by the thyroid to produce hormones. Commonly used antithyroid medicines are thionamides, such as propylthiouracil (PTU), and carbimazole (CBZ). Thionamides are actively transported into the thyroid gland where they inhibit both the organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodotyrosines and hence reduce the synthesis of thyroid hormone [99, 100] and inhibit the function of thyroperoxidase, reducing oxidation and the organification of iodide. Anti-thyroid drugs may be administered before or after radioiodine therapy as a supplemental treatment. Methimazole is considered the first choice of antithyroid medicnes as the risk of

liver disease is common in Propylthiouracil. However, propylthiouracil is the preferred anti-thyroid drug during the first trimester of pregnancy, as methimazole has a slight risk of birth defects and can continue the methimazole after the first trimester. Side effects of anti-thyroid drugs are allergic reactions such as skin rash, itching, lower resistance to infection due to decrease in white blood cells and rarely liver disease.

9.3 Beta blockers

Beta blockers do not have the direct effect on thyroid gland to reduce the hormone secretion but can minimize the symptoms until the effect other treatments occur. Beta-blockers, such as propranolol and metoprolol, are often the first line of treatment. The action of beta blockers in hyperthyroidism is to antagonize beta-receptor-mediated effects of catecholamines thereby reduce the heart rate, blood pressure, tremors, anxiety or irritability, heat intolerance, sweating, diarrhea, and muscle weakness. Beta blockers may trigger an asthma attack so aren't often prescribed for people with asthma and also complicate management of diabetes.

9.4 Thyroid surgery

Removal of part or total tissue of thyroid gland namely subtotal or total thyroidectomy is another option for the management of Graves' Disease. Surgery is less common and it is indicated when other treatment fails to manage. Pre-operatively, reduce the size of thyroid gland and bring to the euthyroidal state to reduce the risk of complications post-operatively. The complications of thyroidectomy include hypothyroidism, hypoparathyroidism, recurrent laryngeal nerve, hemorrhage. Patient undergone thyroidectomy has to receive the thyroid replacement hormone medication such as levothyroxine in remaining life.

9.5 Treating Graves' ophthalmopathy

9.5.1 Over-the-counter artificial tears

Mild symptoms of Graves' ophthalmopathy may be managed by using over-the-counter artificial tears during the day and lubricating paraffin-based gels can be applied at night.

If symptoms are more severe:

9.5.2 Corticosteroids

Corticosteroids, such as prednisone, may lessen swelling behind eyeballs. Side effects may include fluid retention, weight gain, elevated blood sugar levels, increased blood pressure and mood swings.

9.5.3 Teprotumumab (Tepezza)

It's given through an IV in the arm every three weeks and is given eight times. TEPEZZA targets and blocks IGF-1R and inhibits fibroblast activation via the IGF-1R/TSHR signaling complex at the source of the disease [101, 102] and decreases proptosis by [103–105] by reducing inflammation, preventing muscle and fat tissue remodeling, and preventing tissue expansion behind the eye. It can cause side effects such as nausea, diarrhea, muscle spasms and elevated blood sugar levels.

9.5.4 Prisms

Prisms in eye glasses may correct the double vision as double vision is one of the effects of Graves' Disease.

9.5.5 Orbital decompression surgery

Removal of bone between eye socket (orbit) and sinuses, the air spaces next to the orbit. This decompression moves the eye back to their original position to release pressure on the optic nerve. This treatment is indicated if pressure on the optic nerve threatens the vision and treats the possible complication of double vision.

9.5.6 Orbital radiotherapy

It is common method of treatment using targeted X-rays to destroy the tissue behind the eyes but the underlying mechanism and benefits are not clear. It can be administered over the course of several days and is recommended if the Graves' ophthalmopathy is worsening and not respond to corticosteroids or not tolerated well.

10. Patient education

10.1 Diet

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) stated that Graves' Disease can cause sensitivity to iodine. The symptoms of Graves' Disease may be worsening when consuming foods rich in iodine such as kelp and dulse or iodine supplements. The NIDDK warns to consult the physician before taking a multivitamin supplement or cough medicine, as these can contain iodine.

10.2 Exercise

Exercising can enhance the improvement in some symptoms during treatment. It controls the metabolism as there is a tendency to gain weight when the hyperthyroidism is corrected. Brittle bones also can occur with Graves' Disease, and weight-bearing exercises can help maintain bone density.

10.3 Stress reduction

It may be helpful, as stress may trigger or worsen Graves' Disease. Yoga, meditation, relaxation technique such as Listening to music, taking a warm bath or walking can help to reduce the stress and plan to follow in daily routine.

10.4 Optimal levels of iodine and selenium

Optimal iodine and selenium intake has been found to attenuate the toxic effects that heavy metals and perchlorate can have on the thyroid.

10.5 Avoid stimulants

Avoid consuming coffee, tea and quit the habit of smoking and alcohol as it worsens the symptoms of Graves' Disease.

10.6 Wear sunglasses

Eyes are more vulnerable to ultraviolet rays and more sensitive to bright light when eyes protrude. Wearing sunglasses that wrap around the sides of head will also lessen the irritation of eyes from the wind.

10.7 Elevate the head end

Keep the head higher than the body lessens fluid accumulation in the head and may relieve the pressure on the eyes.

10.8 Cold compresses

Apply cold compress to the eyes to keep the eyes moisture which may soothe eyes.

11. Prognosis

Many patients with Graves' Disease remain well after the course of treatment with anti-thyroid drugs, radioactive iodine or surgery, but recurrence can happen at any time. Treatment approaches are very effective, but often results in abnormally low levels of thyroid hormones cause hypothyroidism. The Graves' ophthalmology also tends to improve slowly with anti-thyroid drug treatment over years. However, some element of the staring appearance often remains.

12. Conclusion

This chapter briefed on epidemiology, causes and risk factors, pathophysiology, clinical manifestations, diagnostic investigations, management and complications of Graves' Disease. Graves' Disease is the autoimmune disorders of thyroid gland and the common cause of hyperthyroidism. It often poses complex challenges in diagnosing and managing the clients with Graves' Disease. Graves' Disease in some patients is curable within a limited time period with modern treatment but in some patients it is a chronic and relapsing. However untreated Graves' Disease causes the complications of thyroid storm, cardiac and ophthalmic complications and over treated Graves' Disease leads to hypothyroidism. Patient education is also plays an vital role in managing and preventing complications.

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References

[1] Kalra S, Unnikrishnan AG, Sahay R. The global burden of thyroid disease. Thyroid Research and Practice. 2013;10:89-90

[2] Marieb E, Hoehn K. Regulation and integration of the body. The endocrine system. Human Anatomy and Physiology. 7th edition. San Francisco, CA: Pearson Education Inc. 2007: 620-625.

[3] Jameson J, Weetman A, Fauci A, Braunwald E, Kasper D, Hauser S, et al. Disorders of the thyroid gland. Harrison's Principles of Internal Medicine. 17th edition. USA: The McGraw Hill Companies Inc. 2008: 2224-2247.

[4] https://rarediseases.org/rare-diseases/graves-disease/

[5] Ellis H. Robert. Graves: 1796-1852. British Journal of Hospital Medicine. 2006;67(6):313.

[6] Sinha A A., et al. Autoimmune diseases: the failure of self-tolerance. Science 1990;248.4961: 1380-1388.

[7] G Effraimidis, WM Wiersinga. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. European Journal of Endocrinology. 2014; 170(6): R241-R252.

[8] https://www.nhs.uk/conditions/overactive-thyroid-hyperthyroidism/causes

[9] Smith TJ, Hededüs L. Graves' disease. The New England Journal of Medicine. 2016;375(16):1552-1565.

[10] Yeung SJ, Habra MA, Chiu AC. Graves' disease. Medscape emedicine website. http://emedicine.medscape.com/article/120619-overview#a6 External link. Updated March 2017. Accessed December 14, 2020.

[11] Furszyfer J, Kurland LT, McConahey WM, Elveback LR. Graves' disease in Olmsted County, Minnestoa, 1935 through 1967. Mayo Clinic Proceeding. 1970; 45:636.

[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):687-696.

[13] Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmunity Reviews. 2003;2(3):119-125.

[14] Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community the Whickham survey. Clinical Endocrinology. 1977; 7(6):481-493.

[15] Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clinical Endocrinology. 1995;43(1):55-68.

[16] Y S Hussain, J C Hookham, A Allahabadia, S P Balasubramanian. Epidemiology, management and outcomes of Graves' disease-real life data. Endocrine. 2017;56(3):568-578.

[17] Nystrom HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. Clinical Endocrinology. 2013;78(5):768-776.

[18] Glinoer D. Management of hypo- and hyperthyroidism during pregnancy. Growth Hormone IGF Research. 2003;13:S45–S54.

[19] Hollowell JG, Staehling NW, Flanders WD, Hannon WH,

Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). Journal Clinical Endocrinology and Metabolism. 2002 ;87(2):489-499.

[20] Zimmerman D, Lteif AN. Thyrotoxicosis in children. Endocrinology&Metabolism Clinics of North America. 1998;27:109-126.

[21] Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Le'ger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. Journal Clinical Endocrinology and Metabolism. 2008;93:3817-3826.

[22] Lavard L, Ranløv I, Perrild H, Andersen O, Jacobsen BB. Incidence of juvenile thyrotoxicosis in Denmark, 1982-1988. A nationwide study. European Journal of Endocrinology. 1994;130:565-568.

[23] Rivkees SA,Mattison DR. Propylthiouracil (PTU) hepatoxicity in children and recommendations for discontinuation of use. International Journal of Pediatric Endocrinology. 2009:132041.

[24] Philip R, Sivaraman Nair SA, Kuruvilla V, John SM, Amal D, Sankaran KC. Incidentally detected thyrotoxicosis-etiology and natural course: A study from Central Kerala. CHRISMED Journal of Health and Research. 2016;3:203-206.

[25] Jacobson EM, Tomer Y. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. Journal of Autoimmunity. 2007;28(2-3):85-98.

[26] Tomer Y. Mechanisms of autoimmune thyroid diseases: from genetics to epigenetics. Annual Review of Pathology. 2014;9:147-156.

[27] 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. Journal of Clinical Endocrinology and Metabolism. 2001;86:930-934.

[28] Limbach M, Saare M, Tserel L, Kisand K, Eglit T, Sauer S, et al. Epigenetic profiling in CD4+ and CD8+ T cells from Graves' disease patients reveals changes in genes associated with T cell receptor signaling. Journal of Autoimmunity. 2016;67:46-56.

[29] 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):373-376.

[30] Zaletel K, Krhin B, Gaberscek S, Hojker S. Thyroid autoantibody production is influenced by exon 1 and promoter CTLA-4 polymorphisms in patients with Hashimoto's thyroiditis. International Journal of Immunogenetics. 2006;33(2):87-91.

[31] Kincade PW, Medina KL, Smithson G, Scott DC. Pregnancy: a clue to normal regulation of B lymphopoiesis. Immunology Today. 1994; 15:539.

[32] Paavonen T. Hormonal regulation of immune responses. Ann Med 1994; 26:255.

[33] Da Silva JA. Sex hormones, glucocorticoids and autoimmunity: facts and hypotheses. Annals of Rheumatic Disease. 1995; 54:6.

[34] Yin X, Latif R, Tomer Y, Davies TF. Thyroid epigenetics: X chromosome inactivation in patients with

autoimmune thyroid disease. Annals of the New York Academy of Science. 2007; 1110:193.

[35] Smith TJ, Hededüs L. Graves' disease. The New England Journal of Medicine. 2016;375(16):1552-1565.

[36] Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. Thyroid. 1998;8:827-856.

[37] Pearce EN. Braverman LE. Environmental pollutants and the thyroid. Best Practice & Research Clinical Endocrinology & Metabolism. 2009;23:801-813.

[38] Brent GA. Braverman LE. Zoeller RT. Thyroid health and the environment. Thyroid. 2007;17:807-809.

[39] Zoeller RT. Dowling ALS. Herzig CTA. Iannacone EA. Gauger KJ. Bansal R. Thyroid hormone, brain development, and the environment. Environmental Health Perspectives. 2002;110(Suppl 3):355-361.

[40] Strieder TGA. Tijssen JGP. Wenzel BE. Endert E. Wiersinga WM. Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of patients with autoimmune thyroid disease using the thyroid events Amsterdam (THEA) score. Achieves of Internal Medicine. 2008;168:1657-1663.

[41] Prummel MF. Streider T. Wiersinga WM. The environment and autoimmune thyroid diseases. European Journal of Endocrinology. 2004;150:605-618.

[42] Burek CL. Talor MV. Environmental triggers of autoimmune thyroiditis. Journal of Autoimmunity. 2009;33:183-189.

[43] Tanda ML. Piantanida E. Lai A. Lombardi V. Dalle Mule I. Liparulo L. Pariani N. Bartalena L. Thyroid autoimmunity and environment. Hormone and Metabolic Research. 2009;41:436-442.

[44] Weetman AP. Autoimmune thyroid disease: propagation and progression. European Journal of Endocrinology. 2003;148 1-9.

[45] Benvenga S, Guarneri F, Vaccaro M, et al. Homologies between proteins of Borrelia burgdorferi and thyroid autoantigens. Thyroid. 2004;14:964-966.

[46] Gangi E, Kapatral V, El-Azami El-Idrissi M, et al. Characterization of a recombinant Yersinia enterocolitica lipoprotein; implications for its role in autoimmune response against thyrotropin receptor. Autoimmunity. 2004;37(6-7):515-520.

[47] Menconi F, Hasham A, Tomer Y. Environmental triggers of thyroiditis: hepatitis C and interferon-α. Journal of Endocrinological Investigation. 2011; 34:78.

[48] Bagnasco M, Bossert I & Pesce G. Stress and autoimmune thyroid diseases. Neuroimmunomodulation. 2006;13:309-317.

[49] Winsa B, Karlsson A, Bergstrom R, Adami HO, Gamstedt A, Jansson R, Adamson U & Dahlberg PA. Stressful life events and Graves' disease. Lancet. 1991;338: 1475-1479.

[50] Sonino N, Girelli ME, Boscaro M, Fallo F, Busnardo B & Fava GA. Life events in the pathogenesis of Graves' disease, A controlled study. Acta Endocrinologica. 1993;128:293-296.

[51] Kung AW. Life events, daily stresses and coping in patients with Graves' disease. Clinical Endocrinology. 1995;42:303-308.

[52] Radosavljevic´ VR, Jankovic´ SM & Marinkovic´ JM. Stressful life events

in the pathogenesis of Graves' disease. European Journal of Endocrinology. 1996;134: 699-701.

[53] Yoshiuchi K, Kumano H, Nomura S, Yoshimura H, Ito K, Kanaji Y, Ohashi Y, Kuboki T & Suematsu H. Stressful life events and smoking were associated with Graves' disease in women, but not in men. Psychosomatic Medicine. 1998; 60: 182-185.

[54] Martin-du Pan RC. Triggering role of emotional stress and childbirth. Unexpected occurrence of Graves' disease compared to 96 cases of Hashimoto thyroiditis and 97 cases of thyroid nodules. Annales d'Endocrinologie. 1998;59:107-112.

[55] Matos-Santos A, Nobre EL, Costa JGE, Nogueira PJ, Macedo A, Galva˜o-Teles A & De Castro JJ. Relationship between the number and impact of stressful life events and the onset of Graves' disease and toxic nodular goitre. Clinical Endocrinology. 2001;55:15-19.

[56] Ge'raldine Falgarone, Hassan M Heshmati, Re'gis Cohen, and Ge'rard Reach. Role of emotional stress in the pathophysiology of Graves' disease. European Journal of Endocrinology. 2013;168:R13–R18.

[57] Ando T, Davies TF. Clinical Review 160: Postpartum autoimmune thyroid disease: the potential role of fetal microchimerism. Journal Clinical Endocrinology & Metabolism. 2003;88:2965.

[58] Fainboim L, Arruvito L. Mechanisms involved in the expansion of Tregs during pregnancy: role of IL-2/STAT5 signalling. Journal of Reproductive Immunology. 2011; 88:93.

[59] Stagnaro-Green A. Postpartum thyroiditis. Best Practice & Research Clin Endocrinology & Metabolism. 2004;18:303.

[60] Jansson R, Dahlberg PA, Winsa B, et al. The postpartum period constitutes an important risk for the development of clinical Graves' disease in young women. Acta Endocrinologica. 1987;116:321.

[61] Bartalena L. Bogazzi F. Tanda ML. Manetti L. Dell'Unto E. Martino E. Cigarette smoking and the thyroid. European Journal of Endocrinology. 1995;133:507-512.

[62] Bertelsen JB. Hegedus L. Cigarette smoking and the thyroid. Thyroid. 1994;4:327-331.

[63] P.N. Taylor, D. Albrecht, A. Scholz, G. Gutierrez-Buey, J.H. Lazarus, C.M. Dayan, O.E. Okosieme, Global epidemiology of hyperthyroidism and hypothyroidism. Nature Reviews Endocrinology. 2018;14:301-316.

[64] Muller B. Zulewski H. Huber P. Ratcliffe JG. Staub JJ. Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. New England Journal of Medicine. 1995;333:964-969.

[65] Wiersinga W M. Smoking and thyroid. Clinical Endocrinology. 2013;79:145-151.

[66] Shine B, Fells P, Edwards OM, Weetman AP 1990 Association between Graves' ophthalmopathy and smoking. Lancet 335:1261-1263.

[67] Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, Loviselli A, Pinchera A. More on smoking habits and Graves' ophthalmopathy. Journal of Endocrinological Investigations. 1989;12:733-737.

[68] Hegedius L, Brix TH, Vestergaard P. Relationship between cigarette smoking and Graves' ophthalmopathy. Journal of Endocrinological Investigations. 2004;27:265-271.

[69] Zimmerman MB. Iodine deficiency. Endocrine Reviews. 2009;30:376-408.

[70] Papanastasiou L, Vatalas IA. Koutras DA. Mastorakos G. Thyroid autoimmunity in the current iodine environment. Thyroid. 2007;17:729-739.

[71] Laurberg P, Jorgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IB. Rasmussen LB, Carle A. Vejbjerg P. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. European Journal of Endocrinology. 2008, 71(3):440-445.

[72] Skla C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the childhood cancer survivor study. Journal of Clinical Endocrinology and Metabolism. 2000;85:3227-3232.

[73] Dunkelmann S, Wolf R, Koch A, Kittner C, Groth P, Schuemichen C. Incidence of radiation-induced Graves' disease in patients treated with radioiodine for thyroid autonomy before and after introduction of a high-sensitivity TSH receptor antibody assay. European Journal of Nuclear Medicine and Molecular Imaging. 2004;31:1428-1434.

[74] Simon Z, Ress Z, Toldi J, Trauninger A, Miltenyi Z, Illes A. Rare association of Hodgkins lymphoma, Graves' disease and myasthemia gravis complicated by post-radiation neurofibrosarcoma: coincidence or genetic susceptibility?. International Journal of Hematology. 2009;89:523-528.

[75] National Academy of Sciences 2005 Health Implications of Perchlorate Ingestion. National Research Council, National Academy Press; Washington, DC:

[76] Howdeshell KL. A model of development of the brain as a construct of the thyroid system. Environmental Health Perspectives. 2002;110(Suppl 3):337-348.

[77] Stephanie L Lee, Hyperthyroidism and Thyrotoxicosis. Updated: Oct 19, 2020, https://emedicine.medscape.com/article/121865-overview#a4

[78] Davies TF, Ando T, Lin RY, et al. Thyrotropin receptor-associated diseases: from adenomata to Graves' disease. Journal of Clinical Investigations. 2005; 115:1972.

[79] Latif R, Morshed SA, Zaidi M, Davies TF. The thyroid-stimulating hormone receptor: impact of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on multimerization, cleavage, and signaling. Endocrinology and Metabolism Clinics of North America. 2009; 38:319.

[80] Sai-Ching Jim Yeung, Graves Disease, Updated: Apr 17, 2020. https://emedicine.medscape.com/article/120619-overview#a5.

[81] Iwama S, Ikezaki A, Kikuoka N, et al. Association of HLA-DR, -DQ genotype and CTLA-4 gene polymorphism with Graves' disease in Japanese children. Hormone Research. 2005;63(2):55-60.

[82] Chu X, Pan CM, Zhao SX, et al. A genome-wide association study identifies two new risk loci for Graves' disease. Nature Genetics. 2011;43(9):897-901.

[83] Bell L, Hunter AL, Kyriacou A, Mukherjee A, Syed AA. Clinical diagnosis of Graves' or non-Graves' hyperthyroidism compared to TSH receptor antibody test. Endocrine Connections. 2018;12:7354673.

[84] Paschke R, Brückner N, Eck T, et al. Regional stimulation of thyroid epithelial cells in Graves' disease by

lymphocytic aggregates and plasma cells. Acta Endocrinologica. 1991; 125:459.

[85] McLachlan SM, Pegg CA, Atherton MC, et al. TSH receptor antibody synthesis by thyroid lymphocytes. Clinical Endocrinology.1986;24:223.

[86] Adams, DD, Purves, HD. Abnormal responses in the assay of thyrotropin. Proceedings of the University of Otago Medical School. 1956; 34:11.

[87] Smith BR, Hall R. Thyroid-stimulating immunoglobulins in Graves' disease. Lancet. 1974;2:427.

[88] Morshed SA, Latif R, Davies TF. Characterization of thyrotropin receptor antibody-induced signaling cascades. Endocrinology. 2009; 150:519.

[89] Feig C, Peter ME. How apoptosis got the immune system in shape. European Journal of Immunology. 2007;37 Suppl 1:S61.

[90] Bossowski A, Czarnocka B, Bardadin K, et al. Identification of apoptotic proteins in thyroid gland from patients with Graves' disease and Hashimoto's thyroiditis. Autoimmunity. 2008; 41:163.

[91] Tamai H, Kasagi K, Takaichi Y, et al. Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological, and histological findings in 26 patients. Journal of Clinical Endocrinology & Metabolism. 1989;69:49.

[92] Takasu N, Yamada T, Sato A, et al. Graves' disease following hypothyroidism due to Hashimoto's disease: studies of eight cases. Clinical Endocrinology. 1990; 33:687.

[93] Kraiem Z, Baron E, Kahana L, et al. Changes in stimulating and blocking TSH receptor antibodies in a patient undergoing three cycles of transition from hypo to hyper-thyroidism and back to hypothyroidism. Clinical Endocrinology. 1992; 36:211.

[94] Tamai H, Ohsako N, Takeno K, et al. Changes in thyroid function in euthyroid subjects with a family history of Graves' disease: a follow-up study of 69 patients. Journal of Clinical Endocrinology & Metabolism. 1980; 51:1123.

[95] Terry F Davies, Douglas S Ross, Jean E Mullder. Pathogenesis of Graves' disease, Uptodate.

[96] White A, Bozso SJ, Moon MC. Thyrotoxicosis induced cardiomyopathy requiring support with extracorporeal membrane oxygenation. Journal of Critical Care. 2018;3.45:140-143.

[97] Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. Current Heart Failure Reports. 2008;5(3):170-176.

[98] Park SE, Cho MA, Kim SH, Rhee Y, Kang ES, Ahn CW. The adaptation and relationship of FGF-23 to changes in mineral metabolism in Graves' disease. Clinical Endocrinology. 2007;66(6):854-858.

[99] Cooper DS: Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. Journal of Clinical Endocrinology & Metabolism. 2003; 88: 3474-3481.

[100] Cooper DS: Antithyroid drugs. New England Journal of Medicine. 2005; 352: 905-917.

[101] Douglas RS. Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active thyroid eye disease: a focus on proptosis. Eye (Lond). 2019;33(2):183-190.

[102] Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. American Journal of Ophthalmology. 2019;208:281-288.

[103] TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.

[104] Bahn RS. Graves' ophthalmopathy. New England Journal of Medicine. 2010;362(8):726-738.

[105] Dik WA, Virakul S, van Steensel L. Current perspectives on the role of orbital fibroblasts in the pathogenesis of Graves' ophthalmopathy. Experimental Eye Research. 2016;142:83-91.