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Graves' Disease: A Review

Sanjay Saran

Abstract

Graves' Disease (GD) is an autoimmune disorder characterized by presence of TSH receptor autoantibody. It is most common cause of hyperthyroidism worldwide. Though GD can occur any age but peak incidence is seen during adulthood in between 20 to 50 years of age. GD is more commonly seen in female. GD is primarily disease of thyroid gland but affects multi organ system i.e. heart, liver, muscle, eye and skin. Symptoms and signs are result from hyperthyroidism or a consequence of underlying autoimmunity. Weight loss, fatigue, heat intolerance, tremor, and palpitations are the most common symptoms. Diffuse goiter presents in most of younger patients with thyrotoxicosis but less common in older patients. Graves' ophthalmopathy and pretibial myxedema are extrathyroidal manifestations of GD which results from action of TSHR autoantibodies on TSHR present on fibroblast, adipocyte and T cells in extrathyroidal tissue. Treatment of GD remains in between antithyroid drugs, radioiodine or surgery. In this review we discuss the diagnosis and management of GD.

Keywords: autoimmune thyroid disease, Graves' Disease, hyperthyroidism, radioactive iodine

1. Introduction

Graves' Disease (GD) is the most common cause of hyperthyroidism worldwide [1, 2]. It was first described by German physician Carl Adolf Von Basdow. It is an autoimmune disorder characterized by presence of TSH receptor autoantibody [3]. These autoantibodies stimulate TSH receptors on thyroid cells and cause hypertrophy and hyperplasia resulting thyroid gland enlargement. TSHR autoantibodies also cause increased synthesis and secretion of thyroid hormones. GD is primarily disease of thyroid gland but affects multi organ system i.e. heart, liver, muscle, eye and skin. Graves' ophthalmopathy and pretibial myxedema are extrathyroidal manifestations of GD which results from action of TSHR autoantibodies on TSHR present on fibroblast, adipocyte and T cells in extrathyroidal tissue.

2. Epidemiology

Graves' Disease accounts for 70–80% cases of hyperthyroidism in iodine sufficient population, where as it accounts for 50% cases of hyperthyroidism in iodine deficient areas of world [4, 5].

Annual incidence for GD is 20–50 person per 100,000 population and life time risk for developing GD is 3% for women and 0.5% for men [6, 7]. Though GD can occur any age but peak incidence is seen during adulthood in between 20 to 50 years

of age [8]. GD is more common in Caucasians as compare to Asian and least common among black African [9, 10]. The annual incidence of thyroid associated orbitopathy is 16 cases per 100000 in women and 3 cases per 100000 in men and is more in smokers [11]. Pretibial myxedema is a very rare complication of GD, is seen in 1.5 cases per 100000 case of GO [12]. Studies have shown that GD with nodule formation have higher incidence of thyroid carcinoma particularly tall Cell Variant of papillary thyroid cancer (a more aggressive form of cancer) was significantly more common [13, 14].

3. Risk factors

3.1 Genetic factors

Genetic component is considered a major risk factor for development of GD. Twin studies show concordance rate of GD in monozygotic twins in between 0.29 to 0.36, and in dizygotic twins between 0.00 and 0.04 [15]. GD predisposition appears to be polygenic [16]. Recently, bioinformatics and next-generation sequencing (NGS) based pangenomic analyses have identified many predisposing genes which are implicated in autoimmune disease, autoimmune thyroid disease and Graves' Disease [16]. These are various genes which take part into the pathogenesis of GD: cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), TSH-R, Tg, CD40, protein tyrosine phosphatase-22 (PTPN 22), HLA, and CD25 [17]. Association with various HLA region is also seen, DR3 haplotype (i.e. DQB1*02, DQA1*0501, DRB1*03) predisposes to GD, whereas the DR7 haplotype (i.e., DQA1*0201, DQB1*0302, DRB1*07 or DQA1*0201, DQB1*02, DRB1*07) appears to be protective [18].

3.2 Sex

GD is more commonly seen in female, and estrogen receptor ESR2 polymorphisms are frequently seen in GD. Association of disease fluctuation and estrogen level variations which are seen during pregnancy, the menstrual cycle, and menopause further clarify its role in pathophysiology of the disease [19]. Estrogen receptor expression is present on orbital fibroblasts, and glucocorticoids can modulate it [20].

3.3 Environmental factors

Smoking adversely affects immune system and thyroid gland health. Current smoking doubles the risk of Graves' hyperthyroidism and triples the risk of developing Graves' ophthalmopathy (GO) the effect was found to be dose dependent and more pronounced in women [21–23]. Conversely four large studies confirm that smoking decreases the risk of hypothyroidism and autoimmune thyroid diseases (AITD) by decreasing Anti-TPO antibodies [24–27]. Three large studies have shown that smoking lowers the serum TSH level accompanied by slight increase in serum level of FT3 and FT4 and this effect is dose dependent [23, 28, 29].

Pesticides and halogenated organochlorides have thyroid disrupting properties that can alter the thyroid functions by binding to thyroid hormone transport proteins [30].

3.4 Stress

Relationship in between stressful life events and onset of GD was documented in 1825. Major stress is positively associated with increased risk of GD. By modulating the cortisol pathway stress can alter the course of many other autoimmune diseases also [31].

3.5 Pregnancy

Pregnancy is associated with major changes in thyroid anatomy and physiology. Hyperthyroidism of GD is increased in early pregnancy and during postpartum. As pregnancy advances GD tends to improve which may be due to better maternal immune tolerance or altered B cell and T cell functions [32]. Decrease immune tolerance after delivery may cause increase in autoimmune thyroid diseases in postpartum [33].

3.6 Viruses

Many viruses affect the thyroid gland some of which associated with presence of thyroid autoantibodies i.e. congenital rubella, hepatitis C virus, subacute thyroiditis. But these are not appearing to be associated with development or progression of GD [34]. However, the potential influence of various common infections (such as Epstein–Barr virus and influenza virus) on the epigenetic characteristics of a variety of susceptibility genes remains a major hypothesis for the etiology of GD.

3.7 Iodine and related drugs

Iodine and iodine-containing drugs, such as amiodarone and iodine-containing contrast media, precipitate GD or its recurrence in a genetically susceptible individual which may be due to presence of some cryptic epitope on Thyroglobulin antibodies [35, 36]. Amiodarone is an iodinated derivative of benzofuran used in tachyarrhythmias. Each molecule of amiodarone contains two iodine atoms, which constitute 37.5% of its mass and its metabolism results in the daily release of approximately 6 mg of free iodine into the circulation which is 20–40 times higher than the daily iodine intake. Amiodarone can cause hypothyroidism or thyrotoxicosis by various mechanisms depending on duration of therapy, autoimmunity and other characteristics [36].

3.8 Drugs

Various drugs can cause suppression of TSH by their direct cytotoxic effect on thyroid follicular cells. Interferon and ribavirin used in the treatment of HCV disease can aggravate hyperthyroidism associated with GD. Highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection Alectuzumab humanized anti-CD52 monoclonal antibody, Ipilimumab is a monoclonal antibody against CTLA4, Nivolumab and pembrolizumab antibodies against programmed death protein 1 (PD1) can also precipitate hyperthyroidism by immune mechanisms [37–41].

4. Clinical features

Clinical manifestations of Graves' Disease related to age of onset, severity and the duration of hyperthyroidism. Symptoms and signs (**Table 1**) are result from hyperthyroidism or a consequence of underlying autoimmunity. Weight loss, fatigue, heat intolerance, tremor, and palpitations are the most common symptoms, occurring in more than 50% of patients. Elderly person more commonly presents with Weight loss, decreased appetite, and cardiac manifestations. Atrial fibrillation is seen in more than 10% of elderly but rare in younger patients. Goiter presents in most of younger patients with thyrotoxicosis but less common in older patients. Goiter is

<i>Symptoms</i>
Weight loss (weight gain in 10% of patients)
Palpitations
Dyspnea
Tremor
Tiredness, fatigue, muscle weakness
Heat intolerance, increased sweating
Increased stool frequency
Anxiety, altered mood, insomnia
Nervousness, hyperactivity
Pruritus
Thirst and polyuria
Menstrual disturbances in women (oligomenorrhea or amenorrhea)
Loss of libido
Neck fullness
Eye symptoms (swelling, pain, redness, double vision)
<i>Physical signs of hyperthyroidism</i>
Tachycardia, atrial fibrillation
Systolic hypertension, increased pulse pressure
Cardiac failure
Weight loss
Fine tremor, hyperkinesis, hyperreflexia
Warm, moist skin
Palmar erythema and onycholysis
Muscle weakness
Hair loss
Diffuse, palpable goiter and thyroid bruit
Mental-status and mood changes (e.g., mania or depression)
<i>Extrathyroidal physical signs</i>
Ophthalmopathy
Eyelid lag, retraction, or both
Proptosis (exophthalmos)
Double vision (extraocular-muscle dysfunction)
Periorbital edema, chemosis, scleral injection
Exposure keratitis
Optic neuropathy
Localized dermopathy
Acropachy
<i>Developed from: Ref. [7].</i>

Table 1.
Major symptoms and physical signs in Graves' Disease.

present most commonly as diffuse thyroid enlargement but nodular goiter can also be present particularly in those who reside in iodine deficient areas (**Figure 1**).

Varying degree of orbital involvement can be seen in GD which is a consequence of thyroid autoimmunity which occur parallel to the thyroid involvement. It usually present with tearing, congestion, redness and irritation in eyes. In severe cases proptosis may occur due to inflammation and edema of extraocular muscle and retrobulbar tissue expansion owing to fluid accumulation as a result of accumulation of glycosaminoglycan. Double vision and sight threatening complications i.e. corneal ulceration, dysthyroid optic neuropathy can occur as a consequence of damage to extraocular muscles. For selecting appropriate patient for treatment EUGOGO classified GO in mild, moderate to severe and sight threatening. Activity of GO can be easily assessed by clinical activity score (CAS) (**Table 2**). A CAS $\geq 3/7$ is indicative of active GO (**Figure 2**).



Figure 1.
 Graves' orbitopathy.

Spontaneous retrobulbar pain
Pain on attempted up- or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Inflammation of the caruncle and = or plica
Conjunctival oedema

*A CAS $\geq 3/7$ indicates active GO.
 Developed from: Ref. [42].*

Table 2.
 Measures of clinical activity score (CAS).



Figure 2.
Graves' dermopathy.

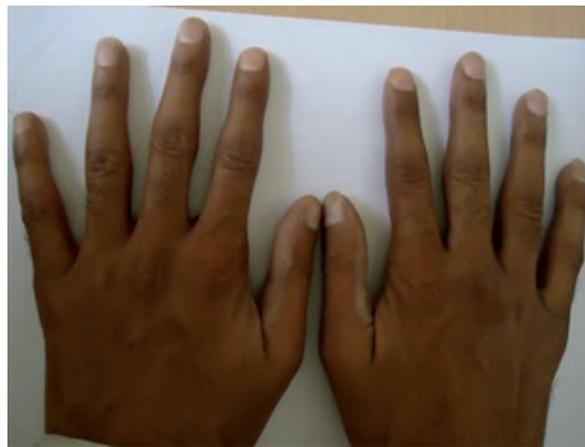


Figure 3.
Thyroid acropachy.

Graves' dermopathy is seen in 1–4% case of GD. It frequently localizes to pretibial region but it may be seen on elbow, feet, toe and areas of trauma. Lesion can be described as erythematous, non-pitting thickening of dermis in pretibial region. In mild cases it gives “orange Peel” appearance. Graves' dermopathy is almost always associated with GO (**Figure 3**).

Acropachy is very rare extrathyroidal manifestation of GD. Acropachy is defined as skin tightness, digital clubbing, small-joint pain, and soft tissue edema progressing over months or years with gradual curving and enlargement of the fingers [43]. The pathogenesis of acropachy is not known. In most of cases acropachy remain asymptomatic.

5. Diagnosis

5.1 Graves' hyperthyroidism

Diagnosis of GD is based on clinical manifestations of thyrotoxicosis and biochemical abnormalities. If orbitopathy is present than diagnosis of GD is certain but

in the absence of orbitopathy serum TSH Receptor Antibody (TRAb) and imaging may be required to for the diagnosis.

5.2 Biochemical evaluation

5.2.1 *Thyroid hormones*

Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected thyrotoxicosis [44]. Diagnostic accuracy improves when a serum TSH, free T4, and total T3 are assessed at the initial evaluation. In overt hyperthyroidism, serum free T4, T3, or both are elevated, and serum TSH is subnormal (usually <0.01 mU/L in a third-generation assay). In mild hyperthyroidism, serum T4 and free T4 can be normal, only serum T3 may be elevated, and serum TSH will be low or undetectable. These laboratory findings have been called “T3-toxicosis” and may represent the earliest stages of hyperthyroidism caused by GD [45]. Ratio of total T3 to T4 may also be useful in differentiating GD from thyroiditis. In one study the ratio of total T3 to total T4 (ng/lg) was >20 in GD and toxic nodular goiter, and <20 in painless or postpartum thyroiditis [46].

5.2.2 *TSH receptor antibodies (TRAb)*

In a hyperthyroid patient with a diffuse goiter and recent history of orbitopathy, the diagnosis of GD is likely so no further testing is required but hyperthyroid patient with a diffuse goiter and no definite orbitopathy, TRAb measurement can be of useful in distinguish GD from other etiologies.

5.3 Imaging

5.3.1 *Thyroid ultrasound*

Currently ultrasonography has become an important and practical tool for the thyroidologist; beside its role in thyroid nodule it can easily distinguish toxic multinodular goiter from GD. Increased blood flow in Doppler ultrasonography can distinguish GD from thyroiditis where blood flow is decreased.

5.3.2 *Radioiodine uptake (RAIU) and thyroid scan*

RAIU measures the percentage of administered RAI that is concentrated into thyroid tissue after a fixed interval, usually 24 hours. Technetium uptake measurements utilize pertechnetate that is trapped by the thyroid, but not organified. A technetium (TcO_4) uptake measures the percentage of administered technetium that is trapped by the thyroid after a fixed interval, usually 20 minutes. Uptake study is not indicated routinely. It is recommended only when diagnosis is difficult. Uptake is increased in GD, toxic multinodular goiter and toxic adenoma. Uptake is decreased in subacute, postpartum, painless thyroiditis.

6. Management

After establishing the diagnosis of GD treatment options include antithyroid drugs, radioiodine, and surgery. Although RAI is preferred in United States and ATDs in Europe but long term quality of life was found to be same in all three treatment group [47]. Selection of treatment depends on local availability, cost of

treatment, presence of active GO and physician preference. The main goal of management is to normalize thyroid hormones level and make the patient asymptomatic.

6.1 Pharmacological therapy

6.1.1 Antithyroid drugs

Thionamides are class of ATDs which inhibit thyroid peroxidase thereby inhibit thyroid hormone synthesis. Methimazole (MMI) and propylthiouracil (PTU) are used in United States where as Carbimazole (converted to methimazole in liver) is used in other part of world. MMI is preferred over PTU as initial therapy because of long duration of action and reduced risk of major side effect, except during first trimester of pregnancy where PTU is preferred because of lesser teratogenic effects [48]. Starting dose of MMI is 10 to 30 mg daily and of PTU is 50 to 10 mg three times daily. Dose of ATDs should be kept lowest to maintain T4 in normal range because higher doses are associated with high risk of adverse effect. Adverse effect of ATDs can be divided in minor allergic reaction and serious allergic/toxic effects agranulocytosis, liver injury and vacuities [48–52]. Hepatotoxicity and agranulocytosis are seen more commonly with propylthiouracil. Initial complete blood cell count and liver function test required before starting these drugs and patient should be instructed to report if he develops high grade fever with sore throat. American Thyroid Association recommends ATDs should be continued for 12–18 months if chosen as primary therapy then can be discontinued if TSH and TRAb levels are normal. Remission rate with ADTs treatment is 40–60% and is not associated with duration and dose of ATDs. If patient becomes hyperthyroid after completion of treatment, RAI or thyroid surgery should be considered.

6.1.2 Beta-adrenergic blocker

Beta-adrenergic blocker should be given to all symptomatic thyrotoxic patients, especially elderly. Goal of beta blocker treatment is to decrease heart rate less than 90 per minute. Propranolol is preferred non-selective beta blocker which decreases deiodination of T4 to T3 [53]. In patient with asthma, obstructive airway disease and Raynaud's phenomenon selective β_1 blocker can be used with cautions. Calcium channel blockers verapamil and diltiazem can be used when β blockers are contraindicated [45].

6.1.3 Lithium

Lithium carbonate inhibits secretion of thyroid hormones. It does not decrease the efficacy of RAI so it can be used to control hyperthyroidism during RAI therapy or in patient who are allergic to ATDs.

6.1.4 Cholestyramine

It interfere with enterohepatic circulation thereby decrease thyroid hormone levels rapidly. It can be used as adjunctive therapy in resistant thyrotoxicosis.

6.2 Radioactive iodine

RAI is one of definitive treatment for GD. It has been used for more than seven decade in the management of GD. Effect of ionizing radiation leads to cellular death and consequently reduction in functioning thyroid tissue and thyroid size. The goal

of RAI is to render the patient hypothyroid for that 10–15 mCi dose is sufficient in most of the patients. RAI can be used as primary therapy in mild cases but in severe thyrotoxic patient β blockers and ATDs are used first to render the patient euthyroid to avoid radiation induced thyroiditis. ATDs should be discontinued 2–3 days prior and till 3–7 day of RAI treatment to enhance the efficacy of treatment. Regular follow up should be at 4–6 weeks interval with biochemical testing include TSH, FT4 and T3 till 6 months or till patient become hypothyroid. Around 40% of patient treated with RAI become hypothyroid by 8 weeks and 80% by 16 weeks [54]. Levothyroxine replacement therapy should be started once patient become hypothyroid. Most of studies found no increase in prevalence of thyroid cancer or secondary malignancy in RAI treated patients. RAI is associated with development and worsening of orbitopathy as compare to ATDs and thyroid surgery [55, 56]. So presence of orbitopathy may influence the treatment option.

6.3 Thyroid surgery

Thyroid surgery is least preferred treatment option for GD. It's preferred when large nodular goiter is present. Total or Near-total thyroidectomy is procedure of choice if surgery is chosen as treatment option. Patient should be rendered euthyroid before surgery by ATDs and β blockers to minimize risk of thyroid storm [57]. Saturated solution of potassium iodide (SSKI) may be used preoperatively to normalize thyroid functions and to decrease the vascularity of thyroid gland [58]. ATA recommends measurement of calcium and 25-hydroxy vitamin D before surgery and if abnormal then should be normalized. Surgery should be performed by experienced surgeon at high volume Centre to minimize postoperative complications [59].

6.4 Treatment of Graves' orbitopathy in patients with Graves' Disease

The optimal treatment of GO require restoration of euthyroidism and management of orbitopathy. Smoking should be discouraged as smoking increases progression and severity of GO and worsens the outcome [60]. Management of orbitopathy depends on its severity and activity. Mild inactive disease can be managed conservatively by artificial tear films only. In severe and active disease intravenous pulse steroid therapy may be required to decrease inflammation. External beam radiotherapy has also been used in severe cases. In patient with sight threatening and dysthyroid optic neuropathy (DON) orbital decompressive surgery is the only option proven to be effective. Rituximab, a anti CD20+ monoclonal antibody that causes B Cell depletion shown to be very effective in decreasing severity and activity of orbitopathy [61].

6.5 Treatment of Graves' Disease during pregnancy

Pregnancy is a hyper vascular state so, clinical signs of thyrotoxicosis and normal pregnancy remarkably overlap. Moreover, estrogen induces high serum levels of thyroid hormones make the diagnosis difficult. Graves' Disease affects 0.1–0.2% of pregnancy and carries a considerable risk to mother and new born if not controlled adequately [62]. All ATDs are teratogenic and having risk of birth defects in new born [63]. During pregnancy ATDs should be used in lowest dose to main thyroid hormone levels in upper normal range and monitoring of thyroid function should be done monthly. As pregnancy is a state of immune tolerance so in about 50% of patients ATDs can be discontinued after first trimester [62]. Breast feeding is considered safe during ATDs treatment. ATA recommends measurement

of TRAb at diagnosis, then at 18–20 weeks of pregnancy, if elevated then repeat at 30–34 weeks to guide decision regarding fetal monitoring.

6.6 Treatment of dermatopathy and acropachy

Treatment of dermatopathy and acropachy remain ineffective. Topical and intra-lesional injection of steroid have been used without substantial success [64]. Trials using systemic steroid, rituximab and immunosuppressive drugs are underway with mixed results.

7. Emerging therapy

For last many years treatment of Graves' Disease has not been substantially changed. In future we can see some great change in management of GD as many newer drugs are under trials. These newer therapies are mainly directed to TSH-receptor. A human anti-TSHR monoclonal antibody (K1-70) is in a phase I trial of development [65]. A novel highly selective inhibitor for the TSHR is has promising potential for further development for the treatment of GO [66].

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