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Thyroid Hormone Excess: Graves' Disease

N.K. Agrawal, Ved Prakash and Manuj Sharma

Additional information is available at the end of the chapter

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1. Introduction

Thyroid hormone excess due to any cause is state of thyrotoxicosis, whereas hyperthyroidism is a state of thyroid hormone excess due to hyperfunctioning of thyroid gland. The major causes of thyrotoxicosis include Graves' disease, solitary toxic adenoma, and toxic multinodular goiter. In thyrotoxicosis, free hormone levels are invariably increased. The reverse is not true in that increased free thyroid hormone levels do not always point to thyrotoxicosis. In illness or resistance to thyroid hormones increased free hormone levels are present while the patients are clinically euthyroid or even sometimes hypothyroid. Subclinical thyrotoxicosis is defined as a state in which free thyroid hormones (FT4 & FT3) are within normal limit, but serum TSH level is low. The most common cause of subclinical thyrotoxicosis is exogenous administration of thyroid hormone rather than Graves' disease. Patients of subclinical thyrotoxicosis either have no symptoms or have mild non specific symptoms.

The various causes of thyrotoxicosis are listed below in table 1

1.1. Clinical features

Clinical manifestations of the thyrotoxicosis are similar for various causes of thyrotoxicosis. However certain features provide some clues about specific cause of throtoxicosis. These features include the duration and mode of onset of thyrotoxicosis, size and shape of the thyroid gland, presence or absence of the extra-thyroidal manifestations like Graves' eye sign, pre-tibial myxoedema, acropachy. Patient presenting with toxic features can be because of thyroiditis or Graves' disease, but the symptoms are of few weeks duration in former while in later condition, it is for several months, most of the time. The common clinical features of thyrotoxicosis are listed below in table 2.

<p>A. Thyroid hormone excess with hyperthyroidism</p> <ol style="list-style-type: none"> a. Primary Hyperthyroidism <ol style="list-style-type: none"> i. Graves' Disease ii. Toxic Thyroid adenoma iii. Toxic Multinodular Goiter iv. Metastases from Thyroid carcinoma v. Mutations of TSH receptor, Gsα (Mc Cune Albright Syndrome) vi. Struma Ovarii vii. Iodine ingestion (Jod-Basedow phenomenon) b. Secondary hyperthyroidism <ol style="list-style-type: none"> i. TSH secreting pituitary tumours ii. Pituitary Thyroid hormone resistance <p>B. Thyroid hormone excess without hyperthyroidism</p> <ol style="list-style-type: none"> a. Thyroiditis: subacute, silent b. Ingestion of thyroid tissue, thyroid hormone c. Thyroid gland destruction by amiodarone, radiotherapy, infarction in thyroid adenoma
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Table 1. Causes of thyroid hormone excess

Symptoms	Signs
Irritability, Hyperactivity, Dysphoria	Tachycardia, Lone Atrial Fibrillation
Heat Intolerance	Fine tremor
Palpitation, Nervousness	Warm moist skin, Goiter
Fatigue, lethargy	Proximal Myopathy
Dyspnoea	Hyperreflexia
Weight loss despite polyphagia	Lid lag, Lid tremors
Hyperdefecation, Polyuria	Gynaecomastia
Oligomenorrhoea	Loss of libido

Table 2. Common clinical features

2. Graves' disease

Diffuse toxic goitre is commonly known as Graves' disease. Classically it is characterized by hyperthyroidism and diffuse goiter. Graves' disease may be associated with an infiltrative orbitopathy and ophthalmopathy and less commonly with an infiltrative dermopathy. Infiltrative orbitopathy is a unique manifestation of Graves' disease.

2.1. Historical perspective

Robert James Graves, an Irish physician, first described 3 females with this disease in 1835¹ and for his contribution, this disease is known as Graves' disease in most part of the world. Although a similar syndrome was described by Caleb Hiller Parry, a physician from Bath,

England, in 1825.² Carl A. Von Basedow from Germany first described the triad of exophthalmos, goiter and palpitation.³ In most non English speaking European countries the disease is still known as Basedow's disease.

2.2. Epidemiology

Graves' disease is the most common cause of thyrotoxicosis and it accounts for 60-80% cases of thyrotoxicosis. Prevalence of Graves' disease varies with the degree of iodine sufficiency, and it is the most common cause of thyrotoxicosis in iodine sufficient countries.⁴ High dietary iodine intake is associated with an increased prevalence of Graves' disease. Prevalence of Graves' disease is about 0.4% in USA,⁵ 0.6% in Italy,⁶ and 1.1% in UK.⁷ A recent meta-analysis of various studies showed that prevalence of the Graves' disease is about 1% in general population.⁷ Prevalence of Graves' disease is 1-2% in women, and it is about 10 fold more prevalent in women than men. Peak age of onset of Graves' disease is in fourth to sixth decade of life,⁸ but it can occur in children and elderly.

2.3. Risk Factors for Graves' disease

Graves' disease is a multifactorial disease in which genetic ,environmental, and hormonal factors play their role.

2.3.1. Genetic factors for Graves' disease

High prevalence of Graves' disease in family members and relatives of Graves' disease and Hashimoto's thyroiditis support that genetic factors are involved in causation of Graves' disease. There is also evidence that occurrence rate of Graves' disease is higher in monozygotic twins than dizygotic twins. The concordance rate in monozygotic twins is only 17-35% which indicate low penetrance of genes.

Graves' disease is a polygenic disease. Polymorphism in HLA-DR, CTLA-4 and PTPN-22 genes are associated with increased risk of Graves' disease. HLA-DR3 (HLA-DRB1*03), HLA-DQA1*0501 and HLA-B8 gives a risk ratio of three fold to fourfold in white population. HLA-DQ3 is involved in patients with African descent whereas HLA-BW46 is involved in patients with Asian descent. The other genes involved in pathogenesis of Graves' disease are CD40 gene, thyroglobulin gene, TSHR gene, immunoglobulin genes, GD-1 gene (on chromosome 14q13), GD-2 gene (on chromosome 20) and GD-3 gene (on chromosome Xq21-22).

2.3.2. Environmental Factors for Graves' disease

Infection

From very early it has been suggested that Graves' disease is associated with infectious agents, but this hypothesis has not been confirmed. Incidence of recent viral infections are high in patients with Graves' disease. The association of Graves' disease with infectious

agents can be explained by molecular mimicry. Molecular mimicry implies structural similarity between infectious agent with a self antigen. Circulating antibody against *Yersinia enterocolitica* has been found in high percentage of patients with Graves' disease. Furthermore, serum from some patients recovering from *Yersinia* infections block the binding of TSH to its receptor. Low affinity binding sites for TSH have also been found with *Leishmania* and *Mycoplasma* species. However, no studies proved that infections agents have causative role in Graves' disease.

Stress

In different studies, it has been found that stressful life events precedes the onset of Graves' disease. Severe emotional and physical stress, like separation from the loved one or following road traffic accident, cause release of cortisol and corticotrophin releasing hormone. So, stress is a relatively immune suppression state. Immune system overcompensates once stress is over which can precipitate disease similar to postpartum period. In conclusion there is limited but significant evidence that stressful life events can precipitate the onset of Graves' disease in genetically susceptible individuals.

Gender

Typically Graves' disease is more prevalent in females than males. It is about 5-10 times more common in females at any age.^{6,7} In children this difference is smaller. The exact cause for female preponderance is not known, but it is similar to other autoimmune disorders. In experimental animal models of autoimmune thyroiditis it has been seen that androgens appear to down regulate the immune system.^{8,9} Other possible explanation for female preponderance is female sex steroids. But Graves' disease also occurs in men and postmenopausal women. These observations have suggested that it is the X-chromosome, not the sex steroids, which is responsible. But most of the x-linked disorders are only present in man, it has been thought that a gene with dose dependent effect on X-chromosome is responsible.

Pregnancy

Postpartum period is an important risk factor for both the onset and relapse of Graves' disease. Postpartum period is associated with a fourfold to eightfold increased risk for the onset of Graves' disease. Rebound immunity is the likely explanation for this increased risk. Graves' disease is associated with low pregnancy rate because thyrotoxicosis decreases the fertility rate. However in women with Graves' disease who became pregnant, successful pregnancy outcome is low because Graves' disease causes increased pregnancy loss and its complications. Graves' disease exacerbates during the first trimester of pregnancy and postpartum period, while it improves during the second and third trimester of pregnancy.

Smoking

Smoking is a minor risk factor for Graves' disease; however it is a major risk factor for Graves' ophthalmopathy. There are number of studies showing relationship between Graves' disease, Graves' ophthalmopathy and smoking.^{11,12}

Other risk factors:

Direct trauma to the thyroid gland, ethanol injection for the treatment of autonomously functioning thyroid nodules, or thyroid injury following radio-iodine treatment for toxic adenoma or toxic multinodular goiter are associated with an increased risk of Graves' disease. Radio-iodine treatment may also cause onset or worsening of ophthalmopathy. Possible explanation is that thyroid injury by any means cause massive release of thyroid antigens, which in turn stimulate an autoimmune reaction to TSHR in susceptible individuals.

Graves' disease onset and recurrence is also associated with iodine and iodine containing drugs like amiodarone and radio-contrast media especially in iodine deficient population.

3. Pathogenesis

Graves' disease is an example of organ specific autoimmune disorder in which both humoral and cell mediated immunity directed against different thyroid antigens are involved. TSHR is the primary autoantigen of Graves' disease, while other autoantigens like thyroglobulin and thyroid peroxidase are secondarily involved.

3.1. Humoral immunity

TSHR is a member of GPCR super family and involves cAMP and phosphoinositol pathways for signal transduction. TSHR has large intracellular domain (subgroup B). It is a glycoprotein consisting of 744 amino acids and having molecular weight of 84 kd. Gene for TSHR is located on chromosome 14q31 and is formed by 10 exons. Circulating autoantibody directed against the TSHR is the primary factor responsible for Graves' disease. TSHR antibodies (TSHR-Ab) are of three types- namely stimulating antibody, blocking antibody and neutral antibody. Stimulating antibodies are those who after binding to TSHR activate adenylate cyclase and cause increased thyroid growth and vascularity, and increases the production of thyroid hormones. Blocking antibodies are those who after binding to TSHR act as an antagonist, whereas neutral antibodies does not have any functional activity.

Almost 50 years ago (in 1956) long acting thyroid stimulators (LATS) was discovered by Adams and Purves during a search for thyroid stimulating activity in patients with Graves' disease.¹³ Later on it was found that LATS are nothing but immunoglobulin of IgG1 subclass.

Transplacental transfer of TSHR stimulating antibodies (TSAb) from TSAb positive pregnant mother to fetus causes transient neonatal thyrotoxicosis that improves spontaneously after the disappearance of TSAb.¹⁴ This provides the definite role of TSAb in the causation of Graves' disease. TSAb are oligoclonal.

TSAb are produced mainly by the lymphocytes infiltrating the thyroid gland and lymphocytes present in the draining lymph nodes, and partly by the circulating blood lymphocytes.^{15,16} There is a positive correlation exists between the TSAb level and serum

triiodothyronine level, serum thyroglobulin level and goiter size. TSAbs are found in 90-100% of untreated Graves' disease patients.^{17, 18} Level of TSAbs decreases after treatment with anti-thyroid drugs and radio-iodine.^{19, 20}

3.2. Assays for TSHR-Ab

Two types of assays are used for TSHR-Ab-Radioreceptor assays and invitro bioassays.

3.2.1. Radioreceptor assay

Radioreceptor assay is most readily available and most widely used in clinical practice. Basic principle of radioreceptor assay is displacement of labeled TSH from solubilized TSHR from patient's serum. This TSH-binding inhibitory immunoglobulins (TBII) assay does not provide information regarding the functionality of TSHR-Ab. TBII assays are cheaper and having good precision. The first generation TBII assays have sensitivity of 75-95% in untreated Graves' disease patients. Most recently a monoclonal human antibody to TSHR is used. This second generation radio-receptor assay has sensitivity of 99% and very high specificity.²¹

3.2.2. In vitro bioassays

In vitro bioassays are based on the ability of patients serum to stimulate adenylate cyclase and produce cAMP from cultured hamster ovary cells transfected with human TSHR (CHO-R),²³ or rat thyroid cell strain (FRTL-5)²⁴ or human thyroid follicular cells²⁵ are used as a source for functional TSHR. CHO-R system is slightly more sensitive, and requires an easier culture condition than other systems. Advantages of bioassays are that it gives information about the functional property of TSHR-Ab, but bioassays are more expensive, not widely available, having poor precision and sensitivity of more than 90%. These problems have been solved in newer bioassays.

3.2.3. Cellular immunity

The thyroid gland in Graves' disease is characterized by non-homogenous lymphocytic infiltration. Majority of the intrathyroidal lymphocytes are T lymphocytes. B-lymphocytes are much less common than Hashimoto's thyroiditis. Cytokine profile produced by intrathyroidal T lymphocytes suggested that both TH1 & TH2 cells are present in thyroid. Majority of the T-lymphocytes are of TH1 subtype.^{26,27}

TH1 cells are mainly involved in delayed type of hypersensitivity reactions, and it produces the cytokines like TNF- β , IFN- γ , IL-2, IL-10 and IL-17. TH1 cells are implicated in the pathogenesis of organ specific autoimmune diseases that is mediated mainly by TNF- β subtype, which uniquely produces IL-17. TH2 cells are mainly responsible for humoral immune responses and they produce cytokines like IL-4, IL-5, IL-6 and IL-13. TH1 cells may also induce antibody formation through secretion of IL-10²⁸. IgG1 subclass of antibody are selectively induced by TH1 cells. Most of the intrathyroidal T cells are of memory (CD4⁺, CD29⁺) subtype. Concentration of cytotoxic T cells (CD8⁺) are much less in Graves' disease

patients than patients of Hashimoto's thyroiditis. So the functional role of T cells in Graves' disease is primarily a helper than a suppressor or cytotoxic role.

4. Pathogenic mechanisms

4.1. Molecular mimicry or specificity crossover

Structural or conformational similarity between different antigens like infectious agent with a self antigen can lead to crossover of specificity or molecular mimicry. Molecular mimicry has been reported between Reoviral antigen and a tissue antigen expressed in multiple endocrine tissues, *Yersinia enterocolitica* and TSHR, Retroviral sequences and TSHR & *Borrelia* and TSHR.

4.2. Bystander effect

There is evidence that bystander activation of local resident antigen specific and nonspecific T- cells by a local viral infection would induce an inflammatory reaction and stimulates the production of cytokines induce autoimmunity. This bystander activation can also occur in any infections and antigens unrelated to the thyroid gland.

4.3. Aberrant expression of class II HLA Antigens

MHC class II molecules (HLA-DP, DQ, and DR) are not expressed on the normal thyroid epithelial cells but they are expressed on thyroid epithelial cells in patients of autoimmune thyroid disease. This aberrant expression of class II HLA antigens on thyroid epithelia cells can be induced by local thyroid insult which causes production of interferon γ and other cytokines. Interferon γ is able to over express HLA class I molecule and induce the expression of class II molecule on thyroid epithelial cells.

4.4. Cryptic antigens

Autoimmunity results from the loss of tolerance or the ability to differentiate between self and non self. Tolerance induction is a staged process that initiates in the thymus during T-cell maturation. This process depends in part on the presence of peripheral antigens in the thymus. Peripheral antigens are antigens normally expressed in tissues outside of the immune system which are expressed at low levels in thymus. T cells that react strongly to these peripheral molecules in the context of MHC are deleted in thymus. T cells that react with peripheral antigens that are not expressed in the thymus have a greater opportunity to escape tolerance.

4.5. Hygiene hypothesis

Hygiene hypothesis implies that infection may protect form autoimmune diseases rather than precipitating it. Decreased exposure to antigens due to improved living standards can lead to increased risk of autoimmune disorder.

4.6. Super antigens

Super antigens are endogenous or exogenous proteins such as microbial proteins, capable of stimulating a strong immune response through molecular interactions with non-variant parts of the T- cell repertoire and the HLA class II proteins.

5. Pathology

Grossly the thyroid gland is diffusely enlarged with smooth and hyperemic surface. Rarely the gland is grossly nodular. Consistency of the gland varies from soft to firm. Pyramidal lobe is often prominent.

Microscopically both hypertrophy and hyperplasia are seen. Follicles are small with scanty colloid, and lined by hyperplastic columnar epithelium which can give a pseudopapillary appearance. Vascularity of the gland is increased. There is varying degree of infiltration by lymphocytes and plasma cells. T cells predominate in the interstitium, whereas B cells and plasma cells predominate in lymphoid follicles.

On electron microscopy there is increased golgi reticulum and mitochondria, and it is also characterized by presence of prominent microvilli.

After treatment with antithyroid drugs and radioiodine, the vascularity of the gland decreases, follicles enlarges and filled with colloid, and papillary projection regresses.

6. Clinical features

Graves' disease is the most common cause of thyrotoxicosis. Most common age of onset is third to fourth decade of life but it can occur in children and elderly. The hallmark of Graves' disease is signs and symptoms of thyrotoxicosis along with diffuse goiter and typical Graves' orbitopathy. Most of the signs and symptoms are similar to other causes of thyrotoxicosis, but some of the signs and symptoms like orbitopathy, dermopathy or pretibial myxedema and thyroid acropachy are unique to Graves' disease.

Onset of Graves' disease is usually gradual. Signs and symptoms are presents months before the diagnosis, and usually patients do not remember the exact date of onset of symptoms. Onset can be abrupt in some cases. The signs and symptoms are usually more severe than other causes of thyrotoxicosis.

6.1. Thyroid gland

Thyroid gland is diffusely enlarged in Graves' disease, but it can be nodular especially in areas of iodine deficiency where nodular goiter preexists before the onset of Graves' disease. Goiter size is variable. It can range from normal size thyroid gland to massively enlarged thyroid. Usually size of goiter is two to three times that of normal. Normal size thyroid gland can be seen in as many as 20% of patients and most of them are elderly. The consistency of the goiter varies from soft to firm but softer than the goiter of Hashimoto's

thyroiditis. Thrill and bruit can be present over goiter in severe cases and it is due to increased vascularity of the gland. Thrill and bruit are present usually on upper or lower pole and continuous in nature, but sometimes can present only in systole. Large goiter with intrathoracic extension can be associated with facial swelling and flushing, and neck vein distension upon raising the arm above the head. This is known as Pemberton sign.

6.2. Graves' ophthalmopathy

Graves' ophthalmopathy is one of the distinctive manifestations of Graves' disease. Overall clinical ophthalmopathy is present in about 50% of Graves' disease patients,²⁹ however CT or MRI reveals extraocular muscle enlargement in about 70% of patients without overt clinical ophthalmopathy.^{30,31} Bimodal age distribution was noted for ophthalmopathy in both men and women. Peak age is 40 to 44 years and 60 to 64 years in women, whereas in men it is 45 to 49 years and 65 to 69 years.

6.2.1. Risk factors for Graves' ophthalmopathy

There is no specific genetic predisposition for Graves' ophthalmopathy. Environmental factors are more important for ophthalmopathy.

Smoking

Smoking is a major risk factor for ophthalmopathy. Smoking also increases the risk for worsening of ophthalmopathy after radioiodine treatment. Possible contributors are orbital hypoxia and free radical present in smoke.^{32,33}

Gender

Graves' disease is predominantly a disease of females (F: M= 8-10:1). In comparison to Graves' disease, ophthalmopathy is relatively more common in males (F: M= 1:1.8-2.8) than females.^{34,35}

Radioiodine

Graves' disease patients treated with radioiodine are at increased risk for onset and worsening of eye disease, as compared to antithyroid drugs alone.^{36,37} This risk can be decreased by concurrent use of corticosteroids.^{38,39}

6.2.2. Pathogenesis

Current evidence supports an autoimmune pathogenesis with important environmental influences, particularly smoking. Orbital muscles, connective tissues, and adipose tissues are infiltrated by lymphocytes and macrophages. TH1 mediated immune response predominates in early stage of disease while TH2 response predominates in late stage.⁴⁰ In response to cytokines secreted by the infiltrating immune cells, orbital fibroblasts start synthesizing and secreting hydrophilic glycosaminoglycans, resulting in edema of orbital

tissues. Additionally adipocytes present in orbit become active and results in expansion of orbital adipose tissues. Both these factors are responsible for expansion of orbital tissues.

6.2.3. *Natural history*

Onset of eye disease usually coincides with that of thyrotoxicosis in 40% of cases, follow it in 40%, and precedes it in 20%.^{41,42} Even when the onset of the two disorders does not coincide, each occurs within 18 months from the onset of the first manifestation. Eye disease usually shows a progressive deterioration lasting for several months followed by a phase of spontaneous improvement lasting upto a year and longer and quiescent stage when inflammatory signs disappear and clinical features stabilizes.

6.2.4. *Signs and symptoms*

The earliest manifestations of ophthalmopathy are usually a sensation of grittiness, eye discomfort, and excess tearing. Other common symptoms are spontaneous retroorbital pain, pain on ocular movement and diplopia. Diplopia is most common in upgaze or in extremes of lateral gaze, because of the involvement of inferior or lateral rectus muscle. About one third of patients have proptosis which can best be detected by visualization of the sclera between the lower border of iris and the lower eyelid when the eyes are kept in primary position.

In severe cases proptosis can cause exposure keratitis and corneal ulcerations. Proptosis is frequently assymetrical. Retraction of the upper eyelid and less commonly of lower eyelid results in lid lag, globe lag, and lagophthalmos. Movements of the lids are jerky, and also there is tremor of lightly closed eyes. These are the non specific manifestations of thyrotoxicosis. Other signs and symptoms are photophobia, swelling of the eyelids, blurring of vision, conjunctival injection and chemosis, periorbital edema.

Decreased visual acuity and color vision, corneal ulceration, and subluxation of globe are present in most severe cases. Blindness may result from corneal ulceration and compression of the optic nerve at the orbital apex due to increased orbital pressure and venous congestion.

Graves' ophthalmopathy can occur in absence of Graves' disease in 10% cases, that's why it is also known as thyroid associated ophthalmopathy, or euthyroid Graves' ophthalmopathy. Graves' ophthalmopathy is usually bilateral but it can be unilateral in upto 10% cases.

6.2.5. *Staging severity of ophthalmopathy*

The acronym NO SPECS was given by American Thyroid Association for severity of ophthalmopathy, where no indicates absence or mild ophthalmopathy, and SPECS indicates more severe degree of involvement, but NO SPECS scheme is inadequate and patients do not necessarily progress from one class to other.

Classes	Ocular symptoms and signs
0	No signs and symptoms
1	Only signs (lid retraction, lid lag, proptosis upto 22 mm)
2	Soft tissue involvement (periorbital edema)
3	Proptosis (>22 mm)
4	Extraocular muscle involvement (diplopia)
5	Corneal involvement
6	Sight loss (optic nerve involvement)

Table 3.

6.2.6. Clinical activity of ophthalmopathy

To know the clinical activity of ophthalmopathy is important, because active disease is more likely to respond to immunosuppressive therapy. Clinical Activity Score (CAS) is used to know the clinical activity. Seven parameters are used in the clinical activity scoring which include spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, swelling of the eyelids, inflammation of the caruncle and conjunctival edema or chemosis. Each parameter is assigned 1 point. CAS of more than or equal to 3/7 indicates active ophthalmopathy.

6.3. Thyroid dermopathy

Thyroid dermopathy presents in less than 5% of patients with Graves' disease. It is almost always accompanied by moderate to severe ophthalmopathy. Most commonly it is present over anterior and lateral aspects of leg, hence it is also known as pretibial myxoedema. Less commonly it can present over dorsa of the feet, dorsa of the hands, forearm, face and elbows, particularly after trauma. The typical lesion is a noninflamed, indurated plaque with a deep pink or purple color and an orange skin appearance. Nodular form is the intermediate while elephantiasis is the most severe form of thyroid dermopathy. Thyroid dermopathy occurs due to accumulation of glycosaminoglycans in the dermis and subcutaneous tissues.

6.4. Thyroid acropachy

Thyroid acropachy is the least common manifestation of Graves' disease. It is a form of clubbing, and presents in less than 1 percent of patients of Graves' disease. It is almost always associated with the severe and long standing ophthalmopathy and dermopathy. An alternate diagnosis should be considered in the absence of ophthalmopathy and dermopathy. Deposition of glycosaminoglycans in skin is responsible for thyroid acropachy.

7. Laboratory diagnosis

Diagnosis of Graves' disease can be confirmed by measurement of serum TSH and total thyroxine (TT₄) and triiodothyronine (TT₃). Serum TSH level is suppressed or undetectable with increased TT₄ and TT₃ level in patients of Graves' disease. Serum TSH level is the most sensitive test. The free T₄ (FT₄) and free T₃ (FT₃) levels are increased more than that of TT₄ and TT₃. Measurement of FT₄ and FT₃ are expensive, and there is more chance of laboratory errors. FT₄ and FT₃ can be measured in conditions associated with high serum TBG level like pregnancy, oral contraceptive use and chronic liver disease. In patients of Graves' disease serum T₃ level is proportionately more elevated than the serum T₄ level. In upto 12% of patients, especially in the iodine deficient areas, only TT₃ or FT₃ is elevated with a normal TT₄ or FT₄ level, a condition known as T₃ toxicosis. Conversely in some patients (iodine induced hyperthyroidism, drugs like amiodarone and propranolol which block the conversion of T₄ to T₃), only TT₄ or FT₄ is elevated with normal TT₃ and FT₃ (T₄ toxicosis). Serum thyroglobulin level is high in all cases of thyrotoxicosis except factitious thyrotoxicosis.

Anti TPO antibody can be detected in upto 90%^{43,44} of patients with Graves' disease whereas anti-thyroglobulin antibody is present in 50-80% cases.^{45,46} They are useful in confirming the presence of thyroid autoimmunity but they are of limited diagnostic value. TSHR-Ab assay is very sensitive and specific (upto 98%) for the diagnosis of Graves' disease. But TSHR-Ab assay is quite expensive and not widely available. TSHR-Ab assay is indicated only when clinical and laboratory diagnosis are not clear. Indications for TSHR-Ab assay are:

- Euthyroid Graves' disease, especially when it is unilateral
- Pregnant women with Graves' disease to predict the likelihood of neonatal thyrotoxicosis
- Nodular variant of Graves' disease

TSHR-Ab assay is also a useful indicator of the degree of disease activity. It can also predict the prognosis of Graves' disease. There is more chance of relapse in patients with persistently high TSHR-Ab level after cessation of antithyroid drug.⁴⁷

Associated hematological abnormalities include increased RBC mass, leucopenia with relative lymphocytosis, monocytosis and eosinophilia, increased factor VIII level. Other associated abnormalities include elevated liver enzymes, bilirubin and ferritin.

7.1. Radioactive iodine uptake (RAIU)

RAIU is not required in each and every case of Graves' disease, but it is useful in excluding thyrotoxicosis caused by thyroiditis, factitious thyrotoxicosis, and type II amiodarone induces thyrotoxicosis. RAIU is absolutely contraindicated in pregnancy. In Graves' disease RAIU is diffusely increased.

7.2. Thyroid ultrasound

In Graves' disease thyroid tissue typically become hypoechoic because of reduction in colloid content, increase in thyroid vascularity and lymphocytic infiltration. In colour flow doppler there is a distinct pattern characterized by markedly increased signals, inferior thyroid artery and intrathyroidal artery velocities more than 40 cm/s. This pattern, in conjunction with a hypoechoic pattern allows distinction from Hashimoto's thyroiditis.

7.3. Differential diagnosis

If a patient presented with diffuse goiter with clinical and biochemical thyrotoxicosis, ophthalmopathy and positive autoimmune markers like anti TPO antibody or TSHR-Ab, diagnosis of Graves' disease is straight forward. In absence of these classical features radionuclide scan (I^{123} , I^{131} , Tc^{99m}) is the most reliable distinguishing test. In case of Graves' disease there is diffuse and high uptake, whereas in patients with toxic adenoma or toxic multinodular goiter there is patchy uptake. In patients with thyroiditis and factitious thyrotoxicosis there is decreased uptake. In patients with TSH producing adenoma, there is also a diffuse goiter, but TSH is inappropriately normal or increased instead of suppress TSH of graves' disease. Panic attacks, mania, pheochromocytoma and malignancy can be easily ruled out by thyroid function test.

8. Treatment

There is no ideal treatment option present targeting the basic pathogenic mechanisms of Graves' disease. Available treatment options target the increased synthesis of thyroid hormones by antithyroid drugs, or ablation of thyroid tissue by surgery or radioiodine. Antithyroid drugs are the predominant therapy in Europe and Japan whereas radioiodine is first line of treatment in USA. No single treatment is optimal and patients often require multiple treatment.

8.1. Antithyroid drugs

Thionamides are the main antithyroid drugs which includes propylthiouracil, carbimazole and methimazole. Thionamides act by inhibiting the enzyme thyroid peroxidase, reducing the oxidation and organification of iodide and coupling of iodotyrosines. Carbimazole is not an active drug, and in body it is converted to active metabolite methimazole. Propylthiouracil, in addition to inhibit thyroid hormone synthesis, also inhibits the peripheral conversion of T_4 to T_3 . Methimazole is ten times more potent than propylthiouracil. Half life of methimazole is about 6 hours while that of propylthiouracil is about 90 minutes. Duration of action of methimazole is more than 24 hours while that of propylthiouracil is 12-24 hours. Transplacental transfer of propylthiouracil is lowest. Antithyroid drugs do not block the release of preformed hormones, so euthyroidism is not obtained until intrathyroidal hormone store is depleted. These drugs also reduce thyroid antibody level.

Antithyroid drugs can be used as a primary treatment or as a preparatory treatment before radioiodine or surgery. The antithyroid drugs are usually started in higher doses. The starting dose of methimazole or carbimazole is 10-20 mg every 8-12 hours and that of propylthiouracil is 100-200 mg every 6-8 hours. Once euthyroidism is achieved which usually takes 4-5 weeks, methimazole can be given in single daily dose while propylthiouracil is given in multiple daily doses throughout the treatment. There are two treatment strategies for using antithyroid drugs. In titration regimen, antithyroid drugs are started in high doses and dose can be gradually decreased to maintain euthyroid state. In Block and Replace regimen, the antithyroid drugs are maintained in high doses and subsequently levothyroxine is added to maintain the euthyroid status. At present there is no proven advantage of block and replace regimen over titration regimen.

Patient should be reviewed clinically and biochemically after every 3-4 weeks. Dose of antithyroid drugs is adjusted based on the TT_4 or FT_4 level, as TSH level often remain suppressed for several months. The usual daily maintenance dose of carbimazole or methimazole is 2.5 – 10 mg and that of propylthiouracil is 50-100 mg. When TSH level become normal, it can also be used to monitor therapy. Size of the goiter decreases in about 30-50% of patients during treatment. In remaining patients it may remain unchanged or even enlarge. Increase in goiter size is one of the earliest manifestations of iatrogenic hypothyroidism. The other features are weight gain, lethargy, fatigue and other signs of mild hypothyroidism.

Maximum remission rate with antithyroid drugs is 30-50%, which can be achieved by continuation of the drug for 6-18 months or even longer. Most of the relapses occur within first 3-6 months after discontinuation of drug. Suppressed TSH level below the normal limit is the first signal of relapse even in the presence of a normal serum T_4 level. In most of the studies, the relapse rate is 50-80%.^{48,49} Most important predictor of relapse is goiter size.⁵⁰ Other factors influencing recurrence of Graves' disease include high TSHR-Ab concentration, large iodine intake, marked residual goiter, short duration of antithyroid drug treatment and previous recurrence. Factors which favor long term remission after therapy include the initial presence of T_3 toxicosis, a small goiter, decrease in the size of goiter, and return of TSH to normal during treatment, the return of serum thyroglobulin to normal, and low iodine diet.

Most common side effects of thionamides are pruritus, skin rash, urticaria, fever and arthralgia. These may resolve spontaneously or after substituting another drug. Rare but major side effects are hepatitis, cholestasis, SLE like syndrome, ANCA positive vasculitis and most importantly agranulocytosis. Major side effects occur in less than 1% of patients. Antithyroid drugs should be stopped and not restarted if patient develop major side effects.

8.2. Iodine and iodine containing components

Inorganic iodine acts in many ways in thyrotoxicosis. Iodine blocks its own transport in thyroid, inhibits iodine organification and inhibits the release of hormone. Inhibition of iodine organification by inorganic iodide is known as Wolf-Chaikoff effect. Major action of

iodine is inhibition of hormone release. Iodine also decreases the vascularity of thyroid gland. All of these effects of iodine are transient and lasts only for a few days or weeks. Now a days iodine is used only for preoperative preparation for Graves' disease and in the management of thyrotoxic crisis. The usual dose of Lugol's solution is 3-5 drops three times per day and that of SSKI is 2-3 drops twice daily. Iodine decreases the effect of subsequently administered thionamides and radioiodine for several weeks.

Iodinated radio contrast agents like iopanoic acid, and sodium ipodate acts by blocking the peripheral conversion of T4 to T3 and inhibition of hormone release. They are ideally used in emergency situations when rapid control of thyrotoxicosis is needed or in preoperative preparation or while awaiting the response of radioiodine.

8.3. Thiocyanate and perchlorate

They act by interrupting the transport of iodine to thyroid gland.

8.4. Lithium

Lithium also acts as a thyroid constipating agent (block the release of thyroid hormones). Lithium also potentiates the beneficial effect of radioiodine. The usual dose of lithium is 450-900 mg per day in divided doses. Serum lithium concentration should be maintained at 1mEq/L. No adverse effects are reported with this dose of lithium.

8.5. Glucocorticoids

Dexamethasone in high doses (8mg/day) decreases the T4 secretion by the thyroid gland, inhibit the peripheral conversion of T4 to T3, and has immunosuppressive effect. Effect on peripheral conversion of T4 to T3 is additive to propylthiouracil. Glucocorticoids are indicated for the treatment of ophthalmopathy, dermopathy and in thyrotoxic crisis.

8.6. β - blockers

β - blockers do not affect the synthesis or secretion of thyroid hormones. Many of the symptoms & signs of thyrotoxicosis are due to hypersensitivity of the sympathetic nervous system to thyroid hormones. Thus use of β - blockers in thyrotoxicosis, improve the signs and symptoms mediated by the sympathetic nervous system. Tachycardia, palpitation, tremor, anxiety, excess sweating, lid retraction improves with β - blockers. Propranolol has additional advantage over other β - blockers. It inhibits the peripheral conversion of T4 to T3. β - blockers reduce cardiac output without altering oxygen consumption, can have adverse effect in liver, where the arteriovenous oxygen difference is already elevated in the hyperthyroid state. Propranolol is most commonly used agent but other β - blockers can also be used. It is used in a dose of 20-60 mg every 6-8 hours. Short acting agents like esmolol is used for intravenous purpose. Long acting agents like atenolol or metoprolol are used for prolonged treatment. β - blockers should be rapidly tapered and discontinued once stable euthyroidism is achieved.

8.7. Radioiodine

Radioiodine is one of the first line therapy for the Graves' disease. Among different isotopes of radioiodine, I^{131} is the agent of choice. I^{131} is a β -emitter isotope. After oral administration, I^{131} is completely absorbed and rapidly concentrated in thyroid follicular cells. β - particles, which are emitted by I^{131} , destroy the thyroid follicular cells that results in reduced thyroid hormone synthesis. Initially destruction of thyroid follicular cells results in release of preformed hormones that can precipitate the thyrotoxic crisis. Weeks to months are required for control of thyrotoxicosis. Long term effects of radioiodine include atrophy and fibrosis, and a chronic inflammatory response resembling Hashimoto's thyroiditis.

Radioiodine is given as single oral dose. Three outcomes of radioiodine treatment are possible- patients become euthyroid or remain thyrotoxic or become permanently hypothyroid. Dose of radioiodine depends on the size of gland, the uptake of I^{131} and its subsequent rate of release. Dose of radioiodine ranges from 80-200 $\mu\text{Ci/gm}$ of thyroid tissues. A total dose of 20 mCi achieves thyroid ablation in almost all patients and results in permanent hypothyroidisms in 75-90% of patients.⁵¹ The incidence of post radioiodine hypothyroidism in first year is 25% and steadily increases thereafter at a rate of 5% per year. When required, the second dose of radioiodine should be given at least 6 months after the first dose. Failure of radioiodine treatment is more common in patients with large goiter, rapid iodine turnover and adjunctive antithyroid drugs too soon after radioiodine. Prior use of antithyroid drugs decreases the risk of thyrotoxic crisis. Chance of worsening ophthalmopathy can also be reduced by antithyroid drugs. Antithyroid drugs should be stopped 3 to 8 days prior to radioiodine treatment and should be restarted after 7 days when required. Propylthiouracil may cause radio-resistance, but it not a major concern. Short term side effects of radioiodine include transient exacerbation of thyrotoxicosis in the first few months, transient worsening of ophthalmopathy, acute radiation thyroiditis in the first week. Radiation thyroiditis may lead to transient worsening of thyrotoxicosis and ophthalmopathy. Presence of mild to moderate ophthalmopathy is not a contraindication for radioiodine treatment. Concomitant use of oral glucocorticoids, decreases the risk of worsening ophthalmopathy. Long term side effect of radioiodine is permanent hypothyroidism. Initially there was a concern regarding possible carcinogenic effect and risk of genetic damage after radioiodine treatment. But now it is proven that there is no association between radioiodine treatment and thyroid carcinoma, leukemia, solid tumors and genetic damage.⁵² Thyroid cancer is associated with low dose of I^{131} rather than higher dose of I^{131} in children.⁵³ Some centers uses radioiodine even in children of 10 years of age or younger, but still there is no consensus regarding use of radioiodine for persons younger than 16 to 18 years.

8.8. Surgery

Surgery is a form of ablative therapy. Enough thyroid tissue is removed by surgery to reduce the synthesis of thyroid hormones and prevent recurrence. Two type of thyroid surgery are used for Graves' disease. In subtotal thyroidectomy, bulk of the thyroid gland is removed and only about 2 gm (0.5%) of thyroid tissue is left in both lobes. In near total thyroidectomy, most

of the thyroid gland is removed, with only subcentimeter fragment are left around recurrent laryngeal nerve and parathyroid glands. Subtotal thyroidectomy was the procedure of choice in past, but it is associated with higher recurrence rate. Now-a-days near total thyroidectomy is used most often. Near total thyroidectomy is associated with more chance of permanent hypothyroidism but less chance of recurrence than subtotal thyroidectomy.

Complications of thyroid surgery depends on the skill and experience of operating surgeon. In specialized hands, complication rate is as low as 2%, whereas complication rate increases up to 10-15% in non specialized centers. Post Operative bleeding is the most serious complication. It can be fatal by producing asphyxia, if it is not evacuated immediately. Other complications like thyroid storm, injury to recurrent laryngeal nerve and hypoparathyroidism are specific to thyroid surgery. Thyroid storm is rare now-a-days. Injury to recurrent laryngeal nerve causes dysphonia, that usually improves with time, but that may leave the patient slightly hoarse. Hypoparathyroidism can be transient or permanent. Transient hypoparathyroidism is due to removal of the some parathyroid and impairment of blood supply to parathyroid glands, whereas permanent hypoparathyroidism is due to inadvertent removal of all 4 glands. Transient hypoparathyroidism usually occur on day 1-7 postoperatively. Severe symptomatic hypoparathyroidism should be treated by intravenous calcium gluconate. Oral calcium (upto 3 gm/day) is sufficient for milder cases. Immediate postoperative hypocalcemia is due to hungry bone syndrome. Recurrence of hyperthyroidism and permanent hypothyroidism are inversely related and depends on the amount of thyroid tissue left. In case of recurrence, radioiodine should be used as treatment, as second surgery is technically difficult.

Preoperative preparation

Preoperative use of thionamides is associated with lesser morbidity and mortality. Preoperative thionamides are recommended to achieve euthyroidism and to deplete the hormone store. Preoperative use of inorganic iodine decreases the gland size and vascularity. In case of emergency surgery oral cholecystographic agents are the fastest way to obtain euthyroidism. The goal of preoperative management is to maintain euthyroid states by thionamides and then to induce involution of the gland by the inorganic iodine. β blockers can be used in preoperative preparation.

Choice of therapy

Choice of therapy depends on the patient preference, personal experience of the treating doctor and availability of the treatment options. All the three treatment options (antithyroid drugs, radioiodine, surgery) can be used as first line therapy. In most of the Europe, antithyroid drugs are the preferred treatment whereas in USA, radioiodine is the preferred treatment. Primary choice of treatment in children and young adults upto 18 years of age is antithyroid drugs, although radioiodine is not associated with any adverse events. Pregnancy should be delayed for 6-12 months after radioiodine treatment. Presence of severe ophthalmopathy is a contraindication for radioiodine treatment. Surgery is the preferred treatment for patients with large goiter, especially if compressive symptoms are present, endemic goiter with multiple cold nodules, and suspected malignancy.

Thyroid ophthalmopathy

Mild to moderate ophthalmopathy does not require any specific treatment. General measures include control of thyrotoxicosis, smoking cessation, dark glasses with side frame for photophobia and sensitivity to air, artificial tear (1% methyl cellulose) or eye ointment for eye discomfort and dry eye, eye patches or taping during sleep for lagophthalmos, elevation of the head end for periorbital edema, prism for correction of mild diplopia.

Other patients with more severe signs and symptoms affecting daily lives to a significant extent may benefit from immunosuppressive therapy in active disease or surgical decompression in case of inactive disease. Severe ophthalmopathy with optic neuropathy and corneal ulcer is an emergency.

Glucocorticoids

Oral glucocorticoids is initiated at a relatively high dose, such as 40-80 mg of prednisolone per day. After 2-4 weeks, the daily dose is tapered by 2.5-10 mg every 2-4 weeks. Improvement in soft tissue inflammation begins within 1-2 days. Intravenous methylprednisolone pulse therapy is more effective and better tolerated than oral prednisolone.⁵⁴ 500 mg of methylprednisolone per week for 6 weeks followed by 250 mg of methylprednisolone per week for 6 weeks is most commonly used regimen. Cyclosporine can also be used either as a single therapy or in combination with oral prednisolone. Combination therapy of cyclosporine with prednisolone is more effective than either drug alone.⁵⁵

Orbital Radiotherapy

Orbital radiotherapy is well tolerated and provide benefit in approximately two third of patients. This treatment is steroid sparing rather than steroid replacing therapy.

Other immunomodulatory therapy

Rituximab, azathioprine, cyclophosphamide, ciamexon, pentoxifylline and intravenous immunoglobulins have some benefit and are currently under trial.

Orbital decompression

Indications for orbital decompression include optic neuropathy, severe proptosis, vision threatening ocular exposure, debilitating retrobulbar and periorbital pain and intolerable corticosteroid side effects. Transantral orbital decompression with removal of a portion of medial wall and the orbital floor is most commonly used procedure. Upto 5 mm reduction in proptosis can be achieved by orbital decompression. Orbital decompression can cause onset or worsening of diplopia.

Thyroid storm

Thyroid storm or thyrotoxic crisis is a life threatening exacerbation of hyperthyroidism. Most of the cases of thyroid storm are associated with Graves' disease, but it can also occur with toxic multinodular goitre. Precipitating factor for thyroid storm include infection,

trauma, thyroid surgery, radioiodine, diabetic ketoacidosis, stroke etc. It can present with fever, tachycardia, arrhythmias, profuse sweating, diarrhea and vomiting, confusion, delirium, seizures, jaundice, coma, congestive heart failure, hypotension. Thyroid storm is associated with very high mortality rate (upto 30%, even with treatment).

Treatment of thyroid storm requires strict monitoring and proper care. Precipitating factors should be identified and treated. Supportive treatment include cooling blankets and drugs like acetaminophen, chlorpromazine or meperidine for hyperthermia, oxygen inhalation, intravenous fluids. Antithyroid drug of choice is propylthiouracil but carbimazole can also be used. Propylthiouracil 600 mg is given as loading dose by mouth or nasogastric tube or per rectum followed by 200-300 mg every 6-8 hourly. One hour after the first dose of propylthiouracil, stable iodide is given in the form of SSKI (3 drops twice daily) or Lugol's iodine (10 drops twice daily). Propranolol should also be given in a dose of 40-80 mg orally every 6 hours or 2 mg intravenously every 4 hours. If β blockers are contraindicated, calcium channel blockers like diltiazem can be used to control tachycardia. Large dose of dexamethasone (8 mg) by oral or intravenous route should be given to block the release of hormone from gland and peripheral conversion of T4 to T3.

Author details

N.K. Agrawal and Ved Prakash

*Department of Endocrinology and Metabolism, Institute of Medical Sciences,
Banaras Hindu University, Varanasi, India*

Manuj Sharma

Department of Medicine, Gandhi Medical College, Bhopal

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