Thyroid Disorders

Chapter 3

Graves' Disease

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Preface

Hyperthyroidism is a group of diseases leading to excessive TH secretion, increased excitability and hypermetabolism of the nervous digestion and circulation systems. The causes of hyperthyroidism are complicated, while the Graves' disease is the major reason, accounting for about 85% among all hyperthyroidism patients. Graves' hyperthyroidism is mediated by autoantibody stimulation of the thyrotropin receptor on thyrocytes resulting in excess thyroid hormone production. The causes of hyperthyroidism are complex, but Graves' disease is the most common, accounting for about 85% of all hyperthyroidism patients. Graves'disease combines the clinical symptoms and signs of hyperthyroidism, diffuse goiter, characteristic ocular findings, and less frequently unique dermatologic changes.

1. Immunopathogenesis

Graves' disease belongs to organ specific autoimmune disease [1]. TSH receptor (TSHR) was discovery of the in 1966 [2]. T cells specific for the TSHR, their cytokine responses and relationship to MHC antigens, have been described [3-5]. T cells are the key for the generation of IgG class autoantibodies. However, TSHR antibodies are the indisputable immunological markers of Graves' disease. TSHR antibodies can stimulate the receptor (TSAb) in a low level in serum. On the contrary, TSH blocking antibodies (TBAb) at much higher.

2. Epidemiology

In addition to genetic susceptibility, environmental factors also play a role in the development of GD. The prevalence of hyperthyroidism is reported to be 0.5–2.5 in women and 1:4 to 1:10 of that in men [6-10]. From these data the prevalence of GD can be estimated since GD accounts for approximately 70–80 % of cases of hyperthyroidism in iodine-sufficient

geographic regions [11], such as the USA. In a longitudinal epidemiological study performed at the Mayo Clinic, the average annual incidence of GD was 36.8 and 8.3 per 100,000 in females and males, respectively, for a period of 33 years (1935–1967) [12]. In Iceland the incidence of GD was (14.8/100,000) [13]. Similar incidence rates were reported in other iodine-sufficient countries such as New Zealand (15/100,000) [14]. The peak incidence of GD was reported to be in women at ages 20–39. Like many other autoimmune diseases, GD occurs more frequently in women. The female/male (F/M) ratio is reported to be 4:1 to 10:1. GD occurs in all ethnic groups including Caucasians, Asians, and Africans.

3. Genetic Susceptibility

The familial occurrence of AITD is well known to clinicians caring for GD patients and has been reported by many groups [15,16]. There is a significant clustering of GD in families resulting in a sibling risk (λs) that is >10, suggesting a strong genetic susceptibility [17]. The strongest evidence for genetic involvement in the development of GD comes from twin studies.

4. Clinical Presentation

4.1 Symptom

The clinical manifestations are complicated and varied include diaphoresis, heat intolerance, tremor, increased appetite but weight loss, tachycardia, anxiety or nervousness, weakness, fatigue, insomnia, increased stool frequency, irregular menses in women.

Apathetic hyperthyroidism usually present in elderly patients, the symptom are not typical, such as fatigue, weakness, depression, or atrial fibrillation. Some old people with subclinical hyperthyroidism may present with tachycardia or new-onset atrial fibrillation.

4.2 Physical Examination

Patients are usually irritability and restless. Warm and moist in skin. Tremor, proximal muscle weakness, and hyperreflexia. Atrial fibrillation is the most common arrhythmia, the pulse may be rapid and irregular. Thyroid examination may reveal the presence of a goiter, Nodules may be noted, a painful, tender gland suggests subacute (de Quervain) thyroiditis.

4.3 Laboratory Assessment

The levels of free thyroxine (FT4) and triiodothyronine (T3) are high, while thyrotropin (TSH) levels are low. Serum TSH is the most sensitive index of thyroid hormone.

Thyrotropin receptor antibodies (TRAb) are present in more than 90 % of patients with GD. Measurement of these antibodies is helpful in pregnant or lactating women or in

those situations when thyroid uptake and scan are contraindicated or unavailable, and the etiology of hyperthyroidism is not clear on clinical grounds. Measurement of these antibodies is also helpful in the differential diagnosis of patients presenting with proptosis but without biochemical evidence of hyperthyroidism, since 10 % of such patients may have GD [18].

4.4 RAI Uptake

The thyroid radioiodine uptake (RAIU) is the measurement of the proportion of an administered dose of radioactive iodine that accumulates in the thyroid at selected times following ingestion. It helps to distinguish between causes of thyrotoxicosis with normal or elevated uptake in the thyroid gland and those with very low uptake. Thyroid uptake reflects a combination of iodine transport into the thyroid follicular cells, its oxidation and organification, and its release from the thyroid. In general, conditions in which there is increased synthesis and secretion of thyroid hormone will demonstrate elevated thyroid uptake (GD, single toxic adenomas or toxic multinodular goiter). In GD the pattern of RAIU is generally diffuse, while in patients with single toxic adenoma, the uptake is focal, with suppressed uptake in the surrounding and contralateral thyroid tissue. In patients with TMNG, multiple areas of focal increased and suppressed uptake are seen. On the contrary, the RAIU will be near zero in patients with thyrotoxicosis due to painless, postpartum, or subacute thyroiditis, in those with factitious ingestion of thyroid hormone, or in those with recent excess iodine exposure, as seen with patients taking amiodarone or in those recently exposed to intravenous iodinated contrast.

4.5 Ultrasonography

Ultrasound is necessary especially if a nodules with hypofunctioning, since ultrasound-guided FNA is indicated in their evaluation. Also, sonographic assessment of blood flow may help to distinguish Graves' hyperthyroidism from painless thyroiditis [19].

5. Treatment

Antithyroid drugs (ATD), radioactive iodine ablation (RAI), and surgery are usually used in patients. Doctors should give different treatments to patients according to their condition and financial situation. Antithyroid drugs inhibit the synthesis of thyroid hormones. Patients take pills daily for 1.5 to 2 years and see their doctor periodically. Most patients who take the ATD can stop it after two years, but half of them will relapse. Radioactive iodine destroys the thyroid gland within 6–8 weeks. Surgery removes the thyroid gland causing an immediate and definitive cure. Patients need a lifelong replacement of thyroid hormone.

5.1Antithyroid Drug Therapy in Patients with Graves' Disease

Methimazole (MMI) is mild and be recommended for most patients. Most patients could

get a normal thyroid function for >1 year. Patients with milder biochemical disease, a small goiter, and unmeasurable serum TRAb at baseline, bnd much lower in patients with large goiter, severe disease, and very high TRAb levels.

The principle for starting therapy with an ATD are thyrotoxicosis is caused by hyperthyroidism. Patient is expected to tolerate the drug, and accepts the plan for therapy of 1.5 to 2 years.

Therapy with an ATD is often initiated before results of all planned investigations are achieved when patients with clinically and biochemically obvious hyperthyroidism caused by Graves' disease.

5.1.1 Mechanisms of Action

The thionamide ATDs' primary mechanism of action is to inhibit the thyroid peroxidase (TPO)-mediated iodination of thyroglobulin (Tg), and thereby the synthesis of thyroid hormones, T4 and T3. The mechanism likely involves TPO-mediated iodination of the drugs themselves, with the drugs competing for oxidized iodine with the normal biosynthetic pathway, in which oxidized iodineis bound to tyrosine residues in Tg to form iodotyrosines. By inhibiting type I deiodinase the conversion of T4 to T3 could be decreased with PTU in peripheral tissues and deceased in the thyroid gland itself. This effect is important in the management of thyroid storm.

5.1.2 Contraindications to ATD Therapy

Methimazole/Carbimazole are forbidden in early pregnancy, as this may lead to severe birth defects.Propylthiouracil in early pregnancy may also be associated with an increase in risk, but defects tend to be less severe. The drug will have no effect in nonhyperthyroid type of thyrotoxicosis, such as painless thyroiditis.

5.1.3 Doses of ATDs

The clinician should give the initial dose according to the biochemical and clinical severity of the disease. Patients should choose a diet with low iodine.

Propylthiouracil (PTU) should only be used in special situations because it has a less favorable pharmacokinetic profile and more side effects. When the difference in duration of action is taken into account, the relative activity of the two drugs (PTU & MMI) is about 1:20 [20].

The initial drug recommended by most doctors is MMI, and the starting dose should be high enough in order to get euthyroid within time (preferably 4–8 weeks); but not higher than necessary. Recommended dose of MMI is shown in Table 1.

Table 1: Recommended dose of MMI

Dose of MMI	Thyroid level
30 mg a day	>2–3 times the upper reference limit
20 mg a day	>1.5–≤2 times the upper reference limit
10 mg a day	≤1.5 times upper reference limit

We suggest given the drug once a day because no study clearly shows the superiority of splitting.

5.2 Side Effects of ATDs

The side effects of ATDs occur within the first few weeks of beginning the medication. Include an skin rash, abdominal distention, nausea, and arthralgias. It may discontinue the drug when pruritic popular skin eruption is severe enough, but it will resolve with concomitant use of antihistamines in some cases. Switching from MMI to PTU is also a possibility. Agranulocytosis is considered an generally mediated by immune mechanisms. It is an anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis, and hepatotoxicity.

5.2.1Agranulocytosis

Agranulocytosis is defined as an absolute granulocyte count of <1.5×109/L. It typically happens within the first few months of initiating ATDs.

The frequency of agranulocytosis is in the range of 0.2–0.3% and is similar for both MMI and PTU [21]. There is a clear cut dose effect with MMI, but there is no dose relationship with PTU [22]. Some asymptomatic ATD-treated patients have low white blood cell counts, it is suggested that hematologic monitoring could be used in identify the risk. Patients with agranulocytosis are easy to have high fever, malaise, fulminant oropharyngeal infection with odynophagia, and cervical lymphadenopathy, pneumonia, and skin infections.

When agranulocytosis is happened, the first treatment is immediate pause the ATD, and consideration of hematopoietic growth factor therapy (GM CSF or G-CSF). Factors include lower granulocyte counts, older age (>65 years), renal failure or respiratory disease and cardiac always predict worse outcome.

5.2.2 Hepatotoxicity

Both PTU and MMI can lead to hepatotoxicity. Typical symptoms include nausea, malaise, jaundice, and light- colored stools. For MMI, the mean onset of hepatotoxicity in one review was 36 days [23]. It will take seven weeks for complete normalization of hepatic function index after stopping the drugs.

5.2.3 Vasculitis

PTU can induced vasculitis, typically is renal and pulmonary. Presentation includes

polyarthritis, fever, purpura, glomeruloneph ritis and/or pneumonitis. For drug-induced lupus, recovery occurs after discontinuation of the drug, but some patients afflicted with vasculitis require glucocorticoids or other immunotherapies, including cyclophosphamide and plasma pheresis. However, in general, PTU-related vasculitis has a more benign course than idiopathic vasculitis.

5.3 Reduce Dose

The dose of drug should be gradually reduced as thyroid function tests normalize. It is better to give drug once a day in order to improve overall compliance. MMI has a considerably longer duration than PTU and once daily dosing is clearly effective.

The adjustment of the ATD dose to give rapid normalization of thyroid function without inducing hypothyroidism requires frequent assessment of thyroid function. At the beginning of treatment we suggest test thyroid function once a month, gradually lengthen to 2-3 month according to the condition. All patients are instructed about possible side effects of therapy and are given written information about adverse reactions, and women of childbearing age are informed about the association between use of ATD in early pregnancy and birth defects [24].

5.4 ATD Withdrawal

Most patients can get a stable thyroid function with a small dose of MMI (2.5–10 mg given once daily).Assuming that the TRAb has become normal(at least 6 months), the ATD could be withdrawn gradually with no need of medication. Several studies have investigated the association between the duration of therapy and the risk of relapse after ATD withdrawal [25]. There is no evidence that therapy below 1 year increases the risk of relapse, and no evidence show that therapy longer than 18 months will reduce the risk. Notably, a major advantage of more prolonged therapy is that the majority of patients stay euthyroid on such therapy, even if the dose of ATD is low. [26,27]. The decision to withdraw or taper medication is based on the preference of the patient, duration of therapy (usually 12–24 months), TRAb level. We suggest gradually withdraw the medication, guided by thyroid function testing.

Half of the patients will relapsed depending on a number of factors. Relapses tend to occur within the first 6 months after drug discontinuation. The postpartum period is a time when relapse is especially common [28]. The possible mechanism is the release of immunosuppression. After a relapse, ATD therapy may be initiated again following the principles discussed above, or the patient may desire radioiodine therapy or surgery.

5.5 Replacement Therapy-Levothyroxine

Some patients become euthyroid during ATD therapy, the general recommendation is

that the dose of the ATD should be gradually decreased. But the duration is not enough. In this situation, we suggest keeping the high dose of the ATD and to add Levothyroxine to maintain a euthyroid state. We need to keep high dose of ATD to prevent excess thyroid hormone secretion in the event of worsening of disease activity. Meanwhile, the risk of overtreatment leading to hypothyroidism will be lower, because of the replacement therapy that is being given.

5.6 Radioiodine Treatment

5.6.1 Mechanism

Sodium 131-I can be obtained in capsule form or in solution for administration to patients. The isotope is rapidly absorbed and transported from the blood into thyroid follicular cells, where it is organified to tyrosyl residues on thyroglobulin. Beta emissions from the isotope have a path length of 2 mm and result in cell damage and necrosis. After an interval of approximately 8–16 weeks, most thyroid glands have been effectively.

5.6.2 Contraindications of Radioiodine Treatment

Radioiodine can destroy fetal thyroid tissue after 10–12 weeks of gestation. Pregnancy and nursing are absolute contraindications. Cretinism or developmental abnormalities could potentially occur in such infants. Guidelines suggest that all women of childbearing age have a pregnancy test before receiving radioiodine [29]. In order to limit radiation exposure to breast tissue, radioiodine should be delayed until production of breast milk ceases, usually about 6 weeks after weaning.

5.6.3 Pretreatment with ATDs

Thyroid function becomes normal on average 5.7 weeks after methimazole treatment [30]. Hyperthyroid symptoms and the risk for complications are ameliorated more rapidly when ATD prior to radioiodine administration. Beta-adrenergic blocking agents helps to control symptoms and tachycardia.

5.6.4 Stopping ATDs Before Giving Radioiodine

ATDs should be stopped prior to radioiodine administration since ATDs could prevent organification of iodine. The optimal time to stop drug is 2–3 days before radioiodine administration.

5.6.5 Resuming ATDs After Radioiodine

The effective time of radioiodine is 6–18-week after first treatment. It is common to resume ATDs 3–7 days after radioiodine treatment. Purpose is avoid exacerbation of chemical and clinical hyperthyroidism in the initial weeks before administering radioiodine becomes

effective.

5.6.6 Dose and Fixed Versus Calculated

Repetitive low doses will prolong the duration of overt or subclinical hyperthyroidism and increase complications (e.g.reduced bone density or atrial fibrillation). Patients might become hypothyroid with high doses, most patients require thyroid hormone replacement within 3 months or whole life of treatment. In some situations like age, radioiodine uptake, gland size, degree of hyperthyroidism, renal function, dietary iodine intake could influence the effectiveness. Calculated dose regimens use 100–200 μCi/g of thyroid tissue adjusted by the radioiodine uptake, for example:150uCi /g of tissue′ 45 g thyroid / uptake of 55% = 12.3 mCi. In one study using more (128–155 υCi/g of tissue), 80% became hypothyroid, and90 % of patients were cured. The use of high-dose radioiodine with thyroid cancer is indeterminacy, even standard dose regimes may lead to lethal bone marrow. Fortunately, in most situation the doses for treat hyperthyroidism usually not approach maximal permissible which exposures to bone marrow and other organs.

For patients with hemodialysis, since iodine is concentrated in the dialysate, radioiodine administration should be administered a minimum of 10 h before and is usually given shortly after a dialysis session, 24–48 h prior to the next time.

5.6.7 Radioiodine-Resistant

Some patients fail repetitive radioiodine treatments because of rapid turnover of iodine and thyroid hormone. The reasons are the size of the gland, the dose administered, the duration of the retention of radioiodine. The ratio of the 4- to 6-h radioiodine uptake to the 24-h radioiodine uptake has been used as a surrogate marker for radioiodine turnover. One study shows this ratio was efficacy with a 48 % failure rate if the ratio exceeded 1.0 compared to an 11% failure rate for a ratio less than or equal to 1.0 [31]. In another one, patients with a 5-to 24-h uptake ratio greater than or equal to 0.8 had a 34 % rate of failure, compared to 16 % if the ratio was less than 0.8 [32]. The authors of that study utilized 200 υCi/g instead of 100 υCi/g with high turnover and demonstrated a reduction in the failure rate. Another suggested approach is to use lithium in these patients to reduce turnover [33]. Patients with large glands also have higher radioiodine failure rates respectively [34].

5.6.8 Treatment Failure

14% of patients may failed in the first dose of radioiodine.

The reasons might be related thyroid hormone levels and the extent to the goiter. Most of the patients who fail the first dose need to a second dose, and there is no fixed rule for when a second treatment should be administered. Few patients may need more times. Doctors should

clear iodine ingestion and iodine exposures (if using a fixed dose) and have a consideration of the possibility of rapid turnover. An occasional patient who remains minimally hyperthyroid following radioiodine may be treated with nonradioactive iodine to avoid a second exposure.

5.6.9 Management after Radioiodine

After Radioiodine patients occasionally develop transient euthyroidism or even hypothyroidism followed by recurrent hyperthyroidism, or persistent hyperthyroidism (treatment failure).Patients are usually reassessed at 4–8-week intervals until chemically stable. Even with low-dose radioiodine some patients may achieve euthyroidism subsequently become hypothyroid at a rate of 2–3 % a year [35]. Monitoring can be reduced to every 6–12 months when patients achieved a stable TSH level.

5.6.10 Pregnancy after Radioiodine

Similar to hysterosalpingogram or barium enema the dose to the ovary after radioiodine treatment is about 3 rads [38]. Birth defects of children and adolescent are not more common in the offspring who received radioiodine [39]. Risks of genetic damage show a risk of 0.005 % theoretically, which compares to the spontaneous risk of 0.8% [40]. It suggests pregnant 4–6 months after radioiodine therapy. Insure that hyperthyroidism is cured and the hypothyroidism is adequately treated and that thyroid hormone are normal.

5.6.11 Radioiodine in Children and Adolescents

Radioiodine therapy in adolescents have same considerations with adults. Children with Graves' disease are different. It is already established that low levels of radiation exposure predispose to thyroid neoplasia in children through age 20 [41]. However, the exposures risk appears to be greatest from the thyroid equivalent dose of 30 υCi/g of tissue or less and not the ablative doses [42]. It is important in children to use higher ablative doses of radioiodine to prevent thyroid neoplasia.

5.6.12 Adverse Effects-Radiation Thyroiditis and Thyroid Storm

1% of patients who receive radioiodine develop a radiation thyroiditis. Thyroid pain with dysphagia may last 3 weeks. Some patient have transient recurrent laryngeal nerve dysfunction and hypoparathyroidism. Nonsteroidal anti-inflammatory drugs can control the pain, but some sever pain need corticosteroids.

5.7 Thyroidectomy in Patients with Graves' Disease

Thyroid surgery has a long history, it is a common operation by an experienced operator.

5.7.1 Indications for Surgery

Table 2: Indications for Surgery [43,44].

Absolute Indications	Relative Indications
• Thyroid nodules are suspicious/diagnostic of • Malignancy, • Large goiters causing symptomatic compression, • Coexisting hyperparathyroidism, • Females planning pregnancy in <4–6 months, • Persistent disease despite previous treatment with antithyroid medications and/or RAI, • Patients who may prefer or require rapid control of symptoms.	• Large goiter (without significant compressive symptoms) and/or concomitant thyroid nodules with benign cytology, • Moderate-severe Graves' ophthalmopathy, • Fear of radiation exposure with RAI, • Children with Graves' disease.

5.7.2 Surgery for GD in Pregnancy

Pregnancy is a relative contraindication, is optimally performed in the latter portion of the second trimester, given the teratogenic effects of anesthesia and increased risk of fetal distress or loss in the first trimester and the increased risk of preterm labor/delivery in the third trimester. Surgery could be performed for pregnant patients require rapid control of hyperthyroidism and cannot be used and/or antithyroid medications are not effective. It is recommended that TRAb titers be obtained to evaluate the potential risk of fetal hyperthyroidism.

5.7.3 Surgery for GD in Children

Present guidelines recommend consideration of thyroidectomy or RAI in pediatric patients with GD who are not cured after 1–2 years of therapy with methimazole. Patients who are below 5 years and with larger thyroid glands are recommended with thyroidectomy. Thyroidectomy should be performed by experienced surgeons.

5.7.4 Operative Management

Ultrasonography is useful to figure the size of the gland and to identify any nodules weather require fine needle aspiration (FNA) biopsy. Patients should be euthyroid antecedently, as thyrotoxic crisis during or after the procedure can induce sever result. Beta-adrenergic blockade can be added to control heart rate. Antithyroid medications and iodine solution should be given until the day of surgery. We recommend dose of potassium iodide (SSKI; 50 mg iodide/drop) is 3–7 drops, three times a day for 10 days [45]. Purpose for potassium iodide is decreased the risk of thyroid storm; potassium iodide can reduces the vascularity of the thyroid gland, allowing for a technically easier operation. Antithyroid medications should be stopped immediately after operation, and slowly tapered beta-blockade. Thyroid hormone replacement should be given according to the patient's weight and age. TSH and FT4 levels should be measured every 1–2 months until stable, and then annually.

6. Thyroid Storm

6.1 Pathophysiology

The pathophysiology of thyroid storm still not clear. However, some triggers or precipitants are known. Specifically, rapid increase in thyroid hormone levels show a sudden and huge intracellular availability of free thyroid hormone, while those related to intercurrent illness suggest that a diminished physiological reserve plays a central role. Both mechanisms cause unnormal homeostatic mechanisms and even life-threatening. Most of time triggers or precipitants of thyroid storm contains the following: Abrupt discontinuation of ATDs. Rapid rise in thyroid hormone levels. Thyroid surgery or trauma. Exposure of radioiodine therapy. Cerebrovascular or cardiovascular accident. Sever emotional stress. Diabetic ketoacidosis. Sever infection.

6.2 Clinical Presentation

Symptoms are associated with high doses of thyroid hormones. Typically presentation is shown in the **Table 3**.

Table 3: Clinical Presentation of Thyroid Storm.

Temperatures often reach to 104–106 °F (40–41 °C)
Atrial dysrhythmia, ventricular dysfunction, heart failure
Anxiety ,restlessness ,severe agitation, delirium, psychosis, stupor
Gastrointestinal and hepatic involvement (nausea, vomiting, diarrhea, hepatocellular dysfunction with jaundice.)

6.3 Diagnosis

Thyroid storm were rapid deterioration, ending in death within hours to days without early diagnosis and treatment. Typical clinical presentation are shown in table 3. However, diagnosis has not always been directly. Sometimes laboratory values and clinical present are not clear and early diagnostic criteria were far from uniform.

6.4 Treatment

6.5 Against the Thyroid Gland

The primary treatment is to block the synthesis of thyroid hormones. PTU and MMI inhibit iodine organification as well as the coupling of iodotyrosine residues to form T4 and T3. PTU is superior to MMI in decreasing the conversion of T4 to T3 and therefore usually be given at the first 24 hours of therapy.

PTU should be loaded with a dose of 600–1,000 mg and then given at doses of 1,200–1,500

mg daily, divided as 200–250 mg every 4 h. There is no effect on the release of previously formed thyroid hormone from PTU and MMI. Inorganic iodine inhibits colloid proteolysis and the release of T4 and T3 from the thyroid gland and also has inhibitory effects on thyroid hormone synthesis. Recommended oral doses are either saturated solution of potassium iodide (SSKI) (~35–50 mg/drop), five drops every 6 h, or Lugol's solution (8 mg/drop [0.05 ml]), eight drops every 6 h [46].

6.6 Emergent Thyroidectomy

Some doctors have reported that the use of thyroidectomy in thyroid storm patients is effective [47]. Someone advocated early thyroidectomy to treat thyroid storm, particularly in chronically ill elderly patients with concurrent cardiopulmonary and renal failure, who fail to respond to the standard intensive multifaceted therapy for thyroid storm.

6.7 Physical Removal of Thyroid Hormone

Both charcoal plasma perfusion and plasma exchange techniques are effective in the removal of circulating hormone. Plasma exchange is applied to those who are being prepared for emergent thyroidectomy and with a history of antithyroid drug-associated agranulocytosis or moderate hepatocellular dysfunction. However, the effect of plasmapheresis lasting only 24–48 h. Binding resin therapy is another adjunctive measure used to physically remove thyroid hormone.

6.8 Measures Directed against Systemic Decompensation

The treatment for systemic decompensation conclude reversal of hyperthermia, congestive heart failure, dehydration, dysrhythmia, prevent concomitant adrenal crisis. Cooling techniques such as ice packs, alcohol washes, and cooling blankets are used to hypothermia. Salicylates should be avoided, which could aggravate the state of thyrotoxicosis. Fluid losses from gastrointestinal and insensible are probably immense, and should be aggressively supplemented to prevent cardiovascular collapse and shock.

The treatment of cardiovascular disease including antiarrhythmic agents, vasodilators, and diuretics. Compare to other cardiovascular disease the doses of digoxin may be larger [49]. Serum digoxin levels should be closely monitored, particularly as thyrotoxicosis improves, to prevent digitalis toxicity. There are something to concern when use beta- blockers. Propranolol is contraindicated in patients with a history of asthma or chronic obstructive pulmonary disease, and propranolol has also been associated with cases of cardiorespiratory arrest [48]. Dexamethasone and hydrocortisone can prevent conversion from T4 to T3. The initial dose of hydrocortisone is 300 mg, followed by 100 mg every 8 hours. Subsequently reduced and discontinued as allowed by the clinical response of the individual.

7. Effects of Skeletal Muscle

Patient with GD always have muscle weakness, fatigue, poor exercise tolerance and myalgias. Thyroid hormone excess has dissimilatory effects on the muscle, resulting in loss of muscle protein and negative nitrogen balance.3% of hyperthyroidism patients have myasthenia gravis [50,51]. The incidence of thyrotoxic periodic paralysis ranges from 2 to 24 % in Asian people compared to 0.1–0.2 % in non-Asian North Americans [52]. The pathogenesis may related to activity of Na+–K+ ATPase be stimulated by thyroid hormone, hyperinsulinemia, and hyperadrenergic activity.

8. Effects of Cardiovascular System

Short-term hyperthyroidism induces positive cardiovascular changes. However, long-term of excessive thyroid hormone can increase in blood volume and the improvement in diastolic function. The level of T3 have a positive effect on vascular smooth muscle cells and endothelial nitric oxide production result in cardiac afterload reduced. However, hyperthyroid patients have an impaired cardiopulmonary function, which in part reflects their reduced cardiovascular and respiratory reserve. Dyspnea after exercise indicates a lack of cardiac output. There is a low efficiency of cardiopulmonary function and respiratory muscle weakness in overt hyperthyroidism. These function are recovery after normalizing thyroid function in some young patients.

9. GD in Childhood

Graves' disease is the most common cause of hyperthyroidism in children. The prevalence is 1 in 1,000 adults [53,54] and is 1 in 10,000 in the pediatric population [55]. Symptoms include weight loss, tremor, tachycardia, flushing, excessive physical activity, accelerated growth, decreased bone mineralization, and poor school performance. The morbidity of ophthalmopathy in childhood GD is 50% less than adults [56–59]. The way of treatment include ATDs, radioiodine, or surgery. Doctors should consider each of benefits and risks when children are treated.

PTU is only used in short term while plans for 131 I or surgery are planed. Children have the same side effects as adults. If these problems occur, the patient should immediately stop the medication, and have laboratory tests (routine blood indexes, liver function). The Dose of PTU in children is **Table 4**, However, patients can use double doses when there is severe hyperthyroidism.

Table 4: The Dose of PTU in children

Age of children	The Dose of PTU
infants	1.25 mg/day
1–5 years	2.5–5.0 mg/day
5–10 years	5–10 mg/day
10–18 years	10–20 mg/day

Although MMI is the drug of choice for GD, MMI therapy is not without risks. The most common minor adverse side effects related are hives, arthralgia, and neutropenia. Children may also develop major side effects, including Stevens-Johnson syndrome and vasculitis. MMI adverse events most commonly occur within 6 months of therapy onset. Yet, 4 % of children will develop adverse events 18 months of MMI therapy, highlighting the need for constant vigilance while on treatment [60].

Remission of GD in children is lower than adults. The collective literature indicates that remission rates in children are less than 25% following many years of ATD therapy [61-64].

10. Graves' Disease and Pregnancy

10.1 Diagnosis

The combination of a suppressed TSH and elevated free thyroxine is pathognomonic for Graves' disease. The typical symptoms are consistent with general hyperthyroidism. Both a toxic multinodular goiter and can a solitary toxic nodule present as thyrotoxicosis during pregnancy but can usually be differentiated from physical or ultrasound examination, and the absence of TSI. Other causes of thyrotoxicosis during pregnancy like choriocarcinoma, hydatidiform mole, struma ovarii, subacute thyroiditis, and self- or overmedication with thyroid hormone are rare but need to be considered in the setting of TSI-negative thyrotoxicosis.

10.2 Management

TSI can cross the placenta and cause fetal/neonatal thyrotoxicosis. Both the American Thyroid Association and the Endocrine Society recommend measurement of TSI in the second trimester [65,66]. (ATA recommendation is between 20 and 24 weeks and Endocrine Society recommendation is by week 22). Based on that the deficiency of TSI during pregnancy reassure that neonatal or fetal thyrotoxicosis will not occur and no further TSI testing is recommended. However, women with TSI titer surpass three times the upper limit, need close fetal monitoring for the development of fetal thyrotoxicosis and goiter by fetal ultrasound, and concomitant administration of levothyroxine should be given to provide mother euthyroid. As mentioned before radioactive iodine is forbidden during pregnancy. The preferred treatment is antithyroid drugs (PTU/MMI). Once achieve the target free thyroxine level, the dose of ATDs will typically decrease as pregnancy progresses given decreasing TSI titers. It is quite usual that patient of all

antithyroid medications prior to delivery. Surgery can be considered when antithyroid drugs cannot be tolerated and are ineffective or the patient is noncompliant [67]. Surgery is best performed in the second trimester to minimize the risk of fetal loss.

10.3 Preconception Counseling

Women with Graves' disease should undergo preconception counseling [68].

Doctors should counsel women with thyrotoxic to delay pregnancy until euthyroid. Euthyroidism should be achieved before conception, and tests of thyroid function ought to obtained as soon as pregnancy is confirmed. Women who are TSI positive should be made aware of the possibility of fetal and/or neonatal thyrotoxicosis despite the fact that they are euthyroid. Furthermore, doctors tell the patients there is possibility of postpartum recurrence of active Graves' disease.

11. Graves' Orbitopathy

11.1 Pathogenesis

Graves' orbitopathy (GO) is an inflammatory autoimmune disorder that basically with a past or current history of GD. GO usually occurs simultaneously or within 18 months of GD, occasionally precedes or follows [69].

11.2 Signs and Symptoms

Signs and symptoms of GO are various include eyeball forward displacement, eyelid swelling and conjunctival and erythema, ocular pain, and diplopia. These characteristic derive mostly from enlargement of the orbital adipose tissues and extraocular muscles within the confines of the bony orbit. As the resulting orbital pressure increases, proptosis may develop and venous This inflammation appears to be initiated by the migration of T-helper cells into the orbit [70]. Related inflammatory cytokines include interleukin-1 (IL-1), interleukin-16 (IL-16), interferon-γ (IFN-γ), TRAb. In addition, chemoattractant cytokines, including IL-16, regulated upon activation, normal T cell expressed and secreted, and CXCL10, may enhance mononuclear cell infiltration into the orbit [71]. Active inflammation within the enlarged and edematous extraocular muscles may lead to extraocular muscle dysfunction in early state.

11.3 Diagnosis

Symptoms and signs have been described above. Laboratory on T3, T4, and TSH and TRAb, help support the diagnosis. Orbital imaging is helpful in diagnosis. CT Scan is the most useful modality, allowing volume measurements of orbital fat and individual extraocular muscles, as well as identifying orbital apical crowding in optic neuropathy and the structure of the surrounding bone and sinuses for possible surgical decompression. MRI may display

increased muscles edema during the active phase.

While the levator muscle is commonly involved in TED. The onset of muscle involvement may be heralded by aching with eye movement and with conjunctival redness and edema overlying the insertion of the involved muscle. During the active inflammatory phase, progressive restriction of motility develops, initially intermittent or with gaze. Later motility restriction may be due to secondary fibrosis.

11.4 Grading Severity

Several classification systems have been devised to grade severity of these clinical Manifestations (**Table 5**).

Table 5: TAO classification (ATA)

Class	Grade
0	No physical signs or symptoms
1	There are symptoms but no signs
2	Soft tissue involvement [0: absent, a: minimal, b: moderate, c: marked]
3	Proptosis>3cm [0 absent, a>ULN3-5mm, b>ULN5-7mm, c>ULN8mm
4	Extraocular muscle signs [0: absent, a: limitation in extremes of gaze, b: Exercise restriction, c: Monocular/binocular fixation cornea involvement] (Upper Limits of Normal-ULN)
5	Corneal involvement [0: absent, a: stippling, b:nebula,necrotic,perforated c: clouding, necrosis, perforation]
6	Sight loss (optic nerve compression) [0: absent, a vision 0.63–0.5, b vision0.4-0.1, c vision<0.1- no light perception]

11.5 Clinical Activity Score (CAS)

The Clinical Activity Score was introduced in 1989 by Mourits and colleagues as a global scale of soft tissue inflammation, to help identify active TED patients who are likely to respond to immunosuppressive therapy [72] (**Table 6**).

Table 6: Clinical activity score

1. Spontaneous painful feeling behind globe
2. Pain on eye movement
3 erythema on eyelids
4. conjunctival congestion
5.Chemosis
6. carunculae lacrimalis swelling
7. palpebral oedema

CAS score ≥ 3 has been shown to an active period.

11.6 Treatment of Graves' Orbitopathy

ATDs, RAI, thyroidectomy all can be used safely, however, if RAI was selected, steroid prophylaxis is advisable in the majority of cases (prednisone 0.3-0.5mg/kg•d 1-3 days after RAI), gradually reduce the volume. In patients with sight-threatening GO, ATDs are the treatment of choice while GO is being treated. Children rarely develop severe ophthalmopathy and mild proptosis compare to adults. Adjunctive prednisone therapy is not routinely recommended for the majority of children, as most do not have significant eye disease. The prolonged administration of prednisone is also associated with growth failure, weight gain, and immune suppression. Nevertheless, prednisone may be useful for the child who has severe eye disease and will be treated with 131 I. When surgery is considered, near total or total thyroidectomy is indicated, as subtotal thyroidectomy is associated with a higher relapse rate. Surgery is preferred in children younger than 5 years when definitive therapy is needed and can be performed by a skilled thyroid surgeon. Hypothyroidism is nearly universal in children and adults who undergo total thyroidectomy. Thus, surgery is recommended for these patients.

11.7 Surgery in Patients with Graves' Ophthalmopathy

For Graves' Ophthalmopathy, the goal of surgery is to improve eye symptoms, preserve vision and improve appearance.Approaches by surgeon or institution and currently most orbital decompressions are two-wall procedures, either medial (transnasal endoscopic) plus lateral decompression or antral-ethmoidal (transantral, transnasal endoscopic, caruncular). For patients with an extreme amount of chemosis or lid edema, a caruncular approach or through the inferior fornix via a swinging lower eyelid flap can be challenging and this is another reason why working through the sinuses (e.g., transantral approach) can be technically easier.

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