

Current Diagnosis and Management of Graves' Disease

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ABSTRAK

Penyakit Graves atau Graves' disease merupakan penyakit autoimun yang mengenai kelenjar tiroid. Penyakit Graves merupakan penyebab tersering hipertiroidisme dan tirotoksikosis. Pemahaman mengenai patofisiologi penyakit, strategi diagnosis dan terapi, serta pencegahan relaps penting diketahui oleh semua klinisi khususnya spesialis penyakit dalam untuk memberikan manajemen yang optimal dan komprehensif bagi pasien penyakit Graves. Artikel ini memberikan poin-poin klinis untuk manajemen pasien dengan penyakit Graves berdasarkan review dan guidelines terbaru dari American Thyroid Association (ATA), European Thyroid Association (ETA), dan Japan Thyroid Association/ Japan Endocrine Society.

Kata kunci: *penyakit Graves, tiroid, American Thyroid Association (ATA), European Thyroid Association (ETA), Japan Thyroid Association/ Japan Endocrine Society.*

ABSTRACT

Graves' disease (GD) is an autoimmune disorder which affect thyroid gland. Graves' disease is the most common cause of hyperthyroidism and thyrotoxicosis. Understanding of disease pathophysiology, diagnostic and treatment strategies, and prevention of disease relapse are important for all clinicians especially internal medicine specialist to give optimal and comprehensive management for GD patients. This article highlights clinical points to treat GD patients from reviews and latest guidelines from American Thyroid Association (ATA), European Thyroid Association (ETA), and Japan Thyroid Association/ Japan Endocrine Society.

Keywords: *Graves' disease, thyroid, American Thyroid Association (ATA), European Thyroid Association (ETA), Japan Thyroid Association/ Japan Endocrine Society.*

INTRODUCTION

Graves' disease (GD) was originally described by the Irish physician, Robert James Graves in 1835. Graves' disease includes signs and symptoms consisting of goiter, palpitation (tachycardia), and exophthalmus.¹ Graves' disease represents a part of more extensive autoimmune thyroid disease (AITD), leading to dysfunction of

multiple organs, marked by the presence of thyroid stimulating hormone receptor antibody (TRAb).² Moreover, GD is different from any other autoimmune diseases, because it does not correlate with hypo-function, but - on the contrary - causes hyper-function of the organ (thyroid). Hyper-function of the thyroid can lead to thyrotoxicosis and enlarged of the thyroid gland.³

Prevalence of GD is relatively high compared to other hyperthyroidism causes. According to Weetman, from all hyperthyroidism cases, there are 60-80% cases which diagnosed with Graves' disease. These findings are affected by regional factors especially iodine intake.³ Study at Cipto Mangunkusumo General Hospital in 2004 showed that the prevalence of hyperthyroidism cases from all thyroid problems were 21%.⁴

Knowing the fact that GD is an autoimmune disease, relapsing cases are common which can lead to prolonged time to treat the disease. Like any other autoimmune diseases, remission time of this disease cannot be determined. From this statement, we need to understand the concept of treatment concerning the pathophysiology of Graves' disease. The aim of this review is to refresh clinical management points of GD from reviews and the latest guidelines (American Thyroid Association, European Thyroid Association, and Japan Thyroid Association/ Japan Endocrine Society).

DIAGNOSIS

Diagnosis of Graves' disease (GD) made based on signs, symptoms, and the result of the ancillary laboratory tests. Manifestation of this disease is the Merseburger triad that consists of thyrotoxicosis, diffuse goiter, and ophthalmopathy (orbitopathy). Other than those, dermopathy is also one of the manifestation of Graves' although it has low prevalence.⁵

Manifestation of Graves' are various, from mild to full blown. The common signs and symptoms of Graves are shown in **Table 1**.

Clinically, GD can be diagnosed based on the signs and symptoms of thyrotoxicosis.

Table 1. The common signs and symptoms of Graves'

Signs	Symptoms
Hyperactivity	Palpitation
Tachycardia	Agitation
Atrial fibrillation	Fatigue
Systolic hypertension	Heat intolerant
Warm and moist skin	Tremor
Hyper-reflexia	Increase appetite
Muscle weakness	Weight loss
	Menstrual disorder

Although the diagnosis can be determined, treatment should be based on the result of the laboratory test (TSHs and free T4) to confirm the diagnosis and as a basis for treatment evaluation. The same course of action (checking laboratory values) is applied if the signs and symptoms of thyrotoxicosis does not appear or unclear. Based on low concentration of TSHs and high fT4 concentration (depending on the reagents), the diagnosis of GD can be determined.

T3 examination is needed if physical examination leads to GD, but the laboratory result shows low TSHs concentration with normal fT4 value. When there is a doubt on the signs and symptoms of thyrotoxicosis, absence of visible enlargement of thyroid gland, scintigraphy (thyroid nuclear scan) can be done. Even after doing all of those tests, it is not uncommon for the diagnosis of GD to still be undetermined. When that happen, TRAb test is recommended. The concentration of TRAb can be used for diagnostic purpose and evaluation of treatment and remission.⁶

TREATMENT

The goal treatment of GD is to control and correct the condition based on the pathophysiology of Graves' disease (antigen-antibody reactions in the thyroid glands). Glucocorticoid can reduce the conversion of T4 to T3 and lower the thyroid hormone with unknown mechanism. Considering the long duration of GD treatment, prolonged use of glucocorticoid may lead to more harm than benefits, therefore it is not usually used as first line treatment.⁷

Modalities for GD treatment consists of anti-thyroid drugs, surgery, and radioactive iodine treatment (RAI) with iodine-131 (131I). The choice of treatment is based on several factors; severity of the thyrotoxicosis, age, size of the goiter, availability of the modalities, response of the treatments, and other comorbidities.⁷

Anti-thyroid Drugs

There are 2 types of anti-thyroid drugs which are propylthiouracil (PTU) and methimazole. PTU works by inhibiting the organification of iodides and coupling process, while methimazole inhibits the oxidation of iodine in the thyroid

gland. If one of these drugs used as a primary therapy, it should be given for at least 12-18 months, and will be stopped as the concentrations of TSH and TRAb reach normal value. Azizi, et al⁸ reported that prolonged use of anti-thyroid drugs is effective and safe, especially for adults. Therefore, anti-thyroid drugs is the first choice of treatment in Graves' disease.

Indication of oral anti-thyroid drugs: a). High possibility of remission (woman, mild clinical manifestation, mild goiter, negative or low TRAb); b). Pregnant woman with GD; c). Elderly, or comorbidity with other diseases that increases risk of surgery or short life expectancy; d). Patients in nursing home or other health care facilities, unable to follow the regulation of radioactive iodine therapy; e). History of surgery or neck radiation; f). Limited thyroid surgeon in the area; g). Moderate or severe Graves' ophthalmopathy; h). Immediate needs to lower thyroid (fT4) level.⁷

Surgery

Near total and total thyroidectomy are the main types of surgery in hyperthyroidism cases.

Indication of surgery: a). Woman planning on pregnancy in less than 6 months; b). Enlarged goiter and compression of other organs surrounding thyroid gland; c). Low uptake on the thyroid scanning; d). Malignant or suspicious/indeterminate on the cytology examination; e). Thyroid nodules larger than 4cm, or nonfunctioning or hypofunctioning on the thyroid scanning; f). Hyperparathyroidism; g). High TRAb level (difficult of treat with anti-thyroid drugs); h). Moderate or severe active Graves' ophthalmopathy.^{7,9}

Risks of thyroidectomy surgery are bleeding, paralysis of the vocal cord, and hypocalcemia. These risks can be minimized by trained and experienced thyroid of head-neck surgeon.⁹

Radioactive Iodine Therapy (RAI)

RAI can be applied in patients with risks of anti-thyroid drugs side effect and with comorbidities.

Indication of RAI therapy: a). Woman planning on pregnancy more than 6 months after RAI therapy; b). Comorbidities that may increase surgery risks; c). History of surgery or external

neck radiation; d). Limited thyroid surgeon in the area; e). Contraindicated for anti-thyroid drugs or failure to reach euthyroidism with drugs; f). Patients with periodic thyrotoxicosis hypokalemic paralysis, right heart failure caused by pulmonary hypertension or congestive heart failure.⁷

Other than those modalities, inhibition of beta adrenergic is recommended for all thyrotoxicosis patients with clear manifestations, especially in elderly, those with pulse of > 90x/minute, or any other cardiovascular diseases. Benefits of beta blocker are:

- a. Decrease the hyper adrenergic-thyrotoxicosis signs and symptoms (palpitation, tremor, anxiety, and heat intolerant) rapidly before thyroid hormone reaches normal level.
- b. Prevent the episodes of hypokalemic periodic paralysis.
- c. Inhibit the conversion of T4 to T3 in the peripheral with high dose propranolol.
- d. Preparation for surgery.

RELAPSE

As an autoimmune disease, Graves' disease (GD) is a 'relapse and remission' disease. Graves' disease patients have a chance to experience relapse after stopping anti-thyroid drugs. These days, many explanation and evidences about relapse of GD published in many scientific forum and review. Systematic review and meta-analysis from Struja, et al.¹⁰ showed that occurrence of ophthalmopathy, smoking, thyroid volume and goiter size, fT4, fT3, TRAb, and TBII value were associated with disease relapse, while male sex, age, and initial T4 were not associated with relapse. Study from Eliana F, et al.¹¹ in Indonesian population revealed that besides family history, age at diagnosis, second degree of ophthalmopathy, enlarged thyroid gland which exceeded the lateral edge of the sternocleidomastoid muscles and duration of remission period; genetic polymorphisms of CTLA-4 gene, TSHR gene, and number of regulatory T cells and TRAb levels play a role as risk factors for relapse in patients with Graves' disease.

Titration of anti-thyroid drugs regimen for 12-18 months is an optimal strategy for preventing relapse in GD patients. It is not

recommended to administer levothyroxine after successful anti-thyroid drugs treatment. Studies give evidences to add immunosuppressive agents to decrease the recurrence rate after anti-thyroid drugs. Consumption of Vitamin D, selenium, and stop smoking may also beneficial to prevent relapse in GD patients.¹²

THYROID STORM

The most severe and acute condition of GD is thyroid storm or thyroid crisis which is an endocrine emergency. The diagnosis of thyroid storm is made by clinical observation and systemic decompensation of thyrotoxicosis with a known precipitating factors or triggering illnesses. Since the mortality rate is very high, early suspicion, prompt diagnosis, and intensive management are needed by clinician in primary care and hospital.¹³

For decades, clinician used Burch and Wartofsky clinical scoring consists of temperature, central nervous system problems, heart rate and rhythm, congestive heart failure, gastrointestinal problems, and presence of precipitant history.⁷ These scoring system is very sensitive so that all cases with suspicious condition like thyrotoxicosis and other comorbidity (infection, heart condition, or post-operative patients) can be classified as thyroid storm. In 2016, Japan Thyroid Association and Japan Endocrine Society published new guideline for diagnosis and treatment of thyroid storm. This guideline is very comprehensive and clear to guide clinician for making diagnosis of thyroid storm.

In Japanese guideline, for making diagnosis of thyroid storm there must be presence of thyrotoxicosis with elevated level of fT3 or fT4 as prerequisite condition. Definite thyroid storm is a condition when thyrotoxicosis and at least one central nervous system manifestation and fever, tachycardia, congestive heart failure, of GI/hepatic manifestations, or thyrotoxicosis and at least three combinations of fever, tachycardia, congestive heart failure, or GI/hepatic manifestations. Suspected thyroid storm is a condition when thyrotoxicosis and combination of two of the following: fever,

tachycardia, congestive heart failure, of GI/hepatic manifestations, or patients who met diagnosis of definite thyroid storm condition except that serum fT3 or fT4 level are not available.¹³ These diagnostic criteria are more simple and clear than previous clinical score.

The present guideline also includes 15 recommendations for the treatment of thyrotoxicosis and systemic organ dysfunction affected by thyroid storm, such as central nervous system, cardiovascular system, GI/hepatic tract, admission criteria for intensive care unit. They also explain preventive approaches to thyroid storm, roles of definitive and supportive therapy of thyroid storm. Treatment of thyroid storm includes anti-thyroid drugs (propylthiouracil or methimazole), drugs which blocked thyroid hormones secretion such as sodium iodide, potassium iodide and lugol solution, beta blockers (esmolol, propranolol, metoprolol), intravenous fluid resuscitation, glucocorticoid (hydrocortisone, methylprednisolone, or dexamethasone), and treat the precipitant condition (infection, metabolic or post-operative stress, etc).¹³

GRAVES' ORBITOPATHY

One special condition which always discussed and updated in many studies and guidelines of GD, hyperthyroidism, or thyrotoxicosis is Graves' orbitopathy (GO) or Graves' ophthalmopathy or thyroid eye disease (TED) or thyroid associated ophthalmopathy (TAO). This condition needs special attention and close collaboration with ophthalmologist (especially consultant in oculoplastic surgery or thyroid eye disease specialist). The latest guideline focusing on Graves' orbitopathy is the 2016 European Thyroid Association/EUGOGO (European Group on Graves' Orbitopathy) guidelines for management of Graves' orbitopathy.¹⁴ In this guideline, clearly stated all diagnostic modalities to diagnose and comprehensive treatment of GO. The guideline also stressed about quality of life in patients with GO and complete assessment of GO. **Figure 1** is summary treatment algorithm for GO patients.

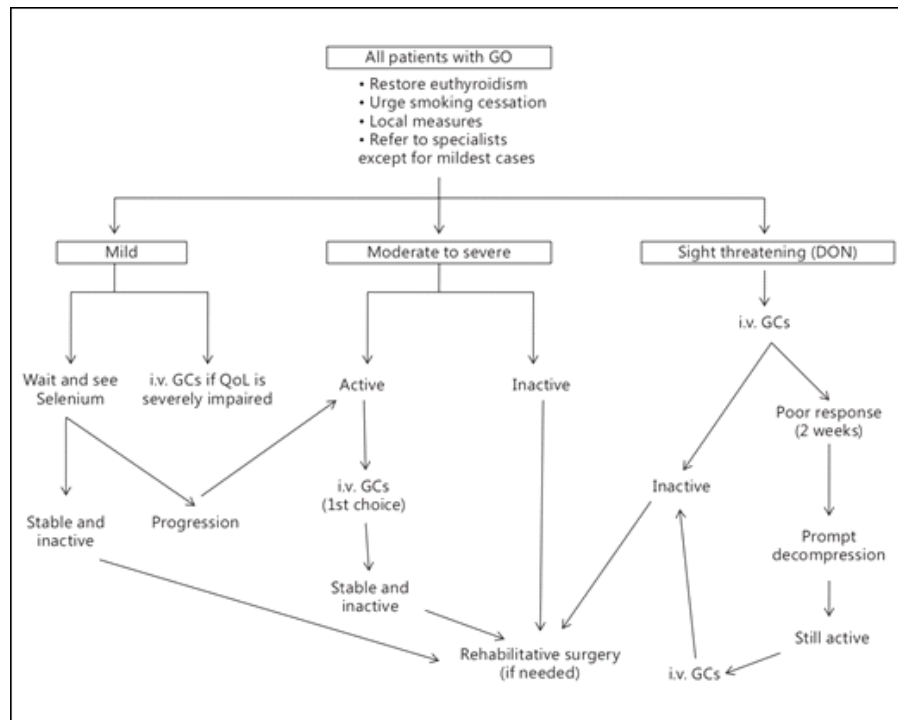


Figure 1. Treatment algorithm of Graves' orbitopathy (GO) from mild, moderate to severe, and sight threatening¹⁴

CONCLUSION

Graves' disease (GD) is an organ-specific autoimmune disorder that is marked by findings of TRAb, with manifestation of diffuse goiter, thyrotoxicosis, and ophthalmopathy. The diagnosis is determined by signs and symptoms of thyrotoxicosis, and confirmed by low TSHs level and high thyroxin (fT4) level. If needed, TRAb examination can be done and diagnosis is confirmed by positive result.

There are three modalities used to treat GD; anti-thyroid drugs, surgery, and RAI therapy. Choice of modality depends on the severity of the thyrotoxicosis, size of goiter, age, availability of the anti-thyroid drugs, response to the treatment, and comorbidities. If drugs were used as the primary therapy, it should be given for at least 12-18 months. If surgery is chosen for primary therapy, near total or total thyroidectomy is the choice of surgery. RAI therapy can be done if there are side effects of the anti-thyroid drugs, history of neck surgery or external neck radiation. Beta blocker can be used to reduce signs and symptoms of thyrotoxicosis and to inhibit the conversion of T4 to T3 in the peripheral organs.

Relapse is common in the treatment course. Risk factors for relapse are presence of ophthalmopathy, smoking, high level of thyroid hormones and antibodies, large thyroid volume, and genetic polymorphisms variations. Titration of anti-thyroid drugs for more than 12 months, immunosuppressive agents, vitamin D, selenium, and stop smoking are beneficial to prevent relapse in GD patients.

Thyroid storm and Graves' orbitopathy are two conditions in GD patients which need collaborative and special treatment. Two latest guidelines from Japan Thyroid Association and European Thyroid Association/EUGOGO explained comprehensive management of thyroid storm and Graves' orbitopathy respectively.

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