ABSTRACT

**Background:** Graves’ disease is the leading cause of hyperthyroidism condition in the world. The incidence of Graves’ disease in the world reaches 20-50 cases per 100,000 population per year. Graves’ disease can cause somatic, psychiatric, and cosmetic problems in the patient. In some cases, it caused a decreased quality of life and death if not appropriately managed. Hence, appropriate diagnosis and management should be made to prevent the progression of the disease.

**Aim:** This literature review aims to review the diagnosis and management of Graves’ disease.

**Conclusion:** Graves’ disease is an autoimmune disease that causes hyperthyroidism by stimulating the thyroid gland to produce thyroid hormone. History taking and laboratory investigation can be done to establish a diagnose of Graves’ disease. Treatment, including the use of anti-thyroid drugs, radioiodine therapy, and surgery. Monitoring should be done periodically during and after the course of treatment to prevent relapse.

**Keywords**: Graves’ disease, hyperthyroidism, thyroid, thyrotoxicosis


INTRODUCTION

Hyperthyroidism is a clinical condition caused by the increased production of thyroid hormones by the thyroid gland. Graves’ disease causes sixty to eighty percent of hyperthyroid conditions in the world. The incidence of Graves’ disease in the world reaches 20-50 cases per 100,000 population per year. This disease can attack various ages, but the peak incidence is 30 to 50 years. Graves’ disease is more often found in female patients than men in the ratio of 8:1. In Indonesia, based on Basic Health Research in 2013, it was found that around 0.4% or approximately 700,000 patients had hyperthyroid. Graves’ disease can decrease quality of life due to somatic, psychiatric symptoms, and cosmetic problems experienced by patients. Appropriate diagnosis and management is essential to prevent the decline in quality of life and death caused by Graves’ Disease.

ETIOLOGY

Genetic and environmental factors are said to play a role in the etiology of Graves’ disease. The genes responsible for causing Graves’ disease and its autoimmune processes include HLA-DR polymorphism, immunoregulatory genes such as CTLA-4, CD25, PTPN22, FCRL3, CD226, and genes that encode thyroid-stimulating hormone receptors (TSH-R). Other things that can increase Graves’ disease risk include stress, smoking, iodine intake, and viral infections.

PATHOGENESIS

In Graves’ disease, the immune system recognizes thyroid cells as antigens and produces Thyrotropin Receptor Antibody (TRAb); these antibodies can increase thyroid gland stimulation and play a role in inhibiting thyroid gland stimulation. Graves’ disease’s severity is influenced by the balance of these antibodies’ stimulatory and inhibitory effects. Besides TRAb, antibodies against thyroid peroxidase are also found in patients with Graves’ disease. The occurrence of hyperthyroidism in Graves’ disease is caused by the formation of Thyroid Stimulating Immunoglobulin (TSI), which is synthesized in the thyroid gland, bone marrow, and lymph nodes. Thyroid Stimulating Immunoglobulin will attach to thyrotropin receptors in the thyroid gland and stimulate thyroid hormone formation by the thyroid gland.

Proinflammatory cytokines also play a role in the clinical manifestations of Graves’ Disease. Infiltration of T cells and B cells into the thyroid gland causes the release of proinflammatory cytokines in the thyroid gland, such as Interleukin 1β, 6, 12, TNF-α, and Interferon γ, which will cause local inflammatory process and thyroid cells hyperplasia. Infiltration of T cells and B cells is also found in the eye muscles, where it also causes an
inflammatory process involving proinflammatory cytokines such as Interleukin 1β, 6, 8, and 16, TNF alpha and CD40 ligand. Inflammatory processes that occur coupled with infiltration of CD34 + fibrocytes stimulate hyaluronan and glycosaminoglycan synthesis, causing tissue remodeling in the orbital region and accumulation of fat tissue and orbital muscle edema. Infiltration of T cells and B cells also occurs in the orbit because the muscle cells in orbit also express thyrotropin receptors on their surface.10,11

**CLINICAL MANIFESTATION**

An increase in thyroid hormone activity causes clinical manifestations of Graves' disease. Some of the symptoms that can arise include hyperactivity, irritability, heat intolerance, fatigue, insomnia, and concentration problems. Unexplained weight loss can also occur due to an increase in body metabolism. Neurological manifestations that can occur include tremors, hyperreflexia, muscle wasting, and myopathy. Hypokalemic periodic paralysis sometimes also occurred in thyrotoxicosis. Cardiovascular manifestations can also occur and are associated with the patient's symptoms of palpitations. Cardiovascular disorders that often occur include supraventricular tachycardia, sinus tachycardia, and increased systolic blood pressure. Some patients, especially those aged over 50 years more often experience atrial fibrillation.12

The patient's skin is usually warm and moist, palmar erythema, and onycholysis can be found. Enlargement of the thyroid gland (Goiter) can also occur due to the thyroid gland's inflammation and hyperplasia. Increased frequency of defecation occurs because of a decrease in food transit time in the gastrointestinal system. Osteopenia can occur due to the effect of thyroid hormone on bone resorption; in some patient's osteopenia can cause fractures. Mild hypercalcemia can happen in 20% of patients, but hypercalciuria is more common.13

Extra-thyroid clinical manifestations can occur in the form of ophthalmopathy, such as lid retraction, proptosis, periorbital edema, sclera injection, and keratitis exposure. Five until ten percent of patients with severe periorbital edema can experience diplopia. Edema can also cause optic nerve suppression and lead to papilledema and loss of vision. Other clinical manifestations that are rarely found include Graves' dermatopathy, in which there is thick pink or purple colored skin that resembles orange skin, usually happened in the tibia. Less than 1% of patients can also experience clubbing fingers called Graves' acropachy.13,14

Thyroid storm is a rare clinical condition caused by exacerbation of hyperthyroid symptoms with multiorgan involvement. The mortality rate of thyroid storm is 30%. Symptoms include fever, delirium, tachycardia, heart failure, nausea, vomiting, agitation, stupor, convulsions, diarrhea, and jaundice. Thyroid storm is usually precipitated in the presence of concomitant diseases such as stroke, diabetic ketoacidosis, trauma, and surgery.13

**LABORATORY INVESTIGATION**

Investigations that are routinely carried out to establish the diagnosis of Graves' disease include examining TSH, FT4, and T3 levels. In Graves' disease, an increase in FT4 and T3 levels is accompanied by decreased TSH levels in the blood. In subclinical hyperthyroidism, normal levels of FT4 and T3 will be found along with low TSH levels. If the lab results lead to subclinical hyperthyroidism, it is necessary to evaluate and doing follow up in 6 to 12 weeks.13

In conditions where the diagnosis is still doubtful with the above examination, several other investigations can be done to establish a diagnosis of Graves' disease, including examination of Thyroid Receptor Antibody (TRAb) where this examination is available in 2 types of assay, namely Thyrotropin Stimulating Immunoglobulin (TSI) and Thyrotropin Binding Inhibitory Immunoglobulin (TBI) assays.13,15 Another possible test is Radioactive Iodine uptake, where this examination uses Radioactive Iodine given to the patient, then determined if there is an increase in the concentration of uptake of radioactive iodine in the thyroid gland. In Graves' Disease, usually, iodine radioactive uptake is high. Finally, a thyroid ultrasound examination can be performed if the above examination cannot be done; thyroid ultrasound in Graves' Disease will increase thyroid activity and increased blood flow and vasculature in the thyroid gland.16,17

**MANAGEMENT**

Management of hypothyroidism in Graves' Disease aims to reduce the activity of thyroid hormone in the body. Some therapeutic modalities are available to date, including anti-thyroid drugs, Radioactive Iodine, and surgery.

**Anti-thyroid drugs**

Anti-thyroid drugs available today and are widely used include thionamides, namely carbimazole, methimazole, and propylthiouracil (PTU). These drugs can reduce thyroid hormone production by inhibiting the action of the enzyme thyroid peroxidase, which functions to oxidize iodide ions in the process of thyroxin and triiodothyronine
formulation. Prophylitiouracil also inhibits the conversion of T4 to T3. Carbimazole and methimazole have lighter side effects than PTU. Prophylitiouracil has hepatotoxic side effects, so its use is mainly aimed at first-trimester pregnant patients, patients with thyroid storm, and patients who cannot tolerate the use of carbimazole or methimazole. The therapeutic dose of carbimazole or methimazole is 10–20 mg every 8 to 12 hours, while the PTU dose is 100–200 mg every 6 to 8 hours. The monitoring of therapy is carried out every 4 to 6 weeks by looking at free T4 levels. If normal T4 levels have been reached, it can be continued with a maintenance dose of Carbimazole and methimazole of 2.5 to 10 mg and a maintenance dose of PTU of 50–100 mg. Remission with anti-thyroid medication is usually achieved in 30–60% of cases after 12–18 months.\textsuperscript{13,16} Recurrence is difficult to predict and is usually determined by geography and demographic factors such as smoking habits, clinical severity, and the patient’s allergic status. If remission has been achieved and the patient is in the euthyroid state, thyroid function monitoring must be continued periodically. Some side effects that may appear on the use of anti-thyroid drugs include minimal side effects in the form of a rash, urticaria, and joint pain, major side effects including hepatitis (especially on PTU), cholestasis, and agranulocytosis. If minimal side effects occur, the drug does not need to be stopped and can be replaced with another anti-thyroid drug; if major side effects appear, the drug should be stopped immediately and replaced with other therapeutic modalities.\textsuperscript{17,18}

Propanolol or other selective beta-blocker B1 can be given to treat cardiovascular manifestations of Graves’ disease. Propanolol 20–40 mg every 6 hours is recommended to treat arrhythmias. In addition, anticoagulants also need to be given to prevent emboli formation in patients with atrial fibrillation. In this case, the administration of warfarin is recommended with cardiologist monitoring.\textsuperscript{13}

**Radioiodine Therapy**

Radioiodine is a therapy that can be started early or used as an alternative after relapse in anti-thyroid drugs. Radioiodine works by destroying thyroid cells. Radioiodine is contraindicated in pregnant women, breastfeeding, and patients with severe ophthalmopathy. In patients who are likely to experience complications from hyperthyroid conditions, such as the elderly and patients with cardiovascular disorders, methimazole and beta-blockers should be administered before being given radioiodine. Methimazole and beta-blockers must be stopped 2–3 days before administration of radioiodine to maximize radioiodine uptake in the thyroid gland and can be continued 3 to 7 days after administration of radioiodine to the patients that risk of developing thyrotoxicosis. Radioiodine I-131 is given orally through capsules or liquids; the dose is given ranges from 10–15 mCi, before I-131 is given, the patients must be educated about radiation safety procedures to prevent family exposure to members and people around them. With radioiodine therapy, the euthyroid state can usually be achieved in 6–8 months. Most patients will experience hypothyroidism after radioiodine therapy; if a hypothyroid condition occurs, which is indicated by a decrease in FT4 levels, levothyroxine can be given, followed by periodic monitoring thyroid function. If the hyperthyroid condition persists after six months of radioiodine therapy, the therapy is considered failed and can be repeated.\textsuperscript{15,19}

**Thyroidectomy**

Thyroidectomy would be one of Graves’ disease’s therapeutic modalities if the use of anti-thyroid medication failed. Before surgery, patients are given anti-thyroid drugs and potassium iodide preparations orally for 7–10 days to prevent thyrotoxicosis due to manipulating the thyroid during surgery and reducing thyroid vascularization to minimize the risk of bleeding. Some complications of surgery include bleeding, laryngeal edema, hypoparathyroidism, and damage to the laryngeal nerve.\textsuperscript{20,21}

**Treatment of Graves’ Disease in pregnancy**

In pregnancy, anti-thyroid drugs are recommended to be used as first-line therapy. In the first trimester of pregnancy, it is recommended to use PTU, and in the second and third trimesters, it is recommended to use carbimazole/methimazole. Because of the ability of anti-thyroid drugs to penetrate the placenta and cause hypothyroid conditions in the fetus, the anti-thyroid medication dose is adjusted until it reaches the target therapy level of FT4 at the upper limit. The thyroid function must be monitored every month. In breastfeeding mothers, the use of anti-thyroid drugs in low doses is said to be safe.\textsuperscript{13,22}

**Ophthalmopathy Management**

In mild ophthalmopathy of Graves’ Disease, artificial tears can be given to prevent eye irritation and oral glucocorticoids from reducing inflammation. Elevation during sleep is also recommended.\textsuperscript{23} In patients with symptoms of moderate to severe ophthalmopathy, an ophthalmologist should be consulted, and a systemic glucocorticoid can be given in the form of oral prednisone 100 mg for one to 2 weeks and then tapered over 6-12 weeks or...
with intravenous methylprednisolone 500 mg per week for six weeks followed by 250 mg per week for six weeks. Therapy with irradiation and emergency decompression can also be an option. In the state of an inactive ophthalmopathy, rehabilitative surgery to reduce proptosis and restore function is preferred, surgery starts from orbital decompression, bony decompression, strabismus repair to eyelid repair.24,25

**Thyroid Crisis Management**

Intensive care and supportive treatment are needed to manage thyroid storm; treatment of comitant diseases also needs to be done. High doses of PTU (500-1000 mg loading dose followed by 250 mg every 4 hours) are given to reduce thyroid hormone synthesis, high dose PTU also has the effect of inhibiting the conversion of T4 to T3. One hour after PTU administration, stable iodides such as potassium iodide or Lugol can be done to inhibit thyroid hormone formation. High dose propranolol (60-80 mg) can be given to reduce tachycardia and other manifestations of beta-adrenergic. High dose propranolol is the first choice because, in high doses, propranolol inhibits the conversion of T4 to T3. The provision of other drugs such as glucocorticoids or antibiotics can be given if there is an infection.3,13

**CONCLUSION**

Graves' disease is the most common cause of hyperthyroid conditions in the world. Graves' disease can attack various age groups and decrease the quality of life and death. Genetic and environmental factors play a role in the development of Graves' Disease. The diagnosis can be made through history taking, physical examination, and laboratory investigation. The main treatments include the administration of anti-thyroid drugs, radioiodine, or surgery. Specific management needs to be considered, especially in pregnancy and exacerbation conditions (thyroid storm). Periodic monitoring is required in patients who have experienced remission to prevent relapse.

**CONFLICT OF INTEREST**

The authors declare that there is no competing interest regarding the manuscript.

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**AUTHOR CONTRIBUTION**

All of the authors equally contributed to the study from the conceptual framework, data gathering, and data analysis until interpreting the study results on publication.

**REFERENCES**


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