GRAVES DISEASE

Prettysun Ang Mellow[1]

ABSTRACT

Graves' disease is one of the most common autoimmune diseases. The disease is named after the scientist Robert James Graves, who first described it in the 19th century as a syndrome with an enlarged and overactive thyroid gland (hyperthyroidism due to circulating autoantibodies), rapid heart rate, and eye abnormalities.

Graves' disease is the most common cause of hyperthyroidism and affects more women than men. Graves' disease can appear at any age, but it most commonly appears for the first time between the ages of 20 and 40. The factor is a predisposition that is more dominant than environmental factors.

There are circulating autoantibodies produced by B lymphocytes induced by autoreactive T lymphocytes that recognize thyrotropin-stimulating hormone (TSH) receptors in thyroid tissue as self-antigens. These autoantibodies are also known as TSH receptor antibodies (TSH-R Ab), thyrotropin stimulating antibodies (TSI), or thyrotropin receptor antibodies (TRAb). TRAb acts like TSH to cause thyroid hyperplasia (diffuse goiter), increased synthesis, and excessive and uncontrolled secretion of thyroid hormones (T4: tetraiodothyronine T4 and T3: triiodothyronine T3).

Investigations to confirm Graves' disease show elevated thyroid hormones (T4 and T3) with very low TSH and increased TRAb. On thyroid ultrasound, most patients have a hypervascular and hypoechoic diffusely enlarged thyroid gland.

The treatment for Graves' disease is to reduce the synthesis of thyroid hormones using antithyroid drugs or to reduce the amount of thyroid tissue with radioactive iodine (RAI) or total thyroidectomy. Methimazole is the first-choice antithyroid drug with good effectiveness and safety. Although the recurrence rate after stopping the drug is still quite high

Keywords: *Graves' disease, hyperthyroidism, review*

ABSTRAK

Penyakit Graves (PG) merupakan salah satu penyakit autoimun yang sering dijumpai. Penyakit ini dinamai sesuai ilmuwan Robert James Graves, yang pertama kali mendeskripsikannya pada abad ke-19 sebagai sindrom dengan kelenjar tiroid yang membesar dan overaktif (hipertiroid akibat autoantibodi yang bersirkulasi), detak jantung yang cepat dan kelainan mata.

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PG merupakan penyebab hipertiroid yang paling sering dan lebih banyak diderita perempuan daripada laki-laki. PG dapat terjadi pada semua umur tapi paling sering muncul pertama kali umur 20-40 tahun. Faktor genetik merupakan predisposisi yang lebih dominan dibandingkan faktor lingkungan.

Terdapat autoantibodi di sirkulasi yang dihasilkan oleh limfosit-B yang diinduksi limfosit T autoreaktif yang mengenali reseptor *Thyrotropin Stimulating Hormone* (TSH-R) pada jaringan tiroid sebagai *self-antigen*. Autoantibodi ini disebut juga sebagai TSH receptor antibody (TSH-R Ab) atau *Thyrotropin Stimulating Antibody* (TSI) atau *Thyrotropin Receptor Antibody* (TRAb). TRAb bekerja seperti TSH yang menyebabkan hiperplasia tiroid (struma difus), peningkatan sintesis dan sekresi berlebihan dan tidak terkontrol dari hormon tiroid (T4: *tetraiodothyronine* T4 dan T3: *triiodothyroxine* T3).

Pemeriksaan penunjang untuk memastikan PG adalah peningkatan hormon tiroid (T4 dan T3) dengan TSH yang sangat rendah, dan TRAb meningkat. Sebagian besar pasien didapatkan pembesaran kelenjar tiroid difus yang hipervaskular dan hipoekhoik pada pemeriksaan ultrasound tiroid.

Tatalaksana PG adalah menurunkan sintesis hormon tiroid menggunakan obat anti tiroid, atau mengurangi jumlah jaringan tiroid dengan *radioactive iodine* (RAI) atau tiroidektomi total. *Methimazole* merupakan anti tiroid pilihan pertama dengan efektivitas dan keamanan yang baik meskipun angka kekambuhan sesudah penghentian obat masih cukup tinggi.

Kata Kunci: Penyakit Graves, Hipertiroidismhipertiroidism, Review*review*.

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BACKGROUND

Graves' disease is one of the most common autoimmune diseases in clinical practice. The disease is named after the scientist Robert James Graves, who first described it in the 19th century as a syndrome with an enlarged and overactive thyroid gland (hyperthyroidism due to circulating autoantibodies), rapid heart rate, and eye abnormalities[1].

Graves' disease is the most common cause of hyperthyroidism and affects more women than men. Although Graves disease can occur at any age, it most often appears for the first time between the ages of 20 and 40. Clinical manifestations in the elderly are often non-specific, and goiter is not always found.[2,3,4].

Autoantibodies were found in thecirculation caused by limfosit-B,

activated by limfosit T, which identified the receptor Thyrotropin Stimulating Hormone (TSH-R) on the thyroid gland as a self-antigen. This autoantibody is also known as TSH receptor antibody (TSH-R Ab), Thyrotropin Stimulating Antibody (TSI), or Thyrotropin Receptor Antibody (TRAb). TRAb functions similarly to TSH it causes thyroid hyperplasia (struma diffuse), increases synthesis and secrecy, and is not controlled by thyroid hormones (T4: tetraiodothyronine T4 and T3: triiodothyronine T3). [2,3]

Most Graves' disease patients have diffuse goiter and clinical manifestations due to increased thyroid hormone (hyperthyroidism), such as weight loss, tachycardia, fine tremors, excessive sweating, difficulty sleeping, anxiety, menstrual disorders, hair loss, intolerance to hot temperatures. Patients with Graves' disease also frequently have exophthalmos (Graves' ophthalmopathy). Other rare manifestations are pretibial myxedema (Graves' dermopathy) and acropachy. [2,3]

Etiology

There is no single etiology for Graves' disease, but rather an interaction between genetic and environmental factors. Approximately 15% of Graves' disease patients have a family history of this disease, and 50% of family members of Graves' disease patients have thyroid autoantibodies detected in their blood. While environmental factors as triggers include stress, smoking, excessive iodine exposure, pregnancy, postpartum, vitamin D deficiency, and use of highly active antiretroviral therapy (HAART) in HIV/AIDS patients due to the immune reconstitution of HIV patients. Graves' disease can also be triggered by infections, such as after infection with SARS CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) and chronic hepatitis C.[3,5,6]

Epidemiology

The annual incidence of Graves' disease is around 20-50 cases per 100,000 people, and it is the most common cause of all cases of hyperthyroidism. The most affected age is between 20-40, but this disease can affect any age. Women are six times more at risk of developing hyperthyroidism than men.[3,5]

According to the 2013 Basic Health Research, approximately 700,000 (0.4%) of Indonesia's population aged >15 years suffer from hyperthyroidism, with a 0.6% incidence rate in women and a 0.2% incidence rate in men.[7]. The cause of hyperthyroidism is graves' disease, while other causes include struma multinodular toxic and toxic adenoma.[3]

Pathogenesis and Clinical Manifestations

Graves' disease is an autoimmunity disorder in which Thyrotropin Stimulating Hormone Receptor Antibody (TSH-R Ab) or Thyrotropin Receptor Antibody (TRAb)

acts as an autoantibody, and Thyrotropin Stimulating Hormone Receptor (TSH-R) acts as a self-antigen.Limfosit B (diinduksi oleh Limfosit T yang autoreaktif) mensintesis TRAb primarily in tiroid sel-sel, but also in kelenjar getah bening dan sumsum tulang.TRAb, also known as TSH-R, is a medication used to prevent thyroid hyperplasia (diffuse thyroid), improve thyroid function, and prevent thyroid hormone (T4: tetraiodothyronine T4; T3: triiodothyronine T3) production. Other self-antigens found in Graves' disease include thyroglobulin, thyroid peroxidase, and sodium-iodide symporter, but not TSH-R. [2,3]

Increased thyroid hormone in circulation, or hyperthyroidism, affects various organ systems of the body, including:

1. Cardiovascular system:

   An increase in the number and affinity of beta-adrenergic receptors in the heart increases inotropic and chronotropic with clinical manifestations of palpitations, wide pulse pressure (very low diastolic blood pressure so that the distance between systolic and diastolic blood pressure is very wide), sinus tachycardia, and atrial fibrillation. Hyperthyroid patients may develop isolated systolic hypertension due to increased cardiac output and heart rate while decreasing systemic vascular resistance. In the long term, heart muscle remodeling can cause congestive heart failure.[8]

2. Musculoskeletal system

   Hyperthyroidism can cause proteolysis so muscle mass will decrease, and there will be muscle weakness. In some patients, especially young Asian men, sudden muscle weakness associated with hyperthyroidism (thyrotoxic periodic paralysis) may occur. Thyrotoxicosis—periodic paralysis—is an emergency due to hyperthyroidism, in which high thyroid hormone causes increased activity of the Na+K+ATPase pump so that potassium ions move quickly from extracellular to intracellular and hypokalemia and muscle weakness occur (often paraparesis).[3]

   Hyperthyroidism also causes accelerated bone remodeling, reduces bone density, causes osteoporosis, and increases the risk of fractures. Abnormalities in this bone can be reversible but irreversible, even though they are euthyroid.[9]

3. Nervous system

   Hyperthyroidism causes a sympathovagal response, which includes increased sympathetic nerve activity (tachycardia, tremor, sweating, anxiety) and decreased vagal or parasympathetic activity. Hyperthyroidism also affects the central

nervous system so thatit can cause insomnia and anxiety.[2,10]

4. Digestive system

   Hyperthyroidism causes an increase in intestinal peristalsis, which can result in hyper defecation. Patients generally eat a lot but continue to lose weight. Lactose intolerance, abdominal pain, nausea, and vomiting may also occur in hyperthyroid patients.[2,10]

5. Metabolism

   Hyperthyroidism increases the basal metabolic rate and increases lipolysis and proteolysis, causing rapid weight loss. Increased LDL receptor expression in the liver causes a decrease in LDL cholesterol levels. Hyperthyroidism can increase gluconeogenesis so that blood sugar levels can increase.[2,3,10]

6. Others

   Graves orbitopathy (ophthalmopathy) is caused by inflammation, cellular proliferation, and growth of extraocular muscles, connective tissue, and retro-orbital fat under the influence of TRAb and cytokines secreted by cytotoxic T lymphocytes. These cytokines and TRAb activate fibroblasts and preadipocytes, leading to the excessive synthesis of hydrophilic glycosaminoglycans (GAG) and the growth of retro-orbital fat. Glycosaminoglycans cause muscle swelling with water retention. These changes lead to proptosis, lid lag, diplopia, congestion, and periorbital edema.[2,11]

   Pretibial myxedema (the skin becomes tight and difficult to pinch) and thyroid acropachy (abnormalities in the joints) are rare manifestations whose pathogenesis is unknown but which are presumably related to cytokines-mediated stimulation of fibroblasts in Graves' disease.[3]

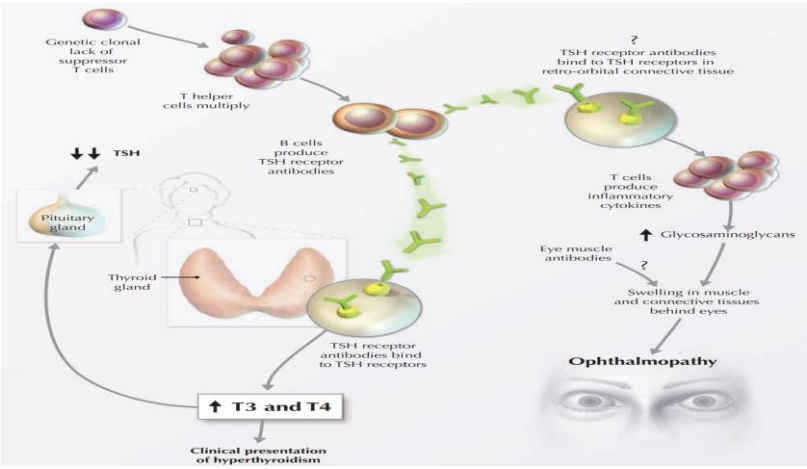

Figure 1. *Grave's Disease Pathogenesis.* TSH = *thyroid-stimulating hormone*, T3 = *triiodothyronine*, T4 = *thyroxine*.

DIAGNOSE

Most graves' disease patients present with the classic clinical signs and symptoms of hyperthyroidism, accompanied by diffuse goiter and exophthalmos, which are confirmed by TSH and FT4 examinations.[2,4] A TRAb examination is theoretically important in determining the cause of hyperthyroidism and a guideline for discontinuing treatment once hyperthyroidism has been controlled.

Clinical appearance may vary depending on age at onset, severity, and duration of hyperthyroidism. In some cases, goiter and exophthalmos were not found, so clinical symptoms and thyroid function tests were the basis for the diagnosis. In the elderly, symptoms may be subtle or mild and may present with nonspecific signs and symptoms such as fatigue, weight loss, and atrial fibrillation. This atypical appearance of hyperthyroidism in the elderly is known as apathetic thyrotoxicosis. If there is unexpected weight loss or tachycardia in elderly patients, thyroid function should be evaluated. Even if a patient is asymptomatic, the American Academy of Family Physicians (AAFP) recommends screening thyroid function tests in patients over the age of 60.[4]

History and Physical Examination

In young patients, the clinical appearance generally includes heat intolerance, sweating, weight loss, palpitations, hyper defecation, and tremors. Other clinical features include insomnia, anxiety, restlessness, hyperkinesia, shortness of breath, muscle weakness, itching, polyuria, oligomenorrhea or amenorrhea in women, loss of libido, and neck fullness. Ocular symptoms include eyelid swelling, ocular pain, conjunctival hyperemia, and diplopia. Palpable goiter is more common in patients under 60 years of age. Approximately 10% of patients, particularly children, and adolescents, may gain weight.[2,10]

Physical examination of hyperthyroidism can reveal tachycardia, systolic hypertension with wide pulse pressure, signs of heart failure (edema, crackles, increased JVP, tachypnea), atrial fibrillation, fine tremor, hyperkinesia, hyperreflexia, warm and clammy skin, palmar erythema, onycholysis, hair loss, diffuse goiter with thyroid bruit, and altered mental status (anxiety, irritability, and restlessness).[2,10]

Extrathyroidal signs of Graves' disease include ophthalmopathy, such as eyelid retraction, proptosis, periorbital edema, chemosis, scleral injection, and exposure keratitis. Thyroid dermopathy causes skin thickening, especially over the tibia; this disorder is rare, making up only 2–3 percent of all Graves disease cases. Thick skin that looks like an orange peel (peau d'orange appearance) and is difficult to pinch is also called pretibial myxedema.

Bone involvement, such as subperiosteal formation and swelling of the metacarpal bones, is called osteopathy or thyroid acropachy. Onycholysis (Plummer nails) and fingers clubbing are rare.[2,3,10]

Diagnostic Examination

Thyroid Function Test to diagnose hyperthyroidism:

The most important results of the initial examination are TSH and free T4. It is called hyperthyroidism if TSHs are suppressed (usually very low), and FT4 is increased. However, if TSHs are suppressed, but FT4 is normal, this condition is called subclinical hyperthyroidism. In addition, FT3 levels are also usually increased, and in graves' disease, the FT3/FT4 ratio is usually > 0.3 (SI units).[2,3]

Test to differentiate Graves' disease from other causes of hyperthyroidism

1. Typical clinical presentations include ophthalmopathy (orbitopathy), diffuse goiter, thyroid bruit, family history of graves' disease, and pretibial myxedema (rare).
2. Ultrasonography of the thyroid found diffuse enlargement of the thyroid gland, hypoechoic tissue, and hypervascularization.
3. TRAb has been increased. This examination is important to confirm the cause of hyperthyroidism and to serve as a guide in determining the discontinuation of antithyroid therapy, also in patients with suspected Graves' ophthalmopathy but normal thyroid function tests. It is sometimes necessary for pregnancies with a previous history of Graves' disease to determine the possibility of fetal or neonatal hyperthyroidism because these antibodies can cross the placenta.
4. Radioactive iodine uptake scan with I-123 or I-131: In Graves' disease, the uptake will be high and diffuse, while in toxic nodules, the uptake is focal, known as "hot nodules." In toxic multinodular goiter, uptake is heterogeneous. In subacute or silent thyroiditis, factitious hyperthyroidism and recent iodine load uptake will be low.
5. Others: Patients with hyperthyroidism may also have microcytic anemia, thrombocytopenia, hyperbilirubinemia, increased serum transaminase, increased alkaline phosphatase, hypercalcemia, low LDL and HDL, and hypokalemia.[2,3]

Differential Diagnosis

1. Toxic multinodular goiter
2. Hashimoto's thyroiditis
3. Anxiety disorders
4. Thyroid cancer[2,3]

THERAPY

Graves' disease management aims to relieve clinical syndromes due to hyperthyroidism, prevent complications,

and control excess thyroid hormone. If serious complications such as heart failure, atrial fibrillation with the rapid ventricular response, severe ophthalmopathy, or a thyroid storm have occurred, multidisciplinary management is required.[2,12]

Treatment of the clinical hyperthyroid syndrome

The clinical syndrome will subside when thyroid hormone levels return to normal, but this situation takes time, so symptomatic therapy is needed to treat complaints related to hyperthyroidism. When euthyroid is reached, the symptomatic medication can be reduced or discontinued.[2,12]

If there is tachycardia, systolic hypertension, a history of cardiovascular disease, or old age, beta blockers can be given. Propranolol, at doses of 10–40 mg every 6–8 hours a day, is often used because, apart from reducing tachycardia, it also has the potential to inhibit the conversion of T4 to T3 in peripheral tissues. Apart from propranolol, atenolol and bisoprolol can also be used at a dose of once a day. If are allergic to beta-blockers, can control heart rate with calcium channel blockers such as diltiazem and verapamil.[2,12]

Patients with insomnia or excessive anxiety may be given a sedative, but they should be evaluated and preferably treated for no longer than two weeks. Alprazolam 0.25–0.5 mg, diazepam 2–5 mg, clobazam 5–10 mg, or escitazolam 1-2 mg may be given once daily at night if needed.[2,12]

Reducing thyroid hormone

Until now, there have been three modalities of hyperthyroid therapy in Graves' disease, namely:

1. Antithyroid drugs (ATDs), which inhibit thyroid hormone synthesis and secretion. Treatment is generally long-term, with dose adjustments based on the results of thyroid function tests. About 30% of patients have complete remission and do not require antithyroid drugs.
2. Radioactive iodine (RAI), damages thyroid tissue so that thyroid hormone synthesis decreases.
3. Total thyroidectomy, removes the entire thyroid gland so that it no longer produces thyroid hormone.[2,12]

Although the use of antithyroid drugs is the most common, there are certain considerations for choosing the modality of radioactive iodine (RAI) or total thyroidectomy. Therefore, every patient needs to get an explanation regarding the modalities of therapy that will be undertaken.[2,12]

Antithyroid drugs (Thionamides)

Methimazole (MMI), carbimazole (an MMI derivative that is rapidly metabolized to methimazole), and

propylthiouracil (PTU) are the available antithyroid drugs. This drug inhibits thyroid peroxidase (TPO), which mediates the iodination of thyroglobulin in the thyroid gland, inhibiting the synthesis of T3 and T4. PTU can inhibit the conversion of T4 to T3 in peripheral tissues, while MMI is thought to inhibit the formation of TRAb autoantibodies. MMI is the drug of choice because of its less frequent side effects, especially hepatotoxicity, once-daily dosing, and faster reach of euthyroid levels. [10.11.15]

In the first trimester of pregnancy, it is preferable to use PTU because of its fewer teratogenic side effects. However, in the second and third trimesters, you can use MMI. In cases of thyroid storm, PTU is preferred because it inhibits the peripheral conversion of T4 to T3. PTU may be considered in patients who are unresponsive to MMI and refuse surgery or RAI therapy.[2,12]

The MMI dose can be given once a day or in divided doses (2–3 times). The following are guidelines for starting therapy based on the patient's FT4 level:

Table 1. Guideline for antithyroid drug administration

Kadar FT4	**Anti Thyroid Dose**
FT4 1-1,5 x ULN (*upper limit normal*)	Methimazole 5-10 mg daily
FT4 1,5 – 2 x ULN	Methimazole 10-20 mg daily
FT4 2 – 3 x ULN	Methimazole 20 – 30 mg daily
FT4 > 3 x ULN	Methimazole 30 – 40 mg daily

The PTU dose is equivalent to methimazole 10:1, but the frequency of administration is 2-3 times a day because of its shorter half-life. If FT4 becomes normal or below normal, the dose is reduced by 30–50% to the smallest dose capable of maintaining normal thyroid hormone. A methimazole maintenance dose is 5-10 mg daily, while PTU is 50 mg, 2-3 times daily. An examination can be repeated every four weeks at the start of therapy to adjust the dose; then it can be extended every 2-3 months or every 3-4 months when thyroid hormones are stable and normal. TSHs also need to be checked, although they often remain suppressed even when thyroid hormones are normal or less than normal[2,12]. Although FT4 is normal, treatment is generally long-term. If the MMI or PTU maintenance dose achieves normal FT4

levels while also normalizing TSHs and TRAb, the drug can be stopped after 12-18 months. After that, it is closely monitored every 2-3 months for the first 6 months, then every 4-6 months for the next 6 months, and every 6 months for the next 12 months. If TSHs remain normal for a year without therapy, yearly monitoring of TSH is sufficient. Approximately 30% of Graves' disease patients can experience complete remission; the rest remain on long-term drugs or undergo other treatment modalities[2,12].

Suppose an increase in serum transaminase is more than 3x ULN, the anti-thyroid drug needs to be stopped while evaluating whether it is related to drug side effects. For mild side effects such as pruritus, urticaria, and rash, antithyroid drugs can still be continued by adding antihistamines or trying to change the type of drug (from MMI to PTU or vice versa). If the skin disorder persists, it is advisable to choose RAI or thyroidectomy. Complete blood count and liver function tests should be performed before starting therapy. Other side effects are arthritis, agranulocytosis, and vasculitis (very rare) [2,12,18].

RAI therapy

Using I-131, which is given in capsule or liquid form, the dose is calculated based on thyroid volume, RAI uptake, and local factors. Although not a primary choice, this therapy is considered in Graves' disease patients who do not respond to thionamide therapy or fail to achieve remission after 18 months of therapy, have allergies or contraindications to the use of thionamide, or are high-risk patients (with co-morbidities) for thyroidectomy surgery.[2,12]

RAI therapy requires an adult patient over 21 who is not pregnant or planning to become pregnant for 6–12 months after treatment. Contraindications to RAI therapy are pregnancy, breastfeeding, thyroid cancer, patients with moderate-to-severe Graves' ophthalmopathy (potentially worsening after RAI therapy), and patients who cannot follow radiation safety protocols.[2,12]

Thyroidectomy

Thyroidectomy is recommended for patients with very large thyroid size (> 80 grams), symptoms of compression of the anterior colli, concomitant thyroid cancer, large thyroid nodules (> 4 cm), cold nodules, concomitant parathyroid adenomas, and high TRAb levels. Very high and moderate to severe Graves' ophthalmopathy.[2,12]

Patients undergoing total thyroidectomy will be prepared with thionamide administration to achieve or approximate euthyroid status and beta blockers (if needed) before surgery. To reduce vascularization, administer potassium iodide, Lugol's solution mixed with water or fruit juice, three times per day, 7–10 days before surgery. Calcium and

vitamin D checks are needed before surgery so that they can be corrected if a deficiency occurs.[2,12]

Other therapies for hyperthyroidism in Graves' disease

Iodinated contrast agents, sodium iodate, and iopanoic acid inhibit the peripheral conversion of T4 to T3. This drug is not used alone but with methimazole because its single-use can cause resistant hyperthyroidism. Glucocorticoids are used as adjuvant therapy in cases of thyroid crises.[2,13]

Rituximab has been used in Graves' disease, both as sole therapy and adjuvant therapy, with remission occurring more quickly and with a lower recurrence rate. Rituximab is a chimeric monoclonal antibody that targets B lymphocytes expressing the CD20 molecule on their surface. Rituximab induces B lymphocyte death through direct antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cell death, or apoptosis signaling so that thyroid autoantibody production decreases and the disease is controlled. However, this research is still on a small scale, so further research is needed.[13,14]

COMPLICATIONS

Hyperthyroidism that is not treated properly can lead to complications that increase patient morbidity and mortality. A thyroid storm is one of the acute complications that can threaten the patient's life. A thyroid crisis is an acute exacerbation of hyperthyroidism triggered by other diseases, such as severe infections, pregnancy, or surgery in patients who are still hyperthyroid.[2,3]

Cardiovascular complications also often occur in Graves' disease, such as atrial fibrillation, congestive heart failure, and mitral valve prolapse. Other complications are Graves' ophthalmopathy and Graves' dermopathy.[3,8]

Untreated hyperthyroidism can also affect bone mass and increase the incidence of high bone turnover osteoporosis. Osteoporosis associated with hyperthyroidism mainly occurs in postmenopausal women.[2,9]

PROGNOSIS

In general, graves' disease patients respond well to treatment. Symptoms of hyperthyroidism can decrease rapidly within the first month of therapy, and after that, continue treatment with dose adjustment based on regular monitoring of thyroid function. However, recurrence after stopping antithyroid drugs is still high enough that some patients continue long-term antithyroid drugs.

A study conducted by Mohlin in Sweden in euthyroid graves' disease patients and then the treatment was discontinued (most used methimazole)

found an average recurrence rate of 43.5%. The recurrence rates were 22.6%, 30.2%, 36.9%, and 41.5%, respectively, at 6 months, 1 year, 3 years, and 5 years after stopping treatment. The most important predictors of the recurrence of Graves' diseases were the presence of palpable goiter and a smoking history, while gender differences and methods of antithyroid drug therapy (dose titration vs. block-replace) were not significantly different.[16]

The optimal duration of therapy is 12–18 months. Treatment for less than six months has a high relapse rate, while treatment for more than 18 months does not increase the remission rate. On treatment with antithyroid drugs, ophthalmopathy, and goiter size generally persist or decrease slightly despite achieving euthyroid status and even complete remission.[2,12]

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