Diagnosis and management of Graves' disease

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Abstract

GRAVES' DISEASE IS CHARACTERIZED BY HYPERTHYROIDISM, diffuse goitre, ophthalmopathy and, rarely, dermopathy. Although diagnostic testing is straightforward once Graves' disease is suspected, physicians need to be aware of heterogeneous and even atypical presentations of the disease, particularly in elderly patients. Because morbidity may be associated with even subtle forms of hyperthyroidism, treatment promoting long-term euthyroidism is necessary. Although all of the available treatments are effective, compliance is best assured by a full discussion of the risks and benefits of each approach. This review focuses on issues of diagnosis and management that will allow the primary care physician to identify patients with Graves' disease and guide them to recovery.

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Graves' disease is an autoimmune disorder characterized by hyperthyroidism, diffuse goitre, ophthalmopathy and, rarely, dermopathy. Although thyroid-stimulating hormone (TSH) screening has facilitated the diagnosis of this condition, a heightened awareness of heterogeneous and even atypical presentations is necessary. Although all the available treatments effectively normalize thyroid function, each is associated with potentially serious side effects. In guiding the patient to a treatment decision, the physician should not only be aware of the immediate risks and benefits of therapy but should also consider approaches to best preserve the patient's long-term metabolic health. This review focuses on issues related to the diagnosis and treatment of Graves' disease that will best help the nonendocrinologist meet these objectives.

Pathogenesis

The pathogenesis of Graves' disease is illustrated in Fig. 1. The hyperthyroidism and goitre of Graves' disease are caused by stimulation of the thyroid by TSH receptor antibodies.[1] Production of these antibodies is primarily within the thyroid gland itself,[2] and the immunology underlying this process has been ably described in detail elsewhere.[3] It has been suggested that a genetic clonal lack of suppressor T cells may be responsible for the unregulated production of TSH receptor antibody.[4] Identified predisposing factors for Graves' disease are outlined in Box 1.

There is substantial evidence linking Graves' disease and Hashimoto's thyroiditis. These diseases may cluster in the same family or even coexist in the same patient. Sera of patients with Graves' disease may contain "Hashimoto's-predominant" antibodies to thyroglobulin and thyroid peroxidase. Rarely, "Hashimoto's antibodies," which bind to the TSH receptor and, instead of stimulating, block TSH action (TSH-blocking antibodies), develop during the course of illness and explain observed improvements in the thyroid status of the patient with Graves' disease.[5]

One proposed hypothesis for the pathogenesis of ophthalmopathy is that the immune response to a TSH receptor–like protein in orbital connective tissue initiates cytokine formation, promoting production by orbital fibroblasts of hydrophilic glycosaminoglycans, resulting in increased osmotic pressure, extraocular muscle volume, fluid accumulation and clinical ophthalmopathy.[6] However, eye muscle antigens such as the flavoprotein (Fp) subunit of mitochondrial succinate dehydrogenase, G2s and the FOX P1 protein, a winged helix transcription factor, have also been described and their respective antibodies are clinically useful markers of disease.[7] The respective roles of the connective tissue response and eye muscle antibodies in the pathogenesis of ophthalmopathy are the subject of ongoing investigation.

Clinical findings

Hyperthyroidism

When thyrotoxicosis, goitre and ocular signs and symptoms coexist, the diagnosis of Graves' disease appears self-evident. The clinical features are shown in Table 1 (see also Boxes 2 and 3). However, 50% of patients with Graves' disease may not have clinically detectable ophthalmopathy at presentation,[8] making the diagnosis less obvious. Rarely, findings may predominate in a single organ system (i.e., altered bowel habit, emotional lability, gynecomastia) and distract from the correct diagnosis. Many manifestations of hyperthyroidism, including palpitations and tremor, are due to increased adrenergic tone[9] and may be confused with an anxiety disorder. Elderly patients commonly present in an atypical fashion with only weight loss and anorexia or isolated atrial fibrillation.[10] Elderly patients also tend to have their symptoms for longer periods, have smaller multinodular goitres and do not have ocular signs or symptoms.[11]

The presence of comorbid conditions may also affect the presenting complaint. Worsening emotional lability in a patient with a pre-existing psychiatric disorder, or worsening angina or heart failure in someone with coronary artery disease, may be a clue to superimposed hyperthyroidism. In the patient with diabetes, hyperthyroidism is usually associated with further glucose intolerance or, rarely, hypoglycemia.[12]

Hyperthyroidism may also precipitate an adrenal crisis in patients so predisposed. The presence of other autoimmune condition(s) in the patient or family members may prompt the diagnosis. Hypokalemic periodic paralysis (especially in Asian males) necessitates a search for precipitating Graves' disease.[13] In the absence of a triiodothyronine (T3) level, there may not be a good correlation between the clinical severity of the disease and the degree of hyperthyroidism.[14] Thus, a heightened sensitivity to the heterogeneity of clinical presentation is the best assurance of a prompt diagnosis.

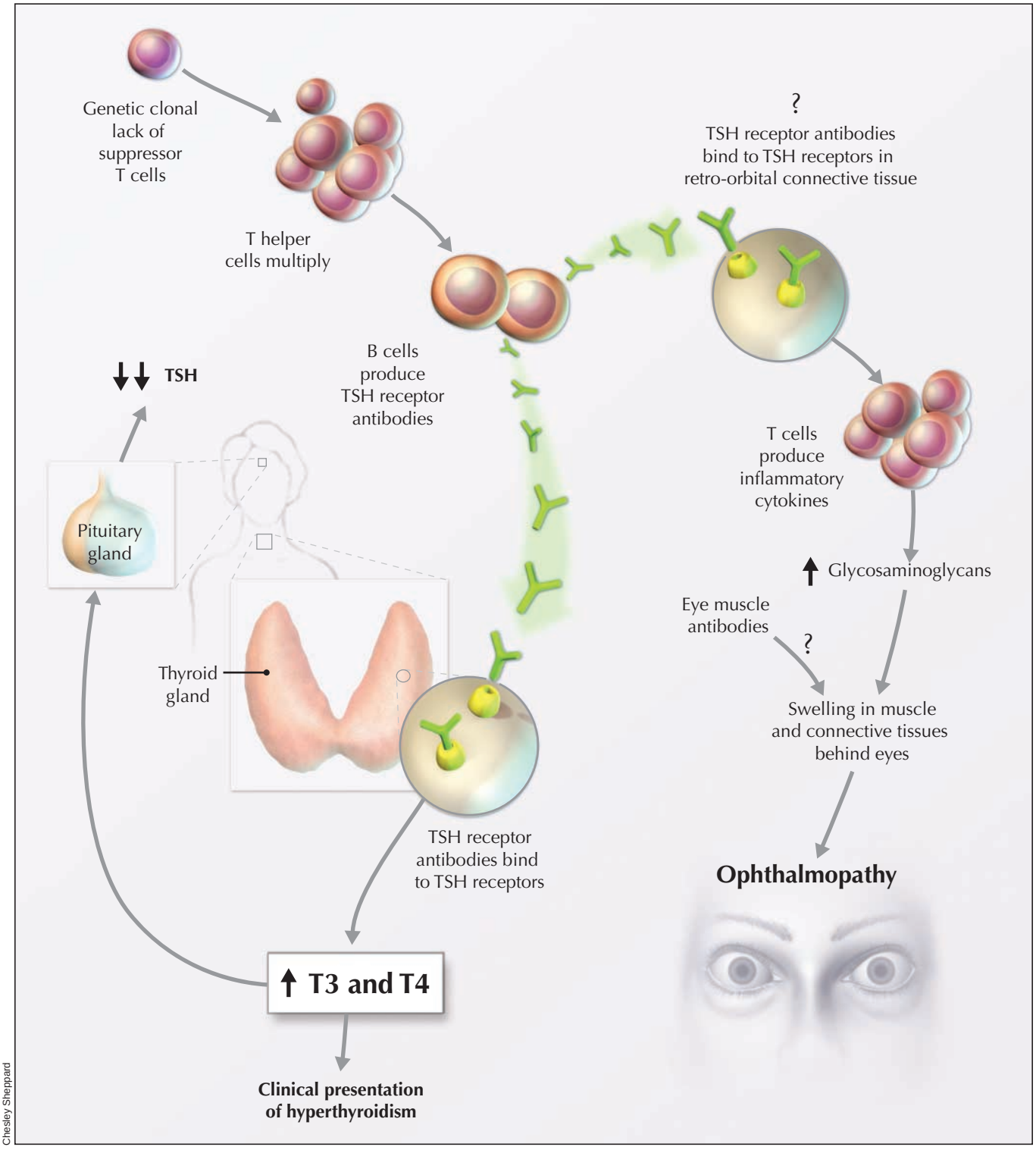

Fig. 1: Proposed pathogenesis of Graves' disease. TSH = thyroid-stimulating hormone, T3 = triiodothyronine, T4 = thyroxine.

Ophthalmopathy and dermopathy

Ophthalmopathy occurs concurrently with hyperthyroidism only 40% of the time.[8] In 10% of patients with ophthalmopathy, thyroid indices are normal, although hyperthyroidism usually ensues within 18 months.[8] Rarely, ophthalmopathy may be associated with Hashimoto's thyroiditis.[8] Ophthalmopathy may worsen with prolonged hyperthyroidism or with hypothyroidism that occurs following treatment.[15] Restoration of euthyroidism in such patients tends to stabilize or improve the coexisting ophthalmopathy.[15] Ophthalmopathy is not necessarily benign. An inability to close the eyelids may lead to corneal ulceration and visual loss. Proptosis and extraocular muscle fibrosis may produce disabling diplopia. A change in colour vision may be the first sign of optic neuropathy caused by optic nerve compression at the apex of the orbit. Correlation among the symptoms, the results of clinical examination and severity of ophthalmopathy may not always be observed, and early consultation with an ophthalmologist experienced in this disorder should be considered for all patients thus affected.

One to 2 percent of patients with ophthalmopathy will also have a localized dermopathy, commonly over the anterior shins (pretibial myxedema), consisting of nonpitting edema with occasional raised, hyperpigmented, violaceous papules. Rarely, lymphedema is observed. Patients with dermopathy have the highest titres of TSH receptor antibodies for reasons that are unclear. Although clinically apparent dermopathy is rare, the prevalence of dermopathy in patients with Graves' disease has been found to be higher when pretibial skin thickness is assessed by ultrasonography.[16] Trauma may initiate or exacerbate this disorder.[17]

Box 1: Predisposing factors for Graves' disease*

Genetic susceptibility (including HLA alleles)

Stress (negative life events)

Smoking (especially associated with ophthalmopathy)

Female sex (sex steroids)

Postpartum period

Iodine (including amiodarone)

Lithium

Rare factors:

- Interferon-α therapy
- Highly active antiretroviral therapy (HAART) for HIV infection
- Campath 1-H monoclonal antibody (for multiple sclerosis)

*See reference 3 for review.

Diagnosis

The hyperthyroidism of Graves' disease may be overt, biochemical or subclinical. All patients exhibit a low or, in most cases, suppressed TSH. In the face of an elevated free thyroxine (FT4) level, hyperthyroidism is confirmed. However, 10% of patients will have an increased total or free T3 level in the face of a normal FT4 and suppressed TSH level, a condition termed "T3 toxicosis."[18] Confirmation of Graves' disease by an increased 24-hour radioiodine uptake (RAIU) is recommended, because painless thyroiditis and Graves' disease have occurred at different times in the same patient.[19] Measurement of levels of circulating TSH receptor antibody may eventually replace the need for the RAIU for confirmation of the diagnosis. However, as thyroid nodules associated with Graves' disease may have a higher likelihood of malignancy and may be more aggressive if cancerous, a thyroid scan is recommended for all patients.[20] Patients whose scans reveal a photopenic ("cold") defect should have directed palpation or ultrasonography to confirm whether a nodule is present, and if so should then undergo fine-needle aspiration biopsy. In patients whose scan reveals a diffuse, patchy uptake with autonomous ("hot") and photopenic areas, the presence of an elevated, circulating TSH receptor antibody level may be the only evidence for coexisting Graves' dis-

Table 1: Clinical features of Graves' disease

Condition	Symptoms	Signs
Hyperthyroidism	Heat intolerance, sweating; palpitations; pruritus; dyspnea on exertion (exacerbation of asthma); weight loss (with hyperphagia), weight gain (rarely); hyperdefecation; tremulousness and tremor; weakness, fatigue; urinary frequency, nocturia, thirst; anxiety, emotional lability, insomnia; restlessness, inability to concentrate; oligomenorrhea/amenorrhea; erectile dysfunction/ gynecomastia; dyspepsia, nausea, vomiting (rare)	Warm, smooth, moist skin; onycholysis (loosening of the nail bed, Plummer's nails), palmar erythema; thinning of the hair; stare, lid retraction (and lag); bright, shiny eyes; tachycardia, atrial fibrillation; widened pulse pressure, hyperdynamic circulation; tremor (fingers); hyperactive reflexes; proximal myopathy
Ophthalmopathy	Eye irritation, dryness, excessive tearing; visual blurring; diplopia; retro-orbital discomfort; pain on eye movement; visual loss	Periorbital edema, conjunctival erythema, chemosis (conjunctival edema), proptosis, ophthalmoplegia, loss of colour vision (optic neuropathy), papilledema (optic neuropathy)

Box 2: Findings associated with Graves' disease

- Diffuse goitre (mild to massive)
- Thyroid bruit
- Thyroid acropachy (clubbing)
- Lymphadenopathy (rare)
- Localized dermopathy (rare)
- Ophthalmopathy

ease (in a pre-existing multinodular goitre) as opposed to a toxic multinodular goitre, especially in older patients. Elderly patients with Graves' disease may also have lower RAIUs because of a pre-existing multinodular goitre. The absence of a raised RAIU in a patient with established features of Graves' disease necessitates the exclusion of a coexisting source of exogenous iodine. An approach to the diagnosis of Graves' disease is shown in Fig. 2.

Antibodies to thyroglobulin and thyroid peroxidase may be present but are not diagnostic. Although TSH receptor antibodies are present in the sera of almost all patients with Graves' disease, their measurement is available only in some areas currently. The most widely used assay for TSH receptor antibodies measures the ability of these immunoglobulins to inhibit the binding of radiolabelled TSH to its receptor in various thyroid tissues (radioreceptor assay). Alternatively, assays to detect thyroid stimulation by TSH receptor antibodies have been established using a well-characterized rat thyroid cell line (FRTL-5) or nonthyroid cells transfected with TSH receptor cDNA and involve the measurement of intracellular cyclic adenosine monophosphate (cAMP) following exposure to Graves' immunoglobulins.[1]

In most patients with Graves' disease who have ophthalmopathy, no further investigation is required. However, in patients with euthyroid or unilateral ophthalmopathy, CT or MRI scanning of the orbits shows the characteristic swelling of the extraocular muscles and increased retroorbital fat associated with Graves' disease.[8]

Treatment

Hyperthyroidism

The goals of treatment of Graves' disease are to control symptoms efficiently and restore euthyroidism. Antithyroid drugs, radioiodine and surgery all effectively restore euthyroidism but have potentially serious side effects. Therefore, it is critical for the patient to be well-informed about available treatment options, their potential effects on future health and to be part of the decision regarding choice of therapy. Accordingly, I recommend that all patients with Graves' disease be seen in consultation by an internist or endocrinologist before instituting specific therapy. The specialist can also arrange for radioiodine therapy if appropriate. The primary care physician will be essential for ongoing support, discussions regarding the choice of therapy, monitoring thyroid function after radioiodine therapy or surgery, and providing ongoing adjustment of β-blockers and antithyroid medication. The most popular treatment for Graves' disease in North America by far is radioiodine.[21] This popularity reflects confidence in its overall safety and effectiveness, concern over the potential consequences of surgery and disappointment in the high relapse rate following treatment with antithyroid drugs. In my experience, failure to treat the hyperthyroidism of Graves' disease definitively may lead to later relapses and subsequent morbidity.

β-Blockers

Increased β-adrenergic activity is responsible for the palpitations, tachycardia, tremulousness, anxiety and heat intolerance associated with this condition. All β-blockers are equally effective in relieving such symptoms,[9] although they have no direct action on thyroid hormone production. Although some β-blockers impair T4-to-T3 conversion, it is unlikely that this effect is of clinical significance. The use of sustained-release propranolol or once daily, long-acting β_1-selective antagonists such as atenolol or metoprolol is recommended.[9] The starting dose of atenolol is 25–50 mg/d but can be increased up to 100 mg/d as required. β-blockade alone is not recommended as sole therapy. Higher doses at the onset of therapy with adjustment as euthyroidism is achieved are required. Treatment with β-blockers can be initiated at presentation before completion of diagnostic testing.

Antithyroid drugs

When considering the use of antithyroid drugs as primary therapy, factors reported to be more likely associated with an immunological remission should be present (Table 2). The presence of high titres of thyroid peroxidase anti-

Box 3: Disorders associated with Graves' disease

Autoimmune disorders

Endocrine: Addison's disease, type 1 diabetes mellitus, primary gonadal failure, hypophysitis, Hashimoto's thyroiditis

Nonendocrine: celiac disease, vitiligo, alopecia areata, myasthenia gravis, pernicious anemia, immune thrombocytopenic purpura, rheumatoid arthritis

Other disorders

Hypokalemic periodic paralysis (particularly in Asian males), mitral valve prolapse

bodies indicates a greater likelihood of remission or even hypothyroidism following antithyroid drug therapy because of autoimmune destruction of the thyroid secondary to superimposed Hashimoto's thyroiditis. Conversely, the absence of these factors should influence the treatment decision to other modalities. The thionamide drugs, propylthiouracil and methimazole, are actively transported into the thyroid gland and inhibit important steps in thyroid hormone synthesis.[22] Propylthiouracil also blocks the 5′-deiodinase that promotes T4-to-T3 conversion; however, it remains uncertain whether this effect is of clinical significance. Although propylthiouracil is more commonly used in North America, there is ample evidence that methimazole should be the antithyroid drug of choice (except for patients who are pregnant or nursing).[22,23] Studies reveal that methimazole is more effective than propylthiouracil at equivalent doses, decreases thyroid hormone levels more rapidly and achieves euthyroidism sooner.[23,24] Because it has a longer half-life, methimazole can be used as a single daily agent and, thus, is more likely to be associated with patient compliance. Most importantly, methimazole would appear to have a more favourable safety profile than propylthiouracil. In one study, agranulocytosis was not observed in subjects taking 30 mg of methimazole or less daily, whereas this complication occurred idiosyncratically with propylthiouracil.[25] Hepatitis and vasculitis also occur more commonly with propylthiouracil.[23] These agents are contrasted in Table 3.

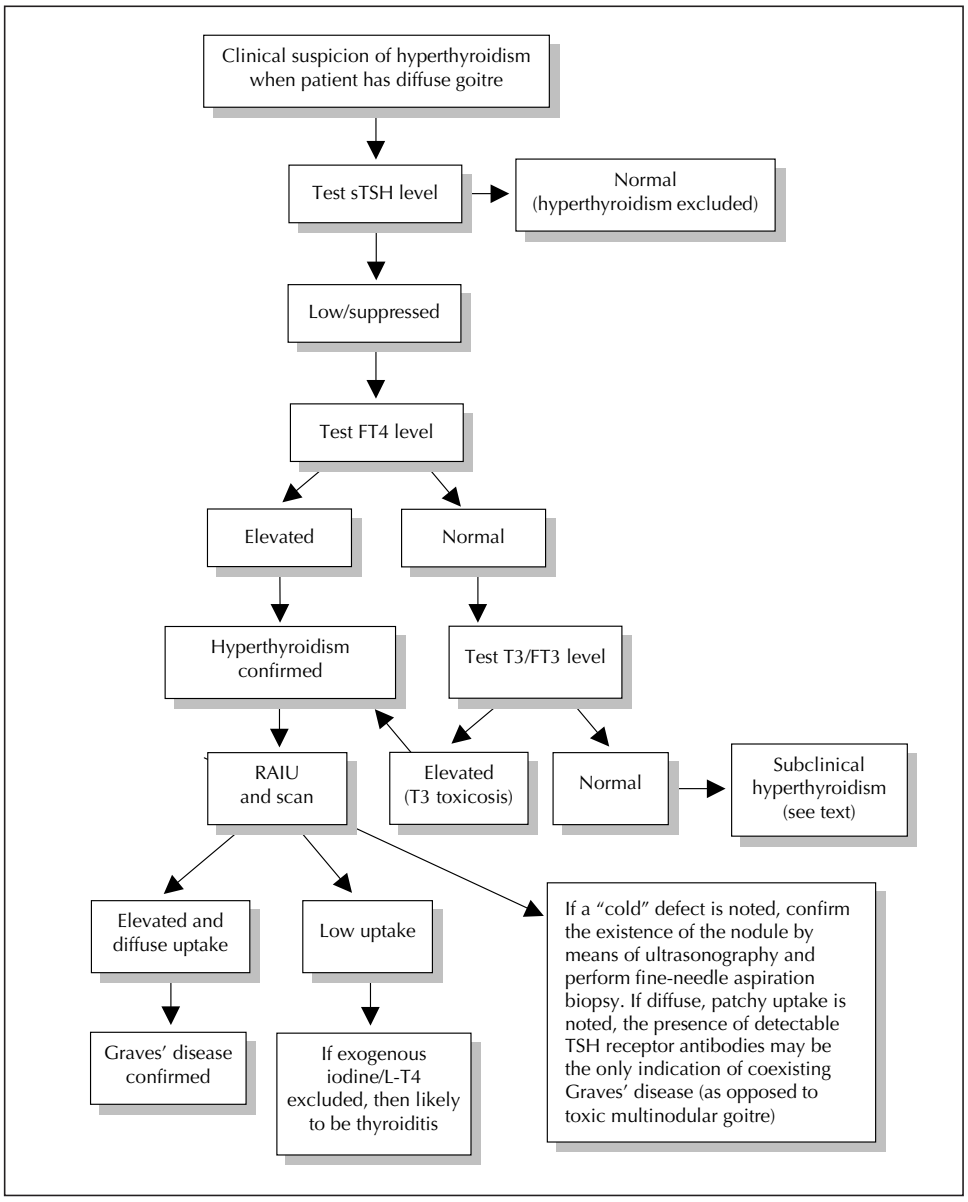

Fig. 2: An approach to the diagnosis of Graves' disease. sTSH = sensitive thyroid-stimulating hormone, FT4 = free thyroxine, RAIU = radioiodine uptake, L-T4 = L-thyroxine.

Large initial doses of antithyroid drugs have been shown to be rarely necessary. Methimazole given at a dose of 15 mg daily was as effective as 30 mg daily in achieving euthyroidism while minimizing side effects.[26] Higher doses of methimazole are only required in patients with severe hyperthyroidism or large goitres. Thyroid indices including T3 should be monitored monthly and the dose adjusted until a maintenance dose of 5–10 mg/d is achieved. The level of TSH may remain low for weeks to months after methimazole is initiated. The block-replace regimen in which T4 is added to methimazole when euthyroidism occurs is not favoured in North America. Prospective studies show 18 months of treatment with antithyroid drugs to be associated with a subsequent higher rate of remission than that following 6 months of therapy, with no further benefit in patients receiving 42 months of therapy.[27,28] Therefore, a patient should receive a course of antithyroid drugs for 1–2 years before determining whether an immunological remission has occurred. The use of antithyroid drugs is shown in Fig. 3.

Several recent reviews state that the remission rate following antithyroid drugs is in the 30%–40% range.[3,29] However, an online opinion states that "there is only a modest hope of achieving a permanent remission,"[30] which reflects my experience. A suppressed TSH level after a course of antithyroid drugs is invariably associated with relapse, and alternative therapy should be considered. In cases where patients refuse radioiodine and continue to take maintenance antithyroid drugs, relapses may occur. Although a prominent report indicated an increased likelihood of remission using combined T4 and antithyroid drugs,[31] these findings have not been confirmed in multiple studies,[32,33] and the practice cannot be justified.

The side effects of antithyroid drugs are shown in Table 3. Minor side effects occur in up to 13% of patients using antithyroid drugs and resolve upon discontinuing the agent. Cross-sensitivity between antithyroid drugs may occur in up to 50% of cases.[22] Potentially fatal agranulocytosis (absolute neutrophil count $< 0.25 \times 10^9$/L) occurs in 0.2%–0.5% of subjects. One study revealed no relation with duration of treatment, age of patient or re-exposure.[34] Routine leukocyte monitoring is not the usual practice. Rather, the patient should be instructed to discontinue the drug and have an immediate complete blood count and differential count performed if side effects occur.

Table 2: Factors associated with either a higher likelihood of immunological remission following a course of ATDs or with increased resistance to RAI

Higher likelihood of immunological remission following a course of ATDs	Increased resistance to RAI
• Female sex	• Age (> 40 yr)
• Age (> 40 yr)	• Female sex
• High TPO antibody positivity	• Severe hyperthyroidism
• Small goitre	• Medium or large goitres (> 40 g, visible)
• Mild hyperthyroidism	• ATD pretreatment (especially with propylthiouracil)
• TSH receptor antibody–negative	

Note: ATD = antithyroid drug, RAI = radioiodine, TPO = thyroid peroxidase, TSH = thyroid-stimulating hormone.

Table 3: Antithyroid drugs

Characteristic	Propylthiouracil	Methimazole
Half-life	75 min	About 4–6 h
Effect on 5′-deiodinase	Blocks 5′-deiodinase	No effect
Effectiveness (at dose equivalents)	++	+++
Time to achieve euthyroidism	Months	Weeks
Dosing schedule	Twice daily	Daily
Side effects		
Agranulocytosis	Idiosyncratic	Dose-dependent
Hepatitis	Rare	Extremely rare
Vasculitis	Rare	Extremely rare
Resistance to RAI	Common	Rare
Minor (13%)	Pruritus, rash, arthralgias, fever, sore throat, mouth ulcers, nausea, jaundice	
Major (0.2%–0.5%)	Agranulocytosis, hepatotoxicity,* aplastic anemia,* vasculitis*	

*Especially with propylthiouracil.

Radioiodine

Radioiodine is administered orally as iodine 131 in solution or as a capsule. Radioiodine is rapidly incorporated into the thyroid and via its β-emissions produces radiation thyroiditis and fibrosis resulting in euthyroidism usually within 6–18 weeks.

There is no association of radioiodine with birth defects, infertility or overall cancer incidence.[35] Patients are reassured by the fact that the gonadal exposure is similar to that observed following a barium enema or intravenous pyelography. Although an increase in thyroid cancer and cancers of the small bowel has been recently reported following radioiodine exposure, the absolute numbers affected are small and it remains unclear whether the risk is due to radioiodine itself.[36,37] A higher incidence of mortality has also recently been reported following radioiodine treatment.[38] However, the higher incidence among older patients, particularly in the first year post therapy, makes the direct role of radioiodine in this outcome questionable.

Although obtaining euthyroidism while limiting hypothyroidism is a therapeutic ideal, it can rarely be achieved. Attempts to provide lower doses of radioiodine result in frequent treatment failure or in persistent subclinical hyperthyroidism.[39] Conversely, the rate of hypothyroidism after 10 years remains at least 50% irrespective of the treatment dose, because 2%–3% of patients per year (from year 2 onward) develop lymphocytic infiltration and tissue destruction.[40] Thus, most endocrinologists favour higher doses to ensure permanent restoration of euthyroidism. A semifixed-dose approach, namely, 185 MBq for small glands, 370 MBq for medium glands and 555 MBq for large glands, appears to be highly effective.[40] The factors that influence radioiodine resistance and mandate higher doses are outlined in Table 2.[41]

At the time of radioiodine treatment, the physician should ensure that the patient is not pregnant. Inadvertent radioiodine treatment after 10–12 weeks' gestation, when the fetal thyroid has developed, can lead to congenital hypothyroidism.[40] Patients are advised not to become pregnant for 3–6 months following treatment. As patients who receive radioiodine may subsequently contaminate their living environments or family members via their secretions (sweat, saliva, urine, stool) or radiation from their neck, simple avoidance of physical contact and transfer of secretions is recommended for several days after treatment.

About 1% of patients who receive radioiodine may experience radiation thyroiditis 5–10 days later with pain over the thyroid area and possibly associated hyperthyroidism due to release of stored hormone.[42] NSAIDs usually provide sufficient analgesia, and prednisone (20–40 mg/d) is rarely required. Although pretreatment with antithyroid drugs does not prevent the rise in thyroid indices following radioiodine, it allows them to rise from a lower baseline value[42] and should be considered for patients with severe hyperthyroidism, elderly patients and those with pre-existing cardiovascular disease. Antithyroid drugs should be stopped only 1–2 days before radioiodine, as more prolonged periods may cause rebound hyperthyroidism.[42] Antithyroid drugs can be resumed 3–5 days after radioiodine but are rarely necessary.

Two prospective randomized clinical trials have shown an association between radioiodine use and development or worsening of ophthalmopathy.[43,44] In the more recent, larger trial, 15% of subjects treated with radioiodine were affected. Concurrent administration of corticosteroids (prednisone, 0.5 mg/kg, starting the day after radioiodine for 1 month followed by tapering and discontinuation over the next 3 months) could prevent radioiodine-induced worsening of ophthalmopathy.[44] However, in two-thirds of those affected, the ophthalmopathy was mild, transient and did not require intervention.[44] In view of this observation and the potential side effects of high-dose corticosteroids, I reserve this measure only for patients with significant diplopia or proptosis, or both. Sensible but unproven measures that I use to reduce the risk of radioiodine-induced ophthalmopathy include ensuring stability of ophthalmopathy for 6 months before radioiodine, pretreatment with antithyroid drugs, smoking cessation and the use of ablative doses of radioiodine. In one study, patients who received L-thyroxine (L-T4) (0.05 mg/d for 2 weeks, then 0.1 mg/d) starting 2 weeks following radioiodine use had less worsen-

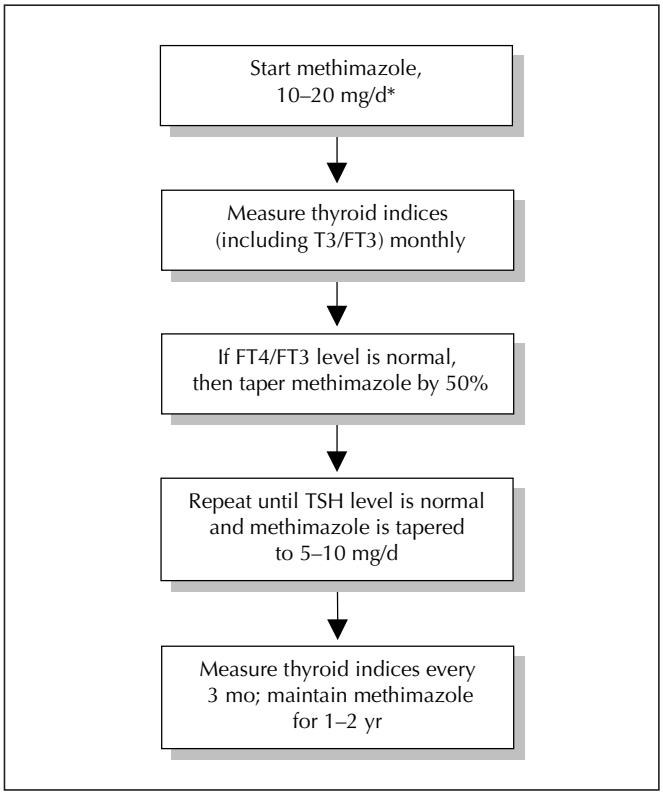

Fig. 3: The use of antithyroid drugs. *Higher doses of 30–40 mg/d may be required if patient has severe hyperthyroidism or a large visible goitre.

ing of their ophthalmopathy than those who received L-T4 after hypothyroidism was established.[45] This protocol starts L-T4 when most patients are still hyperthyroid and may not be generally applicable. However, in view of these results, introducing L-T4 when patients become euthyroid after radioiodine should be considered more often.

Following radioiodine therapy, thyroid indices should be monitored every 1–2 months for the next 6 months to detect hypothyroidism and ensure that euthyroidism has been restored. Thereafter, measuring thyroid indices every 3 months for 1 year and then every 6–12 months is recommended. In the first several months, the TSH level may not be reliable in predicting hypothyroidism, and thyroid hormone treatment should be instituted when FT4 is in the hypothyroid range because delaying therapy is not justified. Transient hypothyroidism has been reported in the first year after radioiodine, and most of those subjects eventually become hypothyroid. Further radioiodine should be considered if thyroid indices (FT4 and T3) do not return to normal by 3 months. It is my practice to re-treat with radioiodine if subclinical hyperthyroidism does not resolve within 6 months. Radioiodine should be considered first-line therapy in patients with a relapse after antithyroid drugs or after thyroidectomy.

Surgery

Thyroidectomy should only be considered in the following circumstances: when patients have large goitres, when patients are intolerant of antithyroid drugs and/or choose to refuse radioiodine therapy, during the second trimester of pregnancy after failure of antithyroid drugs, or when there is concern about worsening of thyroid ophthalmopathy following radioiodine. Surgery should also be performed on all patients with Graves' disease with a coexisting discrete nodule responsible for a photopenic ("cold") area on scanning, the fine-needle aspiration biopsy of which is suspicious or diagnostic of thyroid cancer.[20] The incidence of hypothyroidism is related to the extent of surgery but approximates 50% within 25 years.[29] Specific complications include hypoparathyroidism and vocal cord paresis due to damage to the recurrent laryngeal nerve. Patients should be rendered euthyroid before surgery to reduce the risk of thyroid storm (see later). If antithyroid drugs are not tolerated, propranolol alone, or with iodide, has been used successfully.[29] Patients should receive iodide such as saturated solution of potassium iodide ([SSKI] 2–4 drops/d) for 7 days before the procedure to reduce blood flow to the gland, facilitating surgical removal. Available treatments for Graves' disease are contrasted in Table 4.

Ophthalmopathy

Most patients with mild-to-moderate ophthalmopathy usually require no intervention other than restoration of euthyroidism and topical lubricants. For patients with more severe disease, corticosteroids are the mainstay of medical treatment.[8,46] The benefits of orbital radiation have been recently challenged.[47] The use of other immunosuppressive drugs such as cyclosporine has a high risk–benefit ratio, although methotrexate has been advocated for resistant cases.[46] Short-acting or long-acting sandostatin analogues may be an effective adjunct particularly in patients with positive octreotide scintigraphic scans of the orbits.[46] Surgical intervention is necessary for those with severe proptosis, optic neuropathy, significant diplopia or persistent widened lid aperture.

Pregnancy

The most important intervention for Graves' disease during pregnancy is prevention. Antithyroid drugs have the ability to cross the placenta and cause fetal goitre or hypothyroidism.[22] Allergy or intolerance to antithyroid drugs during pregnancy may mandate a second trimester thyroidectomy under β-blockade. Such concerns can be avoided by definitive radioiodine therapy before conception, and this should be discussed with all female patients of reproductive age. However, TSH receptor antibody levels decrease with pregnancy, and for patients who present during pregnancy treatment with antithyroid drugs usually

Table 4: Treatment for Graves' disease

Therapy	Duration	Worsens ophthalmopathy	During pregnancy	Advantages	Disadvantages
Antithyroid drugs	1–2 yr	No	Yes	Rapid restoration of euthyroidism; potential for immunological remission	Side effects (see Table 3); relapse extremely common
Radioiodine	Usually once	Potentially (in 15% of patients)	Contraindicated	Permanent correction of hyperthyroidism; safe, easily administered	Hypothyroidism (> 50% in 10 yr); environmental precautions required; pregnancy delay of 3–6 mo required
Surgery	Day surgery	No	Yes, during second trimester	Permanent correction of hyperthyroidism usual	Hypothyroidism (50% over 25 yr); general anesthesia required; 1%–2% complications: hypoparathyroidism, recurrent laryngeal nerve paresis

proceeds smoothly.[48] Because there is less potential fetal transfer with propylthiouracil and because of concern over the possible association of methimazole with aplasia cutis and choanal atresia,[22,49] most North American physicians prefer propylthiouracil. The starting dose of propylthiouracil is 100–300 mg/d based on the extent of the hyperthyroidism and is adjusted monthly to maintain the FT4 in the upper portion or slightly above the normal range (to mimic euthyroid pregnancy).[50] Using FT3 or TSH to monitor outcomes may be misleading. It may be possible to reduce propylthiouracil to maintenance levels (50–100 mg/d) or discontinue it entirely, particularly after 26 weeks' gestation. Combined antithyroid drugs and L-T4 is not advocated. A relapse of Graves' disease may be seen post partum.[48] Because infants of nursing mothers who take propylthiouracil have normal thyroid indices, it is considered safe to take the drug when breastfeeding.[51]

TSH receptor antibodies may cross the placenta, causing neonatal hyperthyroidism in 1% of pregnancies of women with Graves' disease.[52] This condition has been associated with craniosynostosis, intellectual and growth retardation, and even early mortality. An elevated fetal heart rate (> 160 beats/min) may indicate its development. However, measurement of TSH receptor antibody in the third trimester may predict neonatal hyperthyroidism[52] (Fig. 4). It is especially important to screen for this in euthyroid mothers who have previously been treated for Graves' disease, as antithyroid drugs have prevented the most severe consequences of neonatal hyperthyroidism in these patients.[52]

Thyroid storm

Thyroid storm is a rare but potentially life-threatening complication of Graves' disease. The symptoms of hyperthyroidism are exaggerated and may include significant tachycardia, hyperpyrexia, congestive heart failure, neurological compromise, and gastroenterological or hepatic dysfunction. Precise criteria for the diagnosis have been formulated by Burch and Wartofsky.[53] Frequently, surgery, trauma, infection or an iodine load may precipitate thyroid storm. Treatment includes supportive measures in an intensive care unit and attention to any reversible identified precipitant. Hyperthermia should be treated with cooling blankets and acetaminophen because ASA may displace thyroid hormones from their binding proteins. Primarily, treatment is directed at the thyroid gland and reducing the peripheral effects of thyroid hormone. This is outlined in Table 5.[53] Because iodine (including that from iodinated radiocontrast agents) may exacerbate hyperthyroidism by being used as substrate for new hormone synthesis, it should be preceded by thionamide treatment by at least 1 hour.

Subclinical hyperthyroidism

Graves' disease may present only with subclinical hyperthyroidism (normal total and free T3 and T4 with suppressed TSH levels). Subclinical hyperthyroidism has been associated with higher nocturnal pulse rates, frequent premature atrial complexes, an increased risk of atrial fibrillation in elderly people and osteopenia.[54] Recently, an increased risk of fracture of the vertebra and hip has been reported in elderly women with subclinical hyperthyroidism. However, there is a spontaneous 40% remission rate during follow-up. Accordingly, treatment of subclinical hyperthyroidism needs to be individualized and based on the patient's age, symptoms and comorbidities. In patients aged over 65 years or those with established cardiovascular disease or osteoporosis, treatment with antithyroid drugs or, preferably, radioiodine is justified. Otherwise, patients can be followed by measuring their thyroid indices every 6 months, with intervention should the FT3/FT4 level become elevated or the patient become symptomatic. My present practice is to treat all patients with subclinical hyperthyroidism for 1 year at least.

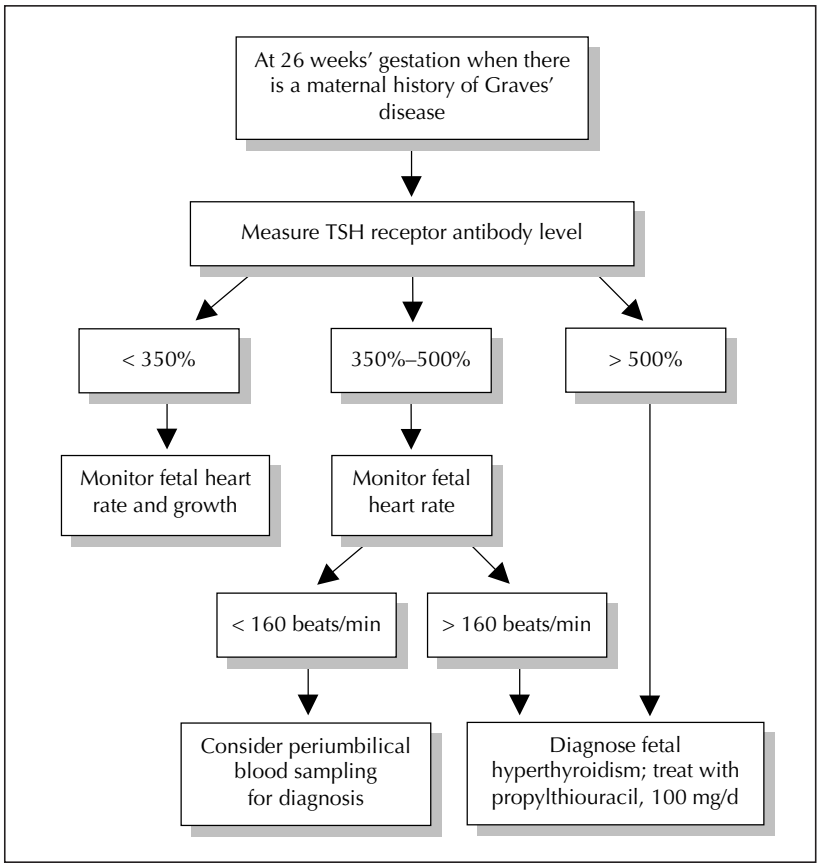

Fig. 4: A strategy to predict neonatal hyperthyroidism. Modified with permission from Mary Ann Liebert (*Thyroid* 1995;5:125-8).

Table 5: Treatment of thyroid storm

Treatment	Dose and route	Action
β-blockers:		
Propranolol	• 1 mg/min IV (as required) and 60–80 mg every 4 h po or by NG tube	Antagonizes effects of increased adrenergic tone, blocks T4-to-T3 conversion
Esmolol (alternative)	• 250–500 μg/kg IV followed by IV infusion 50–100 μg/kg per min	
Thionamides:		
Propylthiouracil	• 800–1000 mg po immediately, then 200 mg every 4 h po or by NG tube	Blocks new thyroid hormone synthesis, blocks T4-to-T3 conversion
Methimazole (alternative)	• 30 mg po immediately, then 30 mg every 6 h po or by NG tube	(propylthiouracil only)
Iodinated contrast agents:*		
Iopanoic acid or ipodate	• 0.5–1.0 g/d po or by NG tube	Blocks T4-to-T3 conversion, blocks thyroid hormone release (via iodine release)
Iodine:		
Lugol's solution	• 10 drops tid po or by NG tube	Blocks thyroid hormone release
or SSKI	• 5 drops every 6 h po or by NG tube	
or Sodium iodide	• 0.5–1.0 g IV every 12 h	
Glucocorticoids:		
Hydrocortisone	• 100 mg IV every 8 h	Blocks T4-to-T3 conversion, immunosuppression
or Dexamethasone	• 2 mg IV every 6 h	

Note: IV = intravenously, po = by mouth, NG = nasogastric, T4 = thyroxine, T3 = triiodothyronine, SSKI = saturated solution of potassium iodide, tid = three times a day.
*Limited availability.

Summary

Graves' disease is a complex disease affecting multiple organ systems. A high level of suspicion is required for the diagnosis in all except the obvious patient. Because all available treatments have serious drawbacks, extensive discussion with the patient about therapeutic options is key to disease control and persistent long-term health. It is hoped that further understanding of the underlying pathogenesis will lead to new therapies capable of restoring the immunological milieu to normal.

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References

1. Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM. The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. *Endocr Rev* 1998;19:673-716.
2. McLachlan SM, Pegg CA, Atherton C, Middleton SL, Clark F, Rees Smith B. TSH receptor antibody synthesis by thyroid lymphocytes. *Clin Endocrinol* 1986;24:223-30.
3. Weetman AP. Graves' disease. *N Engl J Med* 2000;343:1236-48.
4. Volpe R. The immunoregulatory disturbance in autoimmune thyroid disease. *Autoimmunity* 1988;2:55-72.
5. Tamai H, Kasagi K, Takaichi Y, Takamatsu J, Komaki G, Matsubayashi S, et al. Development of spontaneous hypothyroidism in patients with Graves' disease treated with anti-thyroidal drugs: clinical, immunological and histological findings in 26 patients. *J Clin Endocrinol Metab* 1989;69:49-53.
6. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. *N Engl J Med* 1993;329:1468-75.
7. Wall JR. Graves' disease is a multi-system autoimmune disorder in which extraocular muscle damage and connective tissue inflammation are variable features. *Thyroid* 2002;12:35-6.
8. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev* 1993;14:747-93.
9. Geffner DL, Hershman JM. β-Adrenergic blockade for the treatment of hyperthyroidism. *Am J Med* 1992;93:61-8.
10. Nordyke RA, Gilbert FI Jr, Harada AS. Graves' disease: influence of age on clinical findings. *Arch Intern Med* 1988;148:626-31.
11. Thomas FB, Mazzaferri EL, Skillman TG. Apathetic thyrotoxicosis: a distinctive clinical and laboratory entity. *Ann Intern Med* 1970;72:679-85.
12. Nijs HG, Radder JK, Frolich M, Krans HMJ. Increased insulin action and clearance in hyperthyroid newly diagnosed IDDM patient: restoration to normal with anti-thyroid treatment. *Diabetes Care* 1989;12:319-24.
13. Boyages SC. The neuromuscular system and brain in thyrotoxicosis. In: Braverman LE, Utiger RD, editors. *Werner and Ingbar's the thyroid*. Philadelphia: Lippincott-Raven; 2000. p. 631-3.
14. Trzepacz PT, Klein I, Roberts M, Greenhouse J, Levey GS. Graves' disease: an analysis of thyroid hormone levels and hyperthyroid signs and symptoms. *Am J Med* 1989;87:558-61.
15. Wiersinga WM, Prummel MF. An evidence-based approach to the treatment of Graves' ophthalmopathy. *Endocrinol Metab Clin North Am* 2000;29:297-319.
16. Salvi M, DeChiara F, Gardini E, Minelli R, Bianconi L, Alinovi A, et al. Echographic diagnosis of pretibial myxedema in patients with autoimmune thyroid disease. *Eur J Endocrinol* 1994;131:113-9.
17. Rapoport B, Alsabeh R, Aftergood D, McLachlan SM. Elephantiasic pretibial myxedema: insight into and a hypothesis regarding the pathogenesis of the extrathyroidal manifestations of Graves' disease. *Thyroid* 2000;10:685-92.
18. Becker DV, Bigos ST, Gaitan E, Morris JC, Rallison ML, Spencer CA, et al. Optimal use of blood tests for assessment of thyroid function. *JAMA* 1993; 269:2736-7.
19. Umena S, Takano T, Iijima T, Hidaka Y, Yagoro A, Takai S, et al. A case of repeated painless thyroiditis followed by Graves' disease. *Endocr J* 1995;42:821-6.
20. Stocker DJ, Foster SS, Solomon BL, Shriver CD, Burch HB. Thyroid cancer yield in patients with Graves' disease selected for surgery on the basis of cold scintiscan defects. *Thyroid* 2002;12:305-11.
21. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518-24.
22. Cooper DS. Antithyroid drugs. *N Engl J Med* 1984;311:1353-62.
23. Cooper DS. Which antithyroid drug? *Am J Med* 1986;80:1165-8.
24. Okamura K, Ikenoue H, Shiroozu A, Sato K, Yoshinari M, Fujishima M. Re-evaluation of the effects of methylmercaptoimidazole and propylthiouracil in

patients with Graves' disease. *J Clin Endocrinol Metab* 1987;65:719-23.
25. Cooper DS, Goldminz D, Levin AA, Ladenson PW, Daniels GH, Molitch ME, et al. Agranulocytosis associated with anti-thyroid drugs. *Ann Intern Med* 1983;98:26-9.
26. Shiroozu A, Okamura K, Ikenoue H, Sato K, Nakashima T, Yoshinari M, et al. Treatment of hyperthyroidism with a small single daily dose of methimazole. *J Clin Endocrinol Metab* 1986;63:125-8.
27. Allannic H, Fauchet R, Orgiazzi J, Madec AM, Genetet B, Lorcy Y, et al. Anti-thyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. *J Clin Endocrinol Metab* 1990;70:675-9.
28. Maugendre D, Gatel A, Campion L, Massart C, Guilhem I, Lorcy Y, et al. Anti-thyroid drugs and Graves' disease – prospective randomized assessment of long-term treatment. *Clin Endocrinol* 1999;50:127-32.
29. Franklyn JA. The management of hyperthyroidism. *N Engl J Med* 1994;330:1731-8.
30. Ross DS. Thionamides in the treatment of Graves' disease. *UpToDate* 2001;9:1.
31. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, et al. Administration of thyroxine in treated Graves' disease – effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med* 1991;324:947-53.
32. Rittmaster RS, Zwicker H, Abbott EC, Douglas R, Givner ML, Gupta MK, et al. Effect of methimazole with or without exogenous L-thyroxine on serum concentrations of thyrotropin (TSH) receptor antibodies in patients with Graves' disease. *J Clin Endocrinol Metab* 1996;81:3283-8.
33. McIver B, Rae P, Beckett G, Wilkinson E, Gold A, Toft A. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an anti-thyroid drug. *N Engl J Med* 1996;334:220-4.
34. Tamai H, Takaichi Y, Morita T, Komaki G, Matsubayashi S, Kuma K, et al. Methimazole-induced agranulocytosis in Japanese patients with Graves' disease. *Clin Endocrinol* 1989;30:525-30.
35. Graham GD, Burman KD. Radioiodine treatment of Graves' disease. An assessment of its potential risks. *Ann Intern Med* 1986;105:900-5.
36. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999;353:2111-5.
37. Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, et al. Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. *JAMA* 1998;280:347-55.
38. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med* 1998;338:712-8.
39. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ. Long-term follow-up study of compensated low-dose ^{131}I therapy for Graves' disease. *N Engl J Med* 1984;311:426-32.
40. Farrar JJ, Toft AD. Iodine-131 treatment of hyperthyroidism: current issues. *Clin Endocrinol* 1991;35:207-12.
41. Allahabadia A, Daykin J, Sheppard MC, Gough SC, Franklyn JA. Radioiodine treatment of hyperthyroidism – prognostic factors for outcome. *J Clin Endocrinol Metab* 2001;86:3611-7.
42. Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of anti-thyroid drug pretreatment on acute changes in thyroid hormone levels after ^{131}I ablation for Graves' disease. *J Clin Endocrinol Metabol* 2001;86:3016-21.
43. Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *N Engl J Med* 1992;326:1733-8.
44. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998;338:73-8.
45. Tallstedt L, Lundell G, Blomgren H, Bring J. Does early administration of thyroxine reduce the development of Graves' ophthalmopathy after radioiodine treatment? *Eur J Endocrinol* 1994;130:494-7.
46. Krassas GE, Heufelder AE. Immunosuppressive therapy in patients with thyroid eye disease: an overview of current concepts. *Eur J Endocrinol* 2001; 144:311-8.
47. Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. *Ophthalmology* 2001;108: 1523-34.
48. Lazarus JH, Kokandi A. Thyroid disease in relation to pregnancy: a decade of change. *Clin Endocrinol* 2000;53:265-78.
49. Wilson LC, Kerr BA, Wilkinson R, Fossard C, Donnai D. Choanal atresia and hypothelia following methimazole exposure in utero: a second report. *Am J Med Genet* 1998;75:220-2.
50. Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K. Anti-thyroid drug therapy for Graves' disease during pregnancy. Optimal regimen for fetal thyroid status. *N Engl J Med* 1986;315:24-8.
51. Momotani N, Yamashita R, Makino F, Noh JY, Ishikawa N, Ito K. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol* 2000;53:177-81.
52. Wallace C, Couch R, Ginsberg J. Fetal thyrotoxicosis: a case report and recommendations for prediction, diagnosis and treatment. *Thyroid* 1995;5:125-8.
53. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 1993;22:263-77.
54. Toft AD. Clinical practice. Subclinical hyperthyroidism. *N Engl J Med* 2001;345:512-6.6

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