Current concepts in Graves' disease

Ther Adv Endocrinol Metab
(2011) 0(0) 1–10
DOI: 10.1177/2042018811408488

Christian M. Girgis, Bernard L. Champion and Jack R. Wall

***Abstract*:** Graves' disease is the most common cause of hyperthyroidism in the developed world. It is caused by an immune defect in genetically susceptible individuals in whom the production of unique antibodies results in thyroid hormone excess and glandular hyperplasia. When unrecognized, Graves' disease impacts negatively on quality of life and poses serious risks of psychosis, tachyarrhythmia and cardiac failure. Beyond the thyroid, Graves' disease has diverse soft-tissue effects that reflect its systemic autoimmune nature. Thyroid eye disease is the most common of these manifestations and is important to recognise given its risk to vision and potential to deteriorate in response to radioactive iodine ablation. In this review we discuss the investigation and management of Graves' disease, the recent controversy regarding the hepatotoxicity of propylthiouracil and the emergence of novel small-molecule thyroid-stimulating hormone (TSH) receptor ligands as potential targets in the treatment of Graves' disease.

***Keywords*:** autoimmune thyroid disease, Graves' disease, hyperthyroidism, neomercazole, propylthiouracil, radioactive iodine, thionamides, thyroidectomy, thyroid eye disease

Introduction

Originally known as 'exophthalmic goitre', Graves' disease owes its name to the Irish physician, Robert James Graves, who described the condition in 1835. Graves' disease is a syndrome that classically comprises hyperthyroidism with a diffuse goitre, eye disease characterized by inflammation and involvement of intra-orbital structures, dermopathy referred to as pretibial myxoedema, and rare involvement of the nails, fingers and long bones known as acropachy. Prior to its description by Graves, others including the Greek philosopher Aristotle and the English physician Caleb Parry had noted unique aspects of the condition [Weetman, 2003].

Graves' disease is the most common autoimmune disease, affecting 0.5% of the population in the US, and represents 50–80% of cases of hyperthyroidism [Brent, 2008]. It occurs more commonly amongst women, smokers and patients with other autoimmune diseases or a family history of thyroid autoimmunity [Manji *et al.* 2006]. Peak incidence occurs between 40 and 60 years of age but any age group may be affected.

The diverse manifestations of the condition span beyond its local effects on the thyroid, reflecting its systemic autoimmune and sympathomimetic manifestations. The prevalence of particular components of Graves' disease and supporting images are shown in Table 1 and Figure 1, respectively.

Aetiology

Graves' hyperthyroidism results from the production of unique IgG antibodies that bind to and activate the thyroid-stimulating hormone (TSH) receptor on the surface of thyroid follicular cells. This activation stimulates follicular cell growth, causing diffuse thyroid enlargement and increased production of thyroid hormones with an increase in the fraction of triiodothyronine (T3) relative to thyroxine (T4) [Brent, 2008].

The emergence of this autoimmune process is probably due to an underlying genetic susceptibility with superimposed environmental factors. Particular HLA alleles on chromosome 6, namely HLA-DRB1-08 and DRB3-0202, are known to confer an increased risk of Graves' disease [Stenszky *et al.* 1985]. Environmental triggers include stressful life events, infection, exposure to high doses of iodine and recent childbirth [Brent, 2008].

Correspondence to:
Dr Christian M. Girgis
Garvan Institute of Medical Research, Victoria Street, Darlinghurst, Sydney, Australia;
Department of Medicine, University of Sydney, Sydney, Australia
cgirgis@usyd.edu.au

Bernard L. Champion
Department of Medicine, University of Sydney, Sydney, Australia

Jack R. Wall
Department of Medicine, University of Sydney, Sydney, Australia

Clinical features

The onset of Graves' disease is usually acute, reflecting the sudden production of stimulatory TSH-receptor antibodies, but may be indolent or subacute. Patients report the classical symptoms of hyperthyroidism that include weight loss despite increased appetite, heat intolerance, irritability, insomnia, sweatiness, diarrhoea, palpitations, muscular weakness and menstrual irregularity.

Table 1. Components of Graves' disease: prevalence.

Feature	Prevalence (%)
Hyperthyroidism and diffuse goitre	95%
Thyroid eye disease[a]	50%
Pretibial myxoedema	5%
Acropachy	1%
Thyroid eye disease without hyperthyroidism ['Euthyroid Graves' disease']	5%

Percentages are based on a cohort of patients seen by the senior author [El-Kaissi *et al.* 2004].
[a]As defined by the NO-SPECS classification [Van Dyk, 1981].

Clinical signs include diffuse goitre, fine resting tremor, tachycardia, hyperreflexia, eyelid lag, warm, smooth skin and proximal myopathy. Less common findings include atrial fibrillation and a thyroid bruit reflecting the marked increase in thyroid vascularity.

The presentation can vary significantly amongst different patient groups. Older patients are more likely to present with subtle symptoms such as depression and weight loss rather than overt symptoms of sympathetic overactivity. They are also more likely to present with cardiovascular

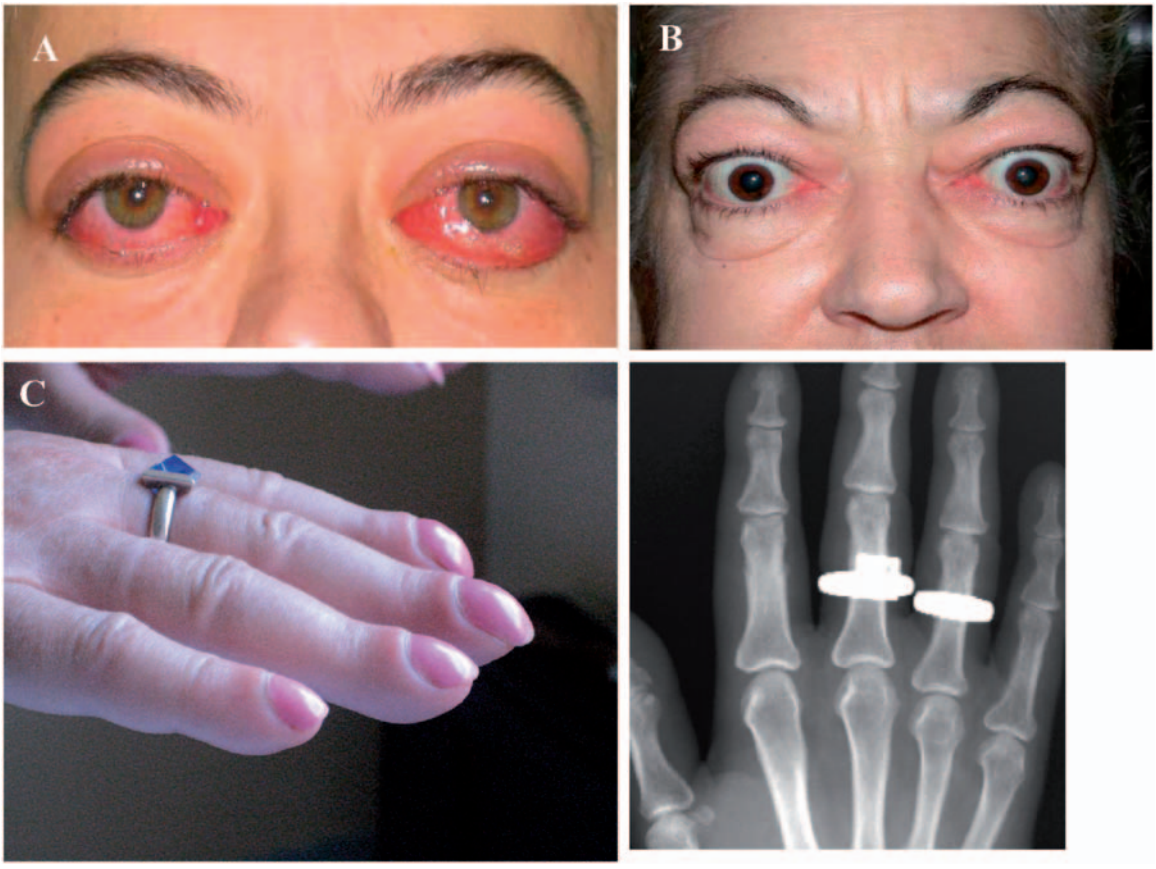

Figure 1. Images of extrathyroidal features of Graves' disease: characteristic features of thyroid eye disease including marked chemosis and eyelid oedema (A); eyelid retraction, swelling and exophthalmos (B). Also shown are features of thyroid acropachy in a patient with Graves' disease including soft-tissue oedema and clubbing (C) with the characteristic eroded bone margins of the phalanges suggestive of new periosteal bone formation and periosteitis (D).

features such as atrial fibrillation or congestive cardiac failure than are younger patients [Klein and Ojamaa, 2001]. Women may present with menstrual irregularity, or for cosmetic reasons, with concerns about goitre, eye changes or hair loss. Unusual presentations of Graves' disease have been summarized in Table 2.

Thyroid eye disease effects up to 50% of patients with Graves' disease and is distinct from the sympathomimetic ocular effects of thyroid hormone excess (i.e. thyroid stare and lid retraction) [El-Kaissi *et al.* 2004]. The cardinal features of thyroid eye disease include exophthalmos, chemosis and when severe, impaired extra-ocular muscle movement. The latter is most prominent on vertical/lateral gaze and may cause diplopia. Chemosis (i.e. conjunctival oedema) and conjunctival injection may lead to the complaint of swollen, congested, watery or gritty eyes (see Figure 1A and B). Acute changes in visual fields or acuity, diplopia or the inability to close the eyelids mandate prompt ophthalmology review as these may indicate risk to vision.

Investigations

Despite the development of highly sensitive tests for thyroid disease, thorough clinical assessment of patients with suspected hyperthyroidism remains paramount. Serum TSH is a sensitive index for primary thyroid disease and therefore a good initial screening investigation. A low TSH indicates likely suppression of the hypothalamic–pituitary axis, and should be followed by the measurement of free thyroxine (T4) and free triiodothyronine (T3), both of which are usually elevated in Graves' hyperthyroidism [Toft, 2003]. Less commonly, patients with Graves' disease may display subclinical hyperthyroidism, characterized by suppression of TSH whilst free T3 and T4 remain within reference range, or T3 toxicosis, that is disproportionate elevation of T3 in comparison to T4 with accompanying TSH suppression [Woeber, 2006; Toft, 2001]. These free hormone assays are highly specific but may be subject to artefacts in critical illness, disturbances in binding proteins due to drugs or pregnancy, and heparin [Topliss and Eastman, 2004].

Table 2. Unusual presentations of Graves' disease [Brent, 2008; Klein and Ojamaa, 2001; Abraham-Nordlin, 2005; Reasner, 1993].

Malabsorption
Hypercalcemia
Proximal myopathy
Hepatitis
Cardiomyopathy
Heart failure
Atrial fibrillation
Gynaecomastia
Deterioration in glycemic control in diabetic patients

The measurement of serum TSH-receptor antibodies may be helpful in confirming the diagnosis of Graves' disease. These antibodies, positive in 90% of patients with presumed Graves' disease, are measured as TSH-receptor binding (TBII) and stimulating antibodies (TSI), the latter reflecting the effect on thyroid function. The measurement of TSH-receptor antibodies may also have a role in assessing the risk of relapse after a course of thionamides for Graves' disease or when assessing the risk of neonatal Graves' disease in pregnant women with Graves' disease. Routine measurement of TSH-receptor antibodies is unnecessary in patients in whom the diagnosis of Graves' disease may be made on clinical grounds, for example thyrotoxicosis with eye changes suggestive of thyroid eye disease.

Other antibodies, including thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies, may be significantly elevated but are not specific to Graves' disease. They may also be detected in Hashimoto's thyroiditis, amongst patients with type I diabetes mellitus and in 5–25% of the general population [Mariotti *et al.* 1990].

Technetium-labelled thyroid scintigraphy may aid diagnosis when the cause of hyperthyroidism remains uncertain. It effectively distinguishes Graves' disease from thyroiditis or an autonomously hyperfunctioning nodule (see Figure 2). Radionuclide uptake by the thyroid may be significantly affected by the use of amiodarone within the past 12 months, the administration an iodine load (usually by intravenous radiocontrast dye) within the past month, the use of thyroxine or high-dose thioamide therapy for prolonged periods. In such patients, thyroid ultrasonography may be useful.

Real-time thyroid ultrasonography may display characteristic and often striking features of Graves' disease including diffuse enlargement

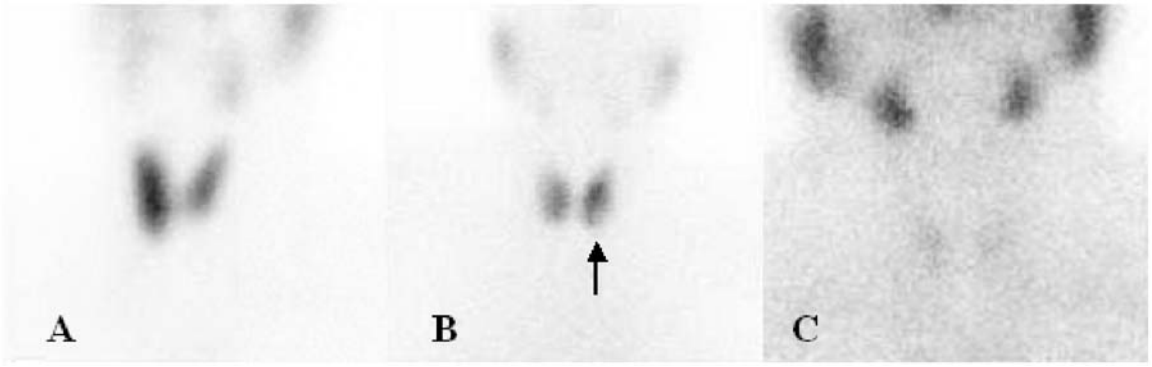

Figure 2. Radionuclide thyroid scintigraphy. ^{99m}TC-pertechnetate thyroid scintigraphy demonstrating diffusely increased uptake in Graves' disease (A); a focal area of increased uptake due to an autonomously hyperfunctioning nodule (arrow, B); diffusely reduced uptake in a patient with thyroiditis (C).

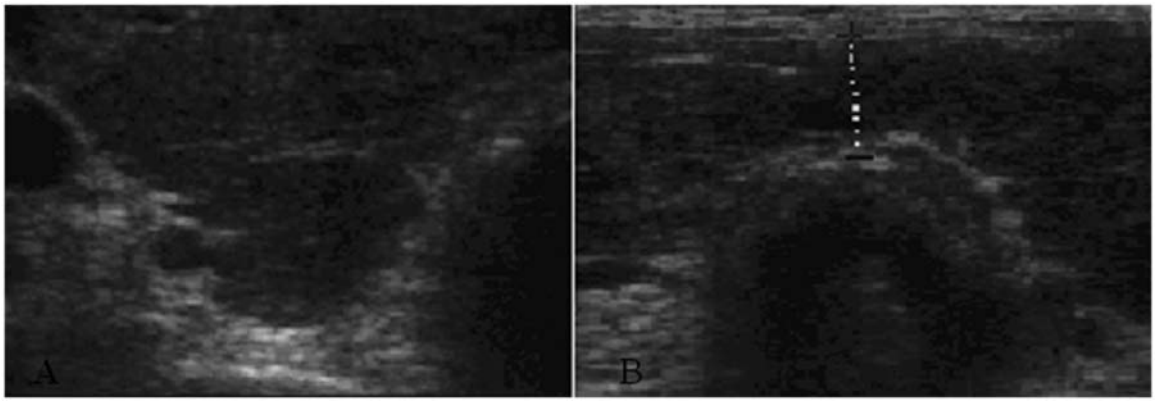

Figure 3. Thyroid ultrasonography in a patient with Graves' disease. Characteristic ultrasonographic features of Graves' disease include diffuse enlargement of the thyroid with hypoechoic areas (A). The isthmus is 2 cm in width, approximately three times its normal thickness (B).

of the thyroid gland, marked increase in glandular vascularity and the presence of small hypoechoic patches that reflect the inflammatory process (see Figure 3). Although the prevalence of thyroid cancer is not increased in patients with Graves' disease, a nodule that has suspicious features, such as hypoechogenicity, irregular edges or microcalcification, should be biopsied to exclude thyroid cancer. Whilst some investigators have demonstrated the utility of thyroid ultrasonography in distinguishing Graves' disease from Hashimoto's thyroiditis and in determining the risk of relapse and grading the severity of Graves' disease [Amodio *et al.* 2001; Vitti *et al.* 1995], the precise role of ultrasonography in the investigation and management of Graves' disease is unclear. Furthermore, it is a particularly operator-dependant investigation.

Investigating the effects of hyperthyroidism

Apart from establishing the diagnosis of Graves' disease, the clinician should also consider investigating a number of important effects of hyperthyroidism. Patients with other risk factors for osteoporosis (particularly postmenopausal women or those with a strong family history of osteoporosis) should receive bone mineral density scanning. Patients with palpitations or an irregular heart rhythm should have an electrocardiogram, followed by a 24-hour ambulatory monitor to assess for tachyarrthymia. Patients with a large goitre and symptoms suggestive of tracheal or oesophageal obstruction may require a CT scan of the neck (without contrast).

Treatment

In untreated patients, Graves' disease not only reduces quality of life [Abraham-Nordling

et al. 2007], it also poses the serious risks of psychiatric illness, cardiac disease, arrthymia and sudden cardiac death [Klein and Ojamaa, 2001]. Therefore, prompt institution of treatment is important.

The three treatment modalities for Graves' hyperthyroidism include the use of thionamides (antithyroid drugs), radioactive iodine (RAI) therapy or surgery. Patients in Australia, the UK and Europe are more likely than their North American counterparts to receive an initial course of thionamide therapy prior to the consideration of RAI. Surgery has the highest long-term remission rate (95%) but is not without risks [Wartofsky *et al.* 1991].

Thionamides

The two thionamides that have been in use since the 1940s are propylthiouracil (PTU) and methimazole (MMI). Carbimazole is a prodrug of MMI and has essentially the same mode of action and side effects. These drugs work by blocking the synthesis of thyroid hormone. PTU has the additional action of inhibiting peripheral conversion of T4 to the more active T3. These drugs may also possess immunosuppressive and anti-inflammatory properties, but this is controversial.

The superiority of either MMI or PTU has not been clearly established. However, MMI is considered to have particular advantages: it has a longer intrathyroidal half-life allowing for once-daily dosing (while PTU is usually administered three or four times daily). It has fewer side effects and some investigators report higher rates of remission [Nakamura *et al.* 2007]. Furthermore, a number of recent case reports of fulminant hepatitis and liver failure in young adults treated with PTU have clouded the situation with regards to the use of this agent [Cooper and Rivkees, 2009].

Patients should be informed of potential side effects including rash, arthralgia, ANCA-positive vasculitis, hepatitis and agranulocytosis (i.e. rapid decrease in white blood cell production leading to bacterial infections). Patients should be advised to stop antithyroid drugs if any potential symptoms of agranulocytosis develop, such as fever, oral ulceration or painful throat. This rare idiosyncratic reaction affects 0.1–0.3% of patients on antithyroid drugs, occurs acutely without prior warning and is not dose related. For this reason, there is no clear consensus recommendation for the routine measurement of the white cell count in patients on thionamide therapy.

Elevations in hepatic transaminase levels may either be a direct effect of thyrotoxicosis or related to medication use [Kubota *et al.* 2008]. While PTU may cause hepatocellular inflammation and, in severe cases, focal necrosis, MMI typically results in cholestatic dysfunction. Both are considered rare [Arab *et al.* 1995]. Recent reports of liver failure associated with the use of PTU have caused concern. Over a period of 20 years in the US, 22 cases of PTU-related liver failure resulted in 9 deaths and 5 liver transplants amongst adults, whilst 12 children developed liver failure resulting in 3 deaths and 6 transplants [Bahn *et al.* 2009]. On this basis, it was estimated that 1 in 10,000 adults taking PTU and a greater proportion of children (1 in 2000) are at risk of this life-threatening reaction. The US Food and Drug Administration has subsequently voiced concern regarding the routine use of PTU and has advised clinicians to be aware of this potential reaction (see http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm). There have also been subsequent changes in the recommendation on the management of Graves' disease during pregnancy, as outlined later in this article (see section 'Management of Graves' disease in pregnancy').

As euthyroidism is re-established, patients are likely to gain weight (on average 4 kg), due to the correction of the increased metabolic rate of untreated Graves' disease [Jacobsen *et al.* 2006].

The dose of thionamides administered should be individualized depending on the initial severity of disease and the rate of response to therapy, with the initial aim of normalization of T4 and T3 followed by serum TSH. An initial daily dose of MMI of 15–30 mg is usually adequate, with monitoring of thyroid function tests after 4 weeks and then 2- to 3-monthly thereafter. The dose of MMI may be eventually weaned to a maintenance daily dose of 5 mg. Although doses of MMI exceeding 30 mg daily are sometimes given to patients with severe hyperthyroidism, this should be done with caution due to an increase in the incidence of thionamide-induced side effects. [Abraham *et al.* 2010]. An equivalent dosing range for the use of PTU would be from

50 to 150 mg three times daily [Abraham *et al.* 2005].

The rationale of combining thionamides with thyroxine (the block-and-replace regimen) is to allow a higher dose and longer duration of thionamide therapy in order to normalize TSH while replacing the subnormal T4 induced by such a dose. Systematic reviews have not demonstrated any improvement in remission rates in patients taking the block-and-replace regimen as compared with a standard regimen of thionamides alone [Abraham *et al.* 2010, 2005].

Irrespective of the duration of thionamide therapy, the best long-term remission rate achieved with the use of these drugs alone is generally about 50% [Maugendre *et al.* 1999; Allannic *et al.* 1990]. This figure may be even lower in older patients, men, those with a large goitre and those with persistently elevated TSH-receptor antibodies [Garcia-Mayor *et al.* 1992]. However, there is no evidence that treatment duration should be determined by changes in the titre of TSH-receptor antibodies.

While randomized trials have shown greater remission rates in those treated for 18 *versus* 6 months [Allannic *et al.* 1990], they have shown no difference in remission rates in those treated for 24 *versus* 12 months [Garcia-Mayor *et al.* 1992] or 42 *versus* 18 months [Maugendre *et al.* 1999]. Therefore, most authors recommend a 12–18-month course of thionamide therapy [Abraham *et al.* 2010]. Our own practice is to discontinue thionamides 12–18 months after establishing a state of euthyroidism. Thereafter, clinical assessment and thyroid function tests within 3 months, followed by annual testing, to assess for relapse are appropriate as is the consideration of definitive therapy with radioiodine or surgery in the event of relapse. In particular patients, such as those averse to the concept of surgery or radioiodine, or elderly patients with significant comorbidities, the decision to avoid definitive therapy and continue long-term treatment with thionamides may be appropriate. A treatment algorithm is displayed in Figure 4.

Other drugs

Nonselective beta-blocker drugs are useful adjuncts for rapid symptomatic relief in hyperthyroidism. Although standard doses reduce the sympathetic overactivity characteristic of hyperthyroidism, beta-blockers have minimal effect on thyroid hormone levels and hypermetabolism. However, propranolol is believed to block the peripheral conversion of T4 to the more active hormone T3 and has greater effect on tremor than other more B-1 selective blockers [Brent, 2008].

Glucocorticoids also inhibit peripheral conversion of T4 to T3 and reduce thyroid hormone secretion in patients with Graves' disease. In spite of their use in patients with severe hyperthyroidism and thyroid storm, their efficacy is not well demonstrated. When used in combination with thionamides, cholestyramine assists in reducing serum T4 and T3 concentrations and may be a useful adjunct in patients who require rapid amelioration of symptoms such as those with thyroid storm [Mercado *et al.* 1996]. Although lithium blocks thyroid hormone release, it is rarely used due to toxicity.

For an in-depth discussion of the management of thyroid storm, a possible but rare complication of Graves' disease, readers are referred to a recent review in this journal [Carroll and Matfin, 2010].

RAI treatment

RAI may be given following an unsuccessful course of thionamides (as per Figure 4) or as initial therapy (as is commonly practiced in the United States) [Baskin *et al.* 2002]. Thionamides should be discontinued several days before the administration of RAI as this improves response rates [Bonnema *et al.* 2006]. In patients with severe hyperthyroidism or those in whom persistent hyperthyroidism poses serious risks (such as the elderly or cardiac patients), thionamides may be restarted shortly after RAI in order to control the hyperthyroidism while awaiting effect.

Following a dose of RAI, approximately 80% of patients eventually become hypothyroid, 10% remain euthyroid and 10% will need a second (or even a third) ablative dose [Leslie *et al.* 2003]. The particular dose of RAI that is administered may be fixed or determined on the basis of the gland's radionuclide uptake and volume in addition to the duration of time that the patient is able to remain in isolation. Patients receiving fixed doses of RAI may have higher response rates but are usually exposed to more radiation and also have higher rates of long-term hypothyroidism [Peters *et al.* 1996].

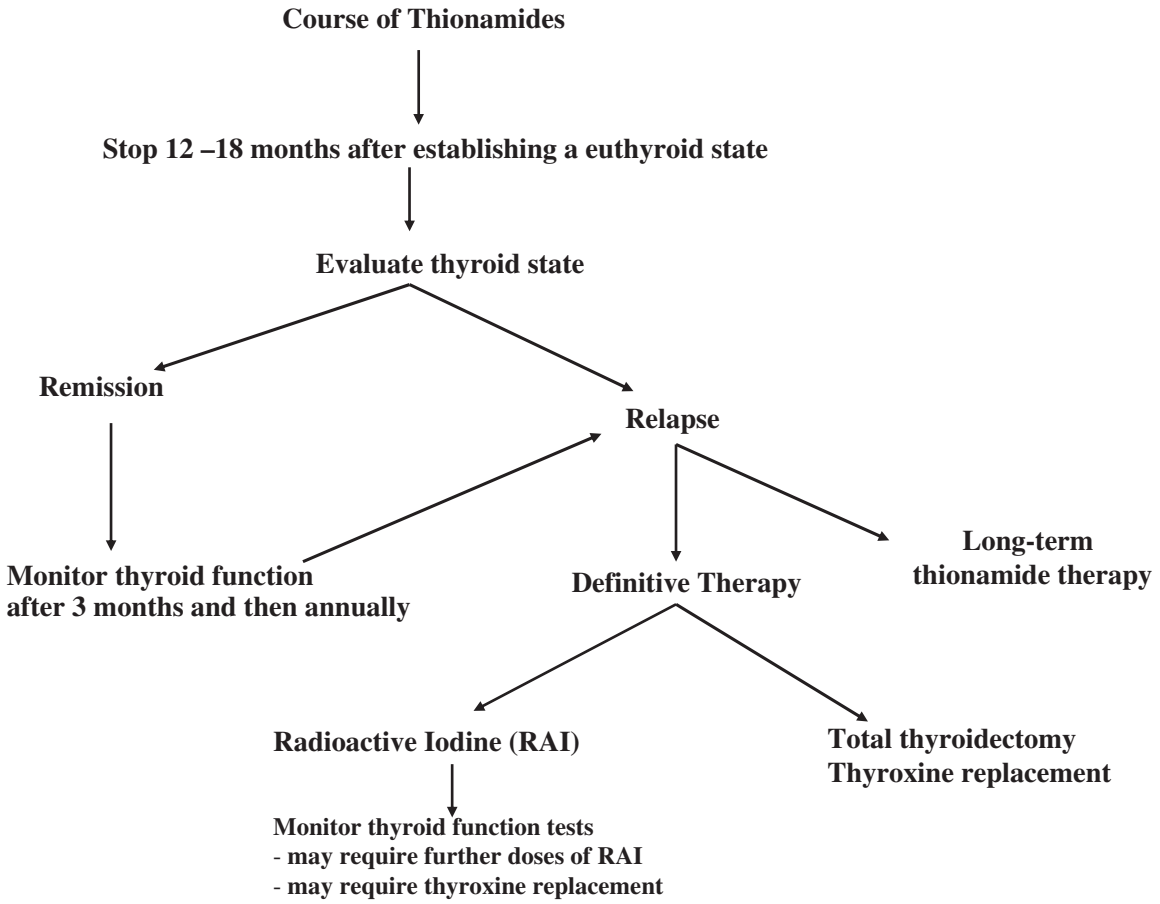

Figure 4. Treatment algorithm for Graves' disease.

Side effects of RAI include transient sore throat and radiation thyroiditis. The latter affects approximately 1% of patients, leading to a transient increase in thyroid hormone production and may be treated with a thionamide. Patients in whom such a flare may be deleterious, such as the elderly, those with pre-existing cardiac disease, or those with severe thyrotoxicosis, should receive a course of thionamide therapy prior to RAI, as this possibly reduces the risk of radiation thyroiditis.

Although some studies have reported an association between RAI and a greater incidence of malignancy and cardiovascular disease [Franklyn *et al.* 1999], this risk is not established and it is unknown whether it relates to the underlying hyperthyroidism rather than the RAI itself [Dobyns *et al.* 1974]. Several studies have suggested an association between RAI and exacerbation or development of thyroid eye disease but a causal link has not been established [Traisk *et al.* 2009]. This may possibly be due to the increased production of TSH-receptor auto-antibodies secondary to either a suppressive effect of RAI on regulatory T cells, or an increase in circulating antigenic stimuli following follicular cell death. Some studies suggest this effect can be mitigated by concurrent glucocorticoid treatment [Bartalena *et al.* 1998]. While some experts consider severe thyroid eye disease to be a contraindication to RAI, our own practice is to treat patients with severe active eye disease with prednisolone in the range of 30–50 mg daily, commencing on the first day of RAI and weaning over 6–8 weeks.

In a recent survey of 311 endocrinologists, surgeons, nuclear medicine radiologists and allied health professionals, the majority of respondents recommended that female patients who received doses of RAI for the treatment of Graves' disease (7–29 mCi) should abstain from intercourse for 24 hours and wait a minimum of 6 months before

attempting pregnancy [Greenlee *et al.* 2011]. However, unplanned pregnancies during this interval should be allowed to proceed to term as the risk of birth defects in offspring of these patients has not been shown to be greater than that of the general population [Ayala *et al.* 1998; Graham and Burman, 1986].

Surgery

Total thyroidectomy is an effective means of achieving remission but poses risks associated with general anaesthesia, recurrent laryngeal nerve palsy and transient or permanent hypoparathyroidism. It is therefore third-line therapy amongst most thyroid physicians. Surgery is particularly useful for patients who decline or cannot tolerate treatment with thionamides or RAI, or those with large, compressive goitres or suspicious nodules. There is some suggestion that thyroidectomy may prevent the later development of thyroid eye disease but this is anecdotal and should not be an indication for surgery in most patients.

Management of Graves' disease in pregnancy

PTU is traditionally considered to be safer in pregnancy due to the association of MMI with a rare birth defect, aplasia cutis. The occurrence of a life-threatening side effect of PTU in young people in the form of fulminant hepatitis has led to revision of the safety of this drug in pregnancy and recommendations that PTU be used during the first trimester (in order to avoid the development of aplasia cutis during organogenesis) and then switched to MMI in the second and third trimesters to minimize the risk of hepatitis [Cooper and Rivkees, 2009]. In spite of this, in many centres, PTU is still used throughout pregnancy.

As pregnancy is an immunomodulatory state, Graves' disease tends to improve or remit as gestation progresses, allowing thionamide therapy to be weaned or ceased. As thionamides cross the placenta, close monitoring of maternal thyroid function tests to minimize the risk of foetal hypothyroidism is important, with the aim of maintaining TSH concentrations in the lower third of the normal range [Marx *et al.* 2008]. Trimester-specific normal ranges for free T4 and TSH are being developed to aid in the precise monitoring of thyroid function during pregnancy. TSH-receptor antibodies also cross the placenta and levels should be measured in the third trimester as high levels correlate with risk of neonatal Graves' disease [Rotondi *et al.* 1998]. The use of ultrasonography to monitor foetal development and check for the presence of foetal goitre may be useful [Luton *et al.* 2005]. In this context, foetal goitre may be due to either overtreatment with thionamides or foetal Graves' disease. Patients should also be warned of the likelihood of relapse of their Graves' disease in the postpartum period [Rosei and Chiovato, 2008].

Novel agents

Rituximab, a monoclonal CD20 antibody, may induce a sustained remission in patients with Graves' disease who have low TSH-receptor antibody levels as well as ameliorating the signs of thyroid eye disease [El Fassi *et al.* 2007]. However, its utility is limited by both cost and toxicity.

A family of novel small-molecule ligands that bind to the transmembrane pocket of the TSH-receptor and inhibit the conformational change necessary for activation have been discovered [Neumann *et al.* 2010]. Seeking to mimic their activity while optimizing the potency of these agents, researchers have synthesized six analogues of these ligands and demonstrated significant inhibition of TSH-receptor basal signalling and TSH-stimulated signalling in HEK-EM 293 cells and primary cultures of human thyrocytes [Neumann *et al.* 2011]. Whilst these small-molecule ligands have emerged as promising targets, the studies remain preliminary and are yet to enter the clinical phase.

Conclusion

Graves' disease is a common condition whose management often poses complex challenges. A 12–18-month course of thionamide therapy is usually first-line therapy in Australia and the UK, with relapse treated with RAI or total thryoidectomy. Recent advances in Graves' disease include increasing characterization of extrathyroidal organ involvement, the emerging role of thyroid ultrasonography in the investigation of Graves' disease and the emergence of novel small-molecule TSH-receptor ligands as potential targets in the treatment of Graves' disease.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no disclosures, financial or otherwise, to report.

References

Abraham, P., Avenell, A., McGeoch, S.C., Clark, L.F. and Bevan, J.S. (2010) Antithyroid drug regimen for treating Graves' hyperthyroidism (Cochrane review). *Cochrane Database Syst Rev* 1: CD003420.

Abraham, P., Avenell, A., Park, C.M., Watson, W.A. and Bevan, J.S. (2005) A systematic review of drug therapy for Graves' hyperthyroidism. *Eur J Endocrinol* 153: 489–498.

Abraham-Nordling, M. (2005) Graves' disease: a long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. *Thyroid* 15: 1279–1286.

Abraham-Nordling, M., Wallin, G., Lundell, G. and Törring, O. (2007) Thyroid hormone state and quality of life at long-term follow-up after randomized treatment of Graves' disease. *Eur J Endocrinol* 156: 173–179.

Allannic, H., Fauchet, R., Orgiazzi, B., Madec, A.M., Genetet, B., Lorcy, Y. *et al.* (1990) Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. *J Clin Endocrinol Metab* 70: 675–679.

Amodio, F., Di Martino, S., Esposito, S., Iorio, S., Hierholzer, J., Rea, G. *et al.* (2001) Role of flowmetric analysis and of color-Doppler ultrasonography with contrast media in the different phases and follow-up of Graves' disease. *Radiol Med* 102: 233–237.

Arab, D.M., Malatjalian, D.A. and Rittmaster, R.S. (1995) Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 80: 1083.

Ayala, C., Navarro, E., Rodriguez, J.R., Silva, H., Venegas, E. and Astorga, R. (1998) Conception after iodine-131 therapy for differentiated thyroid cancer. *Thyroid* 8: 1009–1011.

Bahn, R.S., Burch, H.S., Cooper, D.S., Garber, J.R., Greenlee, C.M. and Klein, I.L. (2009) The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 19: 673.

Bartalena, L., Marcocci, C., Bogazzi, F., Manetti, L., Tanda, M.L., Dell'Unto, E. *et al.* (1998) Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 338: 73–78.

Baskin, H.J., Cobin, R.H., Duick, D.S., Gharib, H., Guttler, R.B. and Kaplan, M.M. (2002) American Association of Clinical Endocrinologists medical guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endo Prac* 8: 457–469.

Brent, G.A. (2008) Graves' disease. *N Engl J Med* 358: 2544–2554.

Bonnema, S.J., Bennedbaek, F.N., Veje, A., Marving, J. and Hegedüs, L. (2006) Continuous methimazole therapy and its effect on the cure rate of hyperthyroidism using radioactive iodine: an evaluation by a randomized trial. *J Clin Endocrinol Metab* 91: 2946–2951.

Carroll, G. and Matfin, G. (2010) Review: Endocrine and metabolic emergencies: thyroid storm. *Ther Adv Endocrinol Metab* 3: 139–145.

Cooper, D.S. and Rivkees, S.A. (2009) Putting propylthiouracil in perspective. *J Clin Endocrinol Metab* 94: 1881–1882.

Dobyns, B.M., Sheline, G.E., Workman, J.B., Tompkins, E.A., McConahey, W.M. and Becker, D.V. (1974) Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. *J Clin Endocrinol Metab* 38: 976–978.

El Fassi, D., Nielsen, C.H., Bonnema, S.J., Hasselbalch, H.C. and Hegeds, L. (2007) B lymphocyte depletion with the monoclonal antibody rituximab in Graves' disease: a controlled pilot study. *J Clin Endocrinol Metab* 92: 1769–1772.

El-Kaissi, S., Frauman, A.G. and Wall, J.R. (2004) Thyroid-associated ophthalmopathy: a practical guide to classification, natural history and management. *Intern Med J* 34: 482–491.

Franklyn, J.A., Maisonneuve, P., Sheppard, M., Betteridge, J. and Boyle, P. (1999) Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 353: 2111–2115.

Garcia-Mayor, R.V.P.C., Luna-Cano, R., Perez-Mendez, L.F., Pérez Mendez, L.F., Galofré, J.C. and Andrade, A. (1992) Antithyroid drug and Graves' hyperthyroidism. Significance of treatment duration and TRAb determination on lasting remission. *J Endocrin Invest* 15: 815–820.

Graham, G.D. and Burman, K.D. (1986) Radioiodine treatment of Graves' disease. An assessment of its potential risks. *Ann Intern Med* 105: 900–905.

Greenlee, C., Burmeister, L.A., Butler, R.S., Edinboro, C.H., McIntyre Morrison, S., Milas, M. *et al.* (2011) Current safety practices relating to I-131 administration for diseases of the thyroid: a survey of physicians and allied practitioners. *Thyroid* 21: 151–160.

Jacobsen, R., Lundsgaard, C., Lorenzen, J., Toubro, S., Perrild, H., Krog-Mikkelsen, I. *et al.* (2006) Subnormal energy expenditure: a putative casual factor in the weight gain induced by treatment of hyperthyroidism. *Diabetes Obes Metab* 8: 220–227.

Klein, I. and Ojamaa, K. (2001) Thyroid hormone and the cardiovascular system. *N Engl J Med* 344: 501–509.

Kubota, S., Amino, N., Matsumoto, Y., Ikeda, N., Morita, S., Kudo, T. *et al.* (2008) Serial changes in

liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis. *Thyroid* 18: 283–287.

Leslie, W.D., Ward, L., Salamon, E.A., Ludwig, S., Rowe, R.C. and Cowden, E.A. (2003) A randomized comparison of radioiodine doses in Graves' hyperthyroidism. *J Clin Endocrinol Metab* 88: 978–983.

Luton, D., Le Gac, I., Vuillard, E., Castanet, M., Guibourdenche, J., Noel, M. *et al.* (2005) Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab* 90: 6093–6098.

Maugendre, D., Gatel, A., Campion, L., Massart, C., Guilhem, I., Lorcy, Y. *et al.* (1999) Antithyroid drugs and Graves' disease—prospective randomized assessment of long-term treatment. *Clin Endocrinol (Oxf)* 50: 127–132.

Manji, N., Carr-Smith, J.D., Boelaert, K., Allahabadia, A., Armitage, M., Chatterjee, V.K. *et al.* (2006) Influences of age, gender, smoking and family history on autoimmune thyroid disease phenotype. *J Clin Endocrinol Metab* 91: 4873–4880.

Mariotti, S., Caturegli, P., Piccolo, P., Barbesino, G. and Pinchera, A. (1990) Antithyroid peroxidase autoantibodies in thyroid diseases. *J Clin Endocrinol Metab* 71: 661.

Marx, H., Amin, P. and Lazarus, J.H. (2008) Hyperthyroidism and pregnancy. *BMJ* 336: 663–667.

Mercado, M., Mendoza-Zubieta, V. and Bautista-Osorio, R. Espinoza-de los Monteros. (1996) Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. *J Clin Endocrinol Metab* 81: 3191–3193.

Nakamura, H., Noh, J.Y., Itoh, K., Fukata, S., Miyauchi, A. and Hamada, N. (2007) Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. *J Clin Endocrinol Metab* 92: 2157–2162.

Neumann, S., Eliseeva, E., McCoy, J.G., Napolitano, G., Giuliani, C., Monaco, F. *et al.* (2011) A new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor. *J Clin Endocrinol Metab* 96: 548–554.

Neumann, S., Huang, W., Eliseeva, E., Titus, S., Thomas, C.J. and Gershengorn, M.C. (2010) A small molecule inverse agonist for the human thyroid- stimulating hormone receptor. *Endocrinology* 151: 3454–3459.

Peters, H., Fischer, C., Bogner, U., Reiners, C. and Schleusener, H. (1996) Reduction in thyroid volume after radioiodine therapy of Graves' hyperthyroidism: results of a prospective, randomized, multicentre study. *Eur J Clin Invest* 26: 59–63.

Reasner, C.A. (1993) Autoimmune thyroid disease and type 1 diabetes. *Diabetes Rev* 1: 343–351.

Rotondi, M., Cappelli, C., Pirali, B., Pirola, I., Magri, F., Fonte, R. *et al.* (1998) Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association. *Eur J Endocrinol* 139: 584–586.

Rosei, E. and Chiovato, L. (2008) The effect of pregnancy on subsequent relapse from Graves' disease following a successful course of anti-thyroid drug therapy. *J Clin Endocrinol Metab* 93: 3985–3988.

Stenszky, V., Kozma, L., Balazs, C., Rochlitz, S., Bear, J.C. and Farid, N.R. (1985) The genetics of Graves' disease: HLA and disease susceptibility. *J Clin Endocrinol Metab* 61: 735–740.

Toft, A.D. (2001) Subclinical hyperthyroidism. *N Engl J Med* 345: 512–516.

Toft, A.D. and Beckett, G.J. (2003) Thyroid function tests and hypothyroidism. *BMJ* 326: 295–296.

Topliss, D.J. and Eastman, C.J. (2004) Diagnosis and management of hyperthyroidism and hypothyroidism. *Med J Australia* 180: 186–193.

Traisk, F., Tallstedt, L., Abraham-Nordling, M., Andersson, T., Berg, G., Calissendorff, J. *et al.* (2009) Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. *J Clin Endocrinol Metab* 94: 3700–3707.

Van Dyk, H.J. (1981) Orbital Graves' disease. A modification of the "NO SPECS" classification. *Ophthalmology* 88: 479–483.

Vitti, P., Rago, T., Mazzeo, S., Brogioni, S., Lampis, M., De Liperi, A. *et al.* (1995) Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. *Endocrinol Invest* 18: 857–861.

Wartofsky, L., Glinoer, D., Solomon, B., Nagataki, S., Lagasse, R., Nagayama, Y. *et al.* (1991) Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. *Thyroid* 1: 129–135.

Woeber, K.A. (2006) Triiodothyronine production in Graves' hyperthyroidism. *Thyroid* 16(7): 687–690.

Weetman, A.P. (2003) Graves' disease 1835–2002. *Horm Res* 59(Suppl. 1): 114–118.

Current concepts in Graves' disease

Christian M. Girgis, Bernard L. Champion and Jack R. Wall

Therapeutic Advances in Endocrinology and Metabolism published online 25 May 2011
DOI: 10.1177/2042018811408488