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DIAGNOSIS AND TREATMENT OF GRAVES' DISEASE

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ABSTRACT

The diagnosis of Graves' disease is mostly straightforward, depending on recognition of the cardinal features of the disease and confirmation by tests including serum TSH, free T4, and TSH receptor antibodies. The differential diagnosis includes other causes of thyrotoxicosis, such as secretory thyroid nodules, various forms of inflammatory or destructive thyroiditis, or thyrotoxicosis factitia. The mainstay of treatment of Graves' disease for most patients remains thionamide antithyroid drugs, with radioiodine (^{131}I) and thyroidectomy surgery being necessary for patients whose hyperthyroidism is not controlled following one or more courses of antithyroid drug or for whom antithyroid drugs are unlikely to result in durable remission. As none of these treatment modalities have limitations, shared decision making should be used to determine each patient's preference. Stratification of disease severity at presentation, based on patient age, goiter size, degree of hyperthyroidism, and concentration of TSH receptor antibodies reliably predicts prognosis and should be used to inform choice of primary therapy. Subclinical hyperthyroidism owing to Graves' disease has a high progression rate to overt hyperthyroidism and antithyroid drug therapy should be the primary mode of therapy for most patients. Graves' disease in children and young adults has a worse outcome than in adults and primary treatment with a prolonged course of antithyroid drugs is recommended, with many cases requiring eventual definitive treatment with thyroidectomy or radioiodine, when timing is appropriate to the educational and social situation. Other special situations including pregnancy and thyroid eye disease are also reviewed. As none of the existing therapies are ideal, there are a range of new therapeutic options currently in clinical trials, including approaches to deplete serum TSH receptor antibodies from plasma and to directly block TSH receptor signaling using both small molecule antagonists and biologics. These advances are likely to change the physician's armamentarium for management of Graves' disease substantially in the next decade.

CLINICAL DIAGNOSIS

There are several guidelines that address the diagnosis and treatment of Graves' disease (1-6). The diagnosis of Graves' disease can often be made on clinical grounds, though this is not always possible. The specificity of symptoms and signs is generally low. The larger the number of symptoms and signs, the higher the probability that the clinical diagnosis is correct (7). The clinical features can vary from none to severe and depend on the duration, severity of thyrotoxicosis, age of the patient, and underlying comorbidities (8). Firstly, the question that needs to be answered is "does the patient have hyperthyroidism?" (Table 1) and secondly "does the patient have features to suggest Graves' disease?" (Table 2).

Table 1. Features of Hyperthyroidism
Symptoms
Weight loss despite normal or increased appetite
Heat intolerance
Excess sweating
Palpitations
Tremor
Tiredness
Reduced exercise tolerance
Dyspnea
Loose / increased frequency of bowel motions
Anxiety / inability to relax
Hyperactivity
Mood disturbance
Weakness
Restlessness
Insomnia
Menstrual disturbances
Loss of libido
Ankle swelling
Polyuria and polydipsia
Hair loss
Signs
Evidence of recent weight loss
Moist skin
Goiter
Upper eyelid retraction / lid lag
Hyperkinesis
Increased pulse pressure
Sinus tachycardia, occasionally atrial fibrillation
Cardiac failure
Proximal myopathy

Bulbar myopathy
Abnormal mental state (hypomania / mania / depression)
Brisk reflexes
Peripheral edema
Diffuse alopecia
Palmar erythema
Onycholysis

Table 2. Features Suggestive of Graves' Disease
Family or personal history of autoimmune diseases
Past history of Graves' disease
Female sex
Middle age
Diffuse goiter with bruit
Graves' orbitopathy (thyroid eye disease)
Dermopathy
Acropachy
Predisposing immunomodulatory drugs: e.g. Alemtuzumab

The four most typical symptoms are unexplained weight loss, palpitation/ awareness of tachycardia, tremors, and heat intolerance or sweating. Tiredness, exercise intolerance, breathlessness, loose bowel motions, anxiety, insomnia, goiter, upper eyelid retraction and lid lag, and menstrual disturbances are also frequently elicited. Less common symptoms are muscle weakness, increased thirst and polyuria, and itch. Older people may present with apathy and few or no other symptoms (9), leading to a delayed presentation with cardiac manifestations (10). Occasionally patients may present with complications of Graves' disease as the presenting feature, for example atrial fibrillation or other tachyarrhythmia, heart failure, thyroid eye disease, diabetes, infertility, or osteoporotic fractures (8,9). Features that point towards Graves' disease being the cause of the hyperthyroidism include personal or family history of autoimmune disease, past history of Graves' disease, female sex, middle age, diffuse goiter associated with bruit, features of thyroid eye disease, dermopathy and acropachy (see chapter Graves' Disease: Complications).

LABORATORY DIAGNOSIS

Biochemical confirmation of hyperthyroidism and of the underlying cause, is mandatory as it is more sensitive than clinical assessment, documents objectively the severity of the hyperthyroidism, and guides choice of treatment (8,9). The thought process about laboratory diagnosis follows the same pattern as clinical diagnosis: hyperthyroidism should first be confirmed biochemically and then specific antibody tests used to diagnose Graves' disease.

Confirmation of Hyperthyroidism

Measurement of serum TSH is the most sensitive initial screening test and TSH is fully suppressed (<0.05 mU/L) in newly presenting Graves' disease. Patients who have low TSH in the 0.1–0.4mU/L range are likely to have another explanation for their symptoms. If TSH is suppressed, both serum free T4 and T3 should be measured (see chapter Clinical Strategies in the Testing of Thyroid Function). In the evolution of Graves' disease, after serum TSH

becomes fully suppressed, the next change is an elevation in serum free T3 and finally elevation in serum free T4. Patients with either elevation in free T3 alone (so called T3 thyrotoxicosis) or elevation in both free T3 and free T4 are considered to have overt hyperthyroidism, are at risk of complications, and should generally be offered treatment. The state of patients with isolated low TSH is termed 'Subclinical Hyperthyroidism' and treatment can be considered but is not mandatory (1,4,5) (see section below).

Confirmation of Graves' Disease

TSH receptor antibodies (TRAb) are elevated in untreated Graves' disease and the test of choice for confirmation of a precise diagnosis. The sensitivity and specificity of TRAb are around 95%, approaching 100% when TRAb bioassays are used (4,9,11). Thyroid scintigraphy using radioiodine or technetium is an alternative means of confirming the diagnosis of Graves' disease. Typically, scintigraphy shows increased uniform and diffuse uptake (Figure 1).

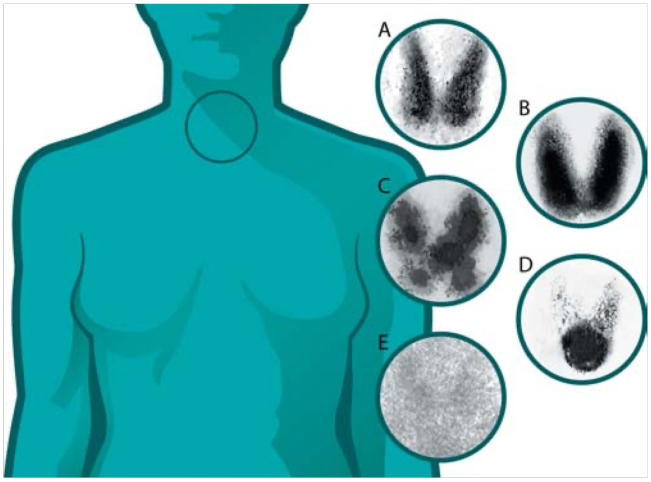

Figure 1. Different patterns of radioiodine uptake of thyroid scintigraphy. (A) Normal. (B) Graves' disease: diffuse increased uptake in both thyroid lobes. (C) Toxic multinodular goiter: "hot" and "cold" areas of uneven uptake. (D) Toxic adenoma: increased uptake in a single nodule with suppression of the surrounding thyroid. (E) Thyroiditis: decreased or absent uptake (figure derived from Perros P. Thyrotoxicosis and pregnancy. PLoS Med. 2005 Dec;2(12):e370. doi: 10.1371/journal.pmed.0020370. Epub 2005 Dec 27. PMID: 16363909; PMCID: PMC1322287 (under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium).

Thyroid ultrasonography using color flow Doppler can distinguish destructive thyroiditis from causes associated with increased vascularity (Graves' disease, toxic adenoma, toxic multinodular goiter), (see chapter Ultrasonography of the Thyroid).

When measurement of TRAb is available, it is the diagnostic test of choice for confirmation of Graves' disease. Initial serum TRAb concentration also gives some prognostic information to guide therapeutic choices (1,4,11).

DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS

Graves' disease must be differentiated from other conditions causing thyrotoxicosis. These are summarized in Table 3.

Table 3. Differential Diagnosis of Thyrotoxicosis						
Diagnosis	**Etiology of thyrotoxicosis**	**Key Clinical Features**	**Serum TSH**	**Serum free T3/T4**	**RAIU**	**Other Diagnostic Features**
Graves' Disease	Autoimmune	Diffuse goiter, thyroid eye disease, rarely thyroid dermopathy	Suppressed	Elevated	High (diffuse uptake)	TRAb positive
Toxic Multinodular Goiter	Nodular thyroid disease	Older age, nodular goiter, no eye signs	Suppressed	Elevated	High Patchy uptake	Often insidious onset Antibodies usually negative
Hyperfunctioning ('Toxic') Adenoma	Solitary nodule	Palpable single nodule, younger adults	Suppressed	Elevated	Hot nodule seen; rest of gland suppressed	Rarely malignant in adults*
Thyroiditis (e.g., subacute, painless, postpartum, drug-induced)	Inflammatory	Tender thyroid (in subacute), recently postpartum, flu-like illness	Suppressed	Elevated	Low	High ESR/CRP in subacute; anti-TPO+ in autoimmune types
Functioning Thyroid Carcinoma	Malignant	Metastases often present	Suppressed	Elevated or normal	Focal uptake	Elevated serum thyroglobulin
Exogenous Thyroid Hormone Intake (Thyrotoxicosis factitia)	Iatrogenic or self-inflicted	Often health-conscious individuals, weight loss without goiter	Suppressed	Elevated	Low	Low thyroglobulin levels Lack of response to ATDs
TSH-Secreting Pituitary Adenoma	Central hyperthyroidism	Goiter, visual field defects, headache	Normal or high	Elevated	Normal or high	Requires MRI pituitary Elevated TSH alpha-subunit
Thyroid Hormone	Genetic-caused by TH	Variable features including	Normal or slightly elevated	Elevated	Normal	Genetic testing

Resistance Syndrome	receptor beta mutations	goiter, tachycardia, attention deficit, or euthyroid; dominant familial.				
Iodine-Induced Hyperthyroidism	Iatrogenic / Triggered	History of iodine load (contrast, amiodarone)	Suppressed	Elevated	Variable	Often seen in multinodular goiter areas; contrast history
Amiodarone-Induced Thyrotoxicosis (AIT)	Drug-induced	On amiodarone, arrhythmias, no classic features	Suppressed	Elevated	Variable	AIT Type 1 (high RAIU), AIT Type 2 (low RAIU)
Biotin assay interference	Dietary supplement use	Biotin can interfere with lab tests that use biotin – streptavidin technology	Suppressed	Elevated	Normal	Mitigated by stopping biotin 48hrs before testing
Familial dysalbuminemic hyperthyroxinemia (FDH)	Genetic	Mutant albumin in FDH has higher affinity for T4 and T3. Enquire about FH. Clinically euthyroid	Normal	Elevated	Normal	Two step assays are less susceptible to interference. Genetic test will confirm.
Choriocarcinoma / Hydatidiform mole/ other HCG producing tumors	Malignant	Increased HCG production- HCG and TSH share same alpha-subunit- binds and activates TSHR	Suppressed	Elevated	Normal / increased	Therapy directed at tumor
Gestational transient thyrotoxicosis	Triggered by pregnancy	Occurs due to HCG/TSH homology.	Suppressed	Elevated	Contraindicated in pregnancy	Usually self-limiting. More frequent in twin or

		Can present with goiter. Often associated with hyperemesis gravidarum. Presents in first trimester (usually weeks 8-14)				multiple pregnancy
Struma ovarii	Hyperfunctioning ectopic thyroid tissue	Ectopic benign or malignant thyroid tissue in ovarian teratoma	Suppressed	Elevated	Neck RAIU reduced; uptake in ectopic tissue may be visible	Cross-sectional imaging usually shows pelvic mass

*Functioning follicular lesions in childhood may be malignant in 15-30% of cases. Abbreviations: ATD: Anti-Thyroid Drug; CRP: C-reactive Protein; ESR: Erythrocyte Sedimentation Rate; RAI: Radioactive Iodine; RAIU: Radioactive Iodine Uptake; TPO: Thyroid Peroxidase; TRAb: Thyrotropin receptor antibody.

An overlooked feature in the history of thyrotoxicosis is the mode of onset, with Graves' disease or toxic nodular goiter having an insidious onset where the patient has difficulty recalling when exactly the first symptoms appeared; whereas thyroiditis, particularly drug-induced or subacute may have a very sudden onset and the patient is able to recall the onset of symptoms within a few days.

TREATMENT OF THYROTOXICOSIS

Selection of Primary Therapy

The hyperthyroidism of Graves' disease may be treated by three different well-established modalities: antithyroid drugs (ATDs), radioiodine (RAI) therapy, or surgical thyroidectomy (1,4,5,8,9,12). As none of these treatments is perfect, the choice of primary therapy depends largely upon patient preference and the likelihood of a favorable outcome given the presenting features (both clinical and biochemical). However, the goals and criteria for a successful outcome differ between treatments: for both radioiodine therapy and thyroidectomy the intention is to ablate or remove all functioning thyroid tissue (thus committing the patient to life-long thyroid hormone replacement therapy), whereas ATD therapy aims for long-term, drug-free remission (8,9,18). For patients presenting with mild hyperthyroidism, without goiter and serum TRAb concentrations less than three-fold above the threshold for positivity, antithyroid drugs provide greater than 50% chance of long-term remission. However, for patients with severe hyperthyroidism or large goiter at presentation, one of the definitive treatments (RAI therapy or surgical thyroidectomy) would be preferable, because the risk of relapse following a standard 12–18 months of ATDs is high (4,5,11). In this situation, RAI is a highly effective treatment, however, thyroidectomy would be the preferred choice in patients with a large goiter or for those with thyroid eye disease at presentation. Because none of these well-established treatments are ideal, new methods of treatment, including novel surgical approaches, minimally invasive radiological procedures and new drug therapies are emerging.

Antithyroid Drugs

Several thionamide (also known as thioureylene) ATDs are available, with methimazole and its pro-drug carbimazole being the most frequent first choice (12,13). Propylthiouracil is also widely available, and its sister compounds methylthiouracil and benzylthiouracil remain available for use in some countries (13). Methimazole and carbimazole have the advantage of being effective in a single daily dose, whereas propylthiouracil is usually taken twice or three times daily. All thionamide ATDs act as a preferential substrate for iodination by thyroid peroxidase, such that once ATD reaches a critical concentration in the thyroid tissue, ongoing iodination of thyroglobulin residues to make thyroid hormone precursors becomes negligible and thus thyroid hormone production is inhibited (14). Depending upon severity of underlying hyperthyroidism and dose of medication, it can take 4 to 8 weeks to normalize serum FT4 or FT3 following initiation of ATD treatment. After normalization of free serum thyroid hormones, the initial ATD dose can be reduced to avoid hypothyroidism, in a dose titration regimen. Alternatively, a higher dose of ATD can be maintained, with the addition of levothyroxine to prevent hypothyroidism, known as a block-replace regimen. There is no convincing evidence that the block-replace regimen gives superior remission rates to titrated ATD treatment, although the incidence of side-effects may be higher (15-18). However, block-replace regimen ATD may still have utility in patients with high concentrations of TRAb antibodies or where there is a mixed population of blocking and stimulating antibodies leading to rapid fluctuations in thyroid hormone levels: typically found in patients with thyroid eye disease or post-alemtuzumab Graves' disease.

Antithyroid drugs are usually administered daily for 12 to 18 months with a remission rate of 50% following this period of treatment being widely quoted (4,5,8,9). However, success at achieving remission is to a large extent determined by the initial presenting features and by the trajectory of TRAb once ATDs have been commenced. Severe hyperthyroidism, very high TRAb concentrations, young age, and large goiter at presentation have been linked to poor remission rate following ATD in numerous studies (see Table 4 for 'GREAT' score) (19,20). Patients with none of these adverse features may expect an approximately 80% chance of remission with ATDs, contrasting to about 30% chance for patients with all 4 adverse factors. Male sex and thyroid eye disease have also been linked to poor outcome of hyperthyroidism in some but not all investigations (21). In addition to these presenting features, the change in TRAb concentration during ATD treatment also has prognostic significance (22,23). Both European and American guidelines agree that ATDs should not be stopped in patients who continue to have detectable TRAb antibodies following 18 months' ATD treatment (4,5). Different TRAb trajectories have also been recognized, including smooth disappearance, fluctuating, and smoldering patterns, with the likelihood of remission being substantially lower in patients with the latter 2 trajectories (22,23).

Table 4. GREAT Score

Factor	Criteria	Score
Age	≥40 yr	0
	<40 yr	1
Free T4	<40pmol/L	0
	≥40pmol/L	1
TRAb	<6 IU/L	0
	6-19.9 IU/L	1

	≥20 IU/L	2
Goiter	Absent/ small	0
	Visible/Huge	2
Total		
GREAT Score	**Remission at 24 months**	
0 or 1	84%	
2 or 3	56%	
4 or more	32%	

SIDE EFFECTS

All thionamide ATDs have the potentially life-threatening side-effect of agranulocytosis, which occurs in one in 300–500 users (24,25). The peak time for agranulocytosis is after one month of treatment (28 to 33 days). The risk declines after six months of treatment but persists for as long as a patient remains on ATD therapy (25,26). ATDs must be stopped immediately if the patient develops fever, sore throat, or other signs of sepsis and an urgent complete blood count must be ordered. In around 10% of cases of agranulocytosis, there will be associated thrombocytopenia and/or aplastic anemia (24-26). Even if ATDs are stopped promptly, there may be a 5-to-7-day interval before neutrophil counts recover, and management with isolation, prophylactic parenteral antibiotics, and granulocyte-macrophage colony stimulating factor (GM-CSF) may be needed. As there is cross reactivity between methimazole/carbimazole and propylthiouracil, the patient should never receive thionamide medication again. In some cases of ATD-induced agranulocytosis, there are detectable circulating anti-neutrophil cytoplasmic antibodies (ANCA) directed at the myeloperoxidase enzyme which has structural homology to the extracellular domain of the TPO molecule, suggesting an immune basis (27). A plan for control of thyrotoxicosis should be hatched as soon as agranulocytosis presents, as the combination of prolonged sepsis and concurrent uncontrolled hyperthyroidism increases the risk of thyroid storm.

Agranulocytosis is fortunately rare, however rash and pruritus on the trunk and arms is the commonest side effects of methimazole/carbimazole and may occur in around 5% of users (26). This usually occurs in the first few weeks of treatment and is self-limiting in most cases: symptomatic management with antihistamine and topical emollient or hydrocortisone cream may be effective. In some patients a swap to propylthiouracil may be warranted if the symptoms persist. Gastritis with immediate vomiting is also sometimes seen with carbimazole and methimazole: splitting the daily dose from once daily into several smaller doses (e.g. from 20 mg once daily to 5 mg taken four times a day) can often be effective. Although rash and gastritis appear less frequently with propylthiouracil, around one in 10,000 adults develop potentially life-threatening hepatotoxicity with it. The incidence in children and younger people may be as much as one in 2,000, so propylthiouracil should be avoided in this age group (28). In contrast, methimazole and carbimazole may cause an isolated but stable elevation in serum alkaline phosphatase up to around 2.5 times the upper limit of normal, with no apparent other detrimental effect on liver function. In addition, acute pancreatitis has rarely been reported with both methimazole and carbimazole (29). Although all ATDs may cause arthralgia, propylthiouracil may rarely cause vasculitis or be responsible for drug-induced lupus (27). Risks to the fetus of ATDs during pregnancy are discussed elsewhere.

LONGER-TERM TREATMENT

After an initial period of 12–18 months of treatment with ATDs, around 50% of adult patients will relapse within one to 2 years and the preferred next step in therapy has conventionally been either RAI therapy or surgical thyroidectomy (4,5,8,9). However, at this stage, many patients prefer the option of either a second course or long-term ATDs (12). There are no high-quality randomized studies to inform treatment decisions in this situation, but observational retrospective studies suggest that the outcome of a second course of ATDs is not significantly different from that of the first course, i.e. a remission rate of about 30–50% (23,30). However, such studies do not take into account those patients who had severe symptoms at relapse, complications of relapsed hyperthyroidism (e.g. atrial fibrillation), side effects from ATDs, or large goiter who then chose definitive management; therefore, interpretation must be guarded. There are two randomized trials of short-term vs longer term antithyroid drug treatment. A French study found no difference in remission rates when comparing 18 and 42 months ATD treatment (31). A larger Iranian study showed a benefit to ATD treatment for an average of 8 years compared to 19 months (32). However, interpretation of this study is compromised by twice the baseline prevalence of large goiter in the short-term ATD group (32). In short, these randomized studies show no conclusive benefit from long-term ATD treatment, and the non-randomized studies are likely biased by selection of uncomplicated and milder cases for ongoing ATD treatment. Nevertheless, patients often prefer to persevere with long-term low-dose ATDs, which is an acceptable option.

In patients who have successful long-term remission of hyperthyroidism following ATDs, there is a continuing risk of hypothyroidism as destructive autoimmune thyroiditis may persist for decades, leading to eventual thyroid failure (33). This risk is between 10 and 25% dependent on the length of follow up (33,34). Because of the insidious onset of hypothyroidism with non-specific symptoms, annual serum TSH measurement is recommended even following apparently successful primary treatment of Graves' disease with ATD.

Non-Thionamide Medical Therapy

Patients with symptomatic tachycardia including tachyarrhythmia or tremor can gain rapid control of these symptoms with oral beta blockers. While historically propranolol has been favored owing to its action of inhibiting T4 to T3 conversion, which leads to a small reduction in serum T3 (35), any beta blocker including cardio-selective compounds are efficacious. Patients who are hyperthyroid may metabolize beta blockers more rapidly than euthyroid patients, so doses of modified-release propranolol up to 80 mg twice or three times daily may be needed to control tachycardia in severe hyperthyroidism. Asthma is a contra-indication to beta blocker usage, but in this situation rate-limiting calcium channel blockers such as diltiazem may be used instead.

For more rapid control of thyrotoxicosis than can be achieved with thionamides alone, inorganic iodide, given as Lugol's iodine or a saturated solution of potassium iodide (SSKI) can be used. These solutions are administered 0.1–0.3 ml three or four times daily and typically result in normalization of serum free T3 within 5 to 7 days through the Plummer effect (36). In addition, cholestyramine or other bile acid sequestrants may lead to improvement in thyrotoxicosis by reducing the enterohepatic re-circulation of thyroid hormones. While iodide and cholestyramine should not be routinely employed in management of Graves' hyperthyroidism, they can be effective interventions either individually or in combination for patients who need rapid control of thyrotoxicosis owing to cardiac decompensation, the need for urgent surgery, or thyroid storm (36).

Lithium carbonate is also effective in reducing thyroid hormone levels in hyperthyroidism by inhibiting thyroid hormone secretion, but its effect is slower than that of iodide, taking 7 to 14 days for significant reduction in thyroid hormones. A starting dose of 600–800 mg has been shown to be effective, with serum monitoring of lithium concentrations if the patient is to have a prolonged course (37). It has the advantage of not blocking thyroidal iodide uptake, so may be used in the run up to RAI therapy (38).

Radioiodine

Radioiodine (^{131}iodine) therapy has been used to treat benign thyroid disease for more than 80 years. This treatment is well tolerated and cost effective in comparison with other treatment modalities. In most parts of the world, thionamide ATDs are used as the first-line treatment for Graves' disease. In the United States, RAI has historically been the preferred therapy, but in the last decade, there has been an increasing trend towards first-line ATD use (12). Several predictive markers of relapse following ATD have been identified as discussed above (Table 4) (19-21, 39,40), and considering these factors, the UK guidance on the assessment and management of thyroid disease (NICE guideline NG145) has recommended RAI as the first-line, definitive therapy in adults, unless ATDs are likely to achieve remission or there are contradictions to RAI (1). The principle being that patients who are highly likely to relapse after ATDs should be offered early definitive therapy.

RAI therapy is the preferred choice of treatment for Graves' disease if the patient is keen to have definitive control of hyperthyroidism and would like to avoid the risks related to thyroid surgery. Patients who have higher surgical risk from comorbidities, previous neck surgery, or prior external-beam irradiation to the neck should also consider RAI. In some special circumstances such as thyrotoxic hypokalemic periodic paralysis, uncontrolled tachyarrhythmia, congestive heart failure or pulmonary hypertension with right heart failure, where rapid control of hyperthyroidism without the risk of anesthesia and surgery is required, primary RAI following a few weeks of ATD is the preferred option. RAI therapy is contraindicated in pregnancy, during breast feeding, or if pregnancy is planned within the next 4 to 6 months (Table 5). RAI should not be offered to a patient who has suspected or untreated thyroid cancer, or who is unable to comply with radiation protection safety measures, which—at lower RAI activities than those used for thyroid cancer—show surprisingly wide variation between countries. Conception should be postponed until at least 6 months after RAI for females, and 4-6 months for males, according to local guidance.

Table 5. Precautions and Restrictions for Therapeutic Radioiodine
Contra-indicated during pregnancy or lactation
Avoid pregnancy for 6 months (woman)
Avoid fathering a child for 4 months (man)
Avoid in active Thyroid eye disease, cigarette users, or consider administering under prednisolone cover.
Social contact
Contact with children or pregnant women

RAI is given as a single dose of ^{131}iodine in liquid or capsule form. It is rapidly absorbed and concentrated by the thyroid gland, with 90% of the remaining radioactive substance cleared by the kidneys. Clearance of RAI is reduced in patients with renal failure and for patients on dialysis, for whom special care and RAI dose adjustment are required (41). Patients are advised not to consume supplements

containing iodine or seaweed for at least 7 days before RAI therapy (42).

TREATMENT REGIMEN

RAI is taken up by the sodium-iodide symporter into thyroid cells and in part organified into thyroglobulin. Once trapped inside the thyroid follicle, the beta particles emitted by the RAI damage the DNA of the thyroid follicular cells, leading to apoptosis. The goal of RAI therapy in Graves 'disease is to control hyperthyroidism by rendering the patient hypothyroid. Historically, clinicians aimed to find the lowest RAI activity needed to render patients euthyroid, as per ALARA (as low as reasonably achievable) principles of radiation protection, but this did not work well. Hyperthyroidism would often recur and a high proportion of patients required re-treatment. There is no single RAI activity regimen that reliably achieves the optimal outcome of euthyroidism without post-ablative hypothyroidism. Hence, RAI is effective if a sufficient radiation dose is deposited in the thyroid to completely destroy the thyroid gland, where 90% of patients would achieve hypothyroidism within 3 to 12 months after treatment. This outcome can be accomplished equally well by either administering a fixed activity or by calculating the activity based on the size of the thyroid and its ability to trap iodine (43).

In general, the use of fixed activity regimens simplifies the treatment approach and saves cost, a position supported by the UK guideline for the last 2 decades (1). The 2016 American Thyroid Association guidelines recommend sufficient activity of RAI should be administered in a single application, typically a dose of 370–555 MBq (10–15 mCi) as guided by thyroid size, to render the patient with Graves' disease hypothyroid (5).

The calculation of a therapeutic RAI activity relies on knowing the thyroid size, RAI uptake and the quantity of radiation to be deposited per gram of thyroid tissue (44). The most frequently used RAI uptake is calculated at 24 hours, and the size of the thyroid is determined by palpation or ultrasound (45). Randomized controlled trials have not found any clinically significant advantage to calculated RAI activity over a fixed activity of RAI (46,47). Neither is there a reliable method to measure individual RAI dose-response relationship. The use of calculated RAI activity adds to the complexity of the procedure and increases costs related to the additional measurements with thyroid uptake and ultrasound.

PRE-TREATMENT WITH ATD

RAI induces destruction of thyroid follicles and release of the stored thyroid hormones, which can increase the circulating levels of thyroid hormones. According to a few small, randomized trials, transient exacerbations of thyrotoxicosis were found in <20% of patients who were overtly hyperthyroid before RAI administration; the majority of these were asymptomatic (48-50). In another study, exacerbation of thyrotoxicosis was noticed in 30-50% of the patients 2 to 6 weeks after RAI therapy and was greater in those not pre-treated with ATD (51). Rarely thyroid storm has been reported following the administration of RAI (52). While many clinicians pre-treat overtly hyperthyroid patients with ATDs prior to RAI, randomized trials have found that ATDs did not protect against the rise in thyroid hormone levels after RAI (48,49).

Pre-treatment with ATDs lowers the free thyroid hormone concentrations, which could protect high risk patients from developing thyroid storm or other complications such as tachyarrhythmia from worsening thyrotoxicosis after RAI. The American, European and the UK guidelines recommend clinicians consider the use of ATDs before RAI to make this treatment safer and to reduce the risk of symptomatic thyrotoxicosis (1,4,5). This is particularly pertinent in patients with severe thyrotoxicosis, usually with free T4 concentration 2–3 times the upper limit of the reference range, or with multiple comorbidities and a greater risk for complications from worsening

hyperthyroidism. This includes patients with atrial fibrillation, heart failure, pulmonary hypertension, renal failure, cerebrovascular, or pulmonary disease. Along with ATDs, beta blockers should be prescribed in symptomatic or high-risk patients prior to RAI and this medication should be tapered down once circulating levels of thyroid hormones return to the reference range.

ATDs reduce intra-thyroidal uptake of RAI and hence pre-treatment with ATD increases the risk of treatment failure. Carbimazole or methimazole should be discontinued 4 to 7 days before the administration of RAI. Pre-treatment with propylthiouracil has been shown to have a higher rate of treatment failure as compared to carbimazole or methimazole (53). Therefore, propylthiouracil should be discontinued 10-14 days before the administration of RAI.

Patients with high concentrations of TRAb have an increased risk of symptomatic or severe hyperthyroidism following RAI (52), as the destructive effect of RAI on thyrocytes will take a few weeks to commence, while TRAb continues to drive thyroid hormone production in the absence of ATDs. ATD should be restarted 7 to 14 days after RAI in this group of patients, to ensure continuous depletion of intrathyroidal hormones. In one study, if ATD was restarted 7 days after RAI, the free T4 measured 3 weeks after RAI was 6% lower than at the time of RAI administration; and if ATD was not restarted after RAI, the free T4 was 36% higher than the values at the time of RAI administration (54). Pre-treatment with ATDs had no effect on either the time required for hypothyroidism or the 1-year success rate of RAI (55).

POST RAI MANAGEMENT

The recommended fixed activity regimen for RAI in Graves' disease, in the range of 370–555 MBq (10–15 mCi), will render 80-90% of patients permanently hypothyroid (56). Hypothyroidism may occur from 4 weeks on, with 40% of patients being hypothyroid by 8 weeks and a median time for hypothyroidism of 18-20 weeks (57,58). This transition can happen rapidly and hence most guidelines recommend measuring of TSH, free T4 and free T3 (or total T3) levels every 4 to 6 weeks for the first 6 months following RAI (5,6). Every effort should be made to avoid patients becoming symptomatically hypothyroid during this transitional phase by timely introduction of thyroid hormone replacement. Circulating levels of thyroid hormones should be used to guide the start of thyroid hormone replacement therapy, as serum TSH levels may not rise immediately after RAI. When thyroid hormone replacement is initiated, the dose should be initially adjusted based on serum free T4 concentration.

Transient or fluctuating hypothyroidism immediately following RAI therapy occurs in 2-5% of patients given lower activities (e.g. ~200 MBq or 5 mCi), with subsequent recovery of thyroid function or recurrent hyperthyroidism (59). Thyroid hormone replacement is generally recommended even if transient hypothyroidism is possible, to avoid the development of, or a flare-up of Graves' orbitopathy. Thyroid hormone replacement can be gradually weaned and discontinued, if serum monitoring suggests recovery of thyroid function or recurrent hyperthyroidism. In patients who maintain euthyroidism a year or more following RAI, lifelong annual thyroid function monitoring is recommended, as the risk of hypothyroidism persists, at a yearly rate of 3-5% (60). For patients established on thyroid hormone replacement, lifelong serum TSH monitoring is recommended at least annually, to ensure adequate thyroid hormone replacement.

Hypothyroidism or euthyroidism is usually achieved within 3 to 12 months of RAI therapy (57,58). Persistent hyperthyroidism beyond 6 to 12 months following RAI therapy suggests treatment failure and retreatment with RAI should be considered. The goal of re-treatment is to achieve a remission rate of 99%.

Surgical management should be considered if patients are refractory to multiple courses of RAI.

LONG-TERM OUTCOMES

RAI is a safe treatment with no significant long term detrimental effects from the modest doses of RAI administered for Graves' disease, in particular on long term fertility or cancer risk, which are common patient concerns. The offspring of treated patients show no increased risk of congenital defects compared to the untreated population (61,62).

Cancer Risk

RAI thyroid ablation is achieved by the ionizing beta radiation that leads to genetic damage and apoptotic cell death of thyrocytes. This raises an important question of whether RAI carries a subsequent risk of cancer development in thyroid and other organs. RAI therapy for thyroid cancer, which typically involves activities 2 to 10-fold higher than for thyrotoxicosis, has been associated with an increased risk of subsequent malignant neoplasms, especially among younger patients.

A large study involving 27,050 people with more than 40 years of follow-up found that RAI therapy for differentiated thyroid cancer among people younger than 45 years old was associated with 23% increased risk of solid cancer and 92% increased risk of leukemia, relative to those who did not receive RAI therapy (63). However, the administered activities of RAI were substantially higher than those used in hyperthyroidism. Furthermore, a large population-based study involving 7417 patients treated for hyperthyroidism in the UK, with 72,073 person-years of follow-up, showed a decrease in overall cancer incidence and mortality in those treated for hyperthyroidism with RAI (64). In another study that included 107 patients treated with RAI before the age of 20 for hyperthyroidism, no increased risk of cancer was seen following 36 years of follow-up (65). The 24-year extension of the large multi-center Cooperative Thyrotoxicosis Therapy Follow-up Study has been following US and UK patients diagnosed and treated for hyperthyroidism with RAI, ATDs, or thyroid surgery, for nearly 7 decades. This study showed no significant increased risk of death or solid cancer mortality across treated groups, when compared with an external cohort of patients without hyperthyroidism (66). However, there was a modest positive association between total administered RAI activity and solid cancer mortality in patients treated with RAI, suggesting a potential dose-dependent association between total administered RAI dose and risk of death from solid cancer in patients treated with RAI (66,67). Taking into account this study and previous reassuring studies, two recent meta-analyses did not find any association between RAI and the risk of incident cancer or cancer mortality in patients with hyperthyroidism (68,69). Reassuringly, the current body of evidence does not show an increased risk of malignant neoplasm in patients treated with RAI for benign thyroid disease.

Weight Gain After RAI

Many patients are concerned about the risk of weight gain after receiving RAI for Graves' disease. Weight loss is a common symptom in majority of patients with Graves' disease. Hyperthyroidism is associated with alterations in satiety signals and increased resting energy expenditure with expected restoration of weight to pre-morbid status when patients are rendered euthyroid. However, there is emerging evidence suggesting that the weight increase following treatment of hyperthyroidism may exceed the pre-morbid weight status. One of the large prospective cohort studies shows that men were 1.7 times and women were 1.3 times more likely to develop obesity after receiving ATDs or RAI for hyperthyroidism, as compared to the general population (70). Weight gain occurred mostly in the first 6 months of treatment but continued until 24 months. Men gained on average 8 kg and women gained about 5.5 kg. When compared with patients treated with ATDs, RAI was associated

with additional weight gain of 1.8 kg for patients who develop hypothyroidism and 0.2 kg for those without (70).

A systematic review of 9 studies with a total of 1273 patients found that RAI is associated with significant weight gain (71). There was a 5-6 kg gain in weight over 6 months to 1-year post-treatment, and approximately 7 kg over 2 years. It is important to note that there was large inter-individual variability with regards to post-RAI weight trajectory. Most of the studies were retrospective in design and post-treatment weight gain was compared with patient weight at presentation, rather than premorbid body weight. Therefore, although it is probable that weight gain after RAI often exceeds premorbid body weight, direct evidence is not yet available.

Several risk factors for excessive weight gain after treatment for hyperthyroidism have been identified, including pre-existing obesity, the diagnosis of Graves' disease, more severe hyperthyroidism at presentation, and hypothyroidism or thyroid hormone replacement therapy after treatment (72). Avoidance of hypothyroidism after treatment could be a key factor to reduce the risk of excessive weight gain after treatment for hyperthyroidism. One small interventional study indicated that dietary interventions may be useful in preventing excessive weight gain, but larger and better-designed studies are required to confirm the finding (73).

PATIENT ACEPTABILITY OF RAI AND SHARED DECISION MAKING

RAI is generally well received by patients with Graves' disease. The treatment decision is affected by patient preference, comorbidities, pregnancy plan, and presence of active Graves' orbitopathy. In view of the above considerations, a patient, shared-decision making model is particularly suited for choosing the most appropriate treatment, incorporating the most up to date scientific information, specific patient circumstances, and patient preferences (74). However, the process of shared decision-making requires optimal ability of the patient to judge the benefits and downsides of each treatment choice, which may be compromised by the thyrotoxic state. It may therefore be necessary to render the patient euthyroid using ATD before a firm shared decision about definitive treatment can be implemented. A comprehensive care plan that matches the patient's needs will influence quality of life and patient satisfaction for years after the treatment.

A few small studies have shown that satisfaction was generally high across ATDs, RAI, and thyroid surgery, if patients feel involved in the decision-making process (75,76). The most important factors affecting the patient's treatment choices are the remission rate, treatment effects on activities of daily living, concern about use of a radioactive substance, the possibility of depression or anxiety, and doctor's recommendations (76,77). A study from Rotterdam found that both patients and clinicians preferred ATDs over surgery and RAI. However, patients were more worried about RAI than surgery whereas clinicians preferred RAI over surgery (77). The differences in the personal attitude toward RAI between clinicians and patients should be taken into consideration in the shared decision-making process (78).

Graves' disease is associated with worse quality of life (QoL) many years after treatment, as compared to the general population. A randomized, prospective study has shown that patients treated for Graves' disease still had decreased QoL 17–21 years later compared to the general population (79). However, the general QoL in patients treated for Graves' disease, as measured by the 36-item Short Form Health Status survey (SF-36) in a few randomized studies, was similar across ATD, RAI, or surgery groups (40,79). In 2019, Torring et al. found a contrary result after assessing QoL using the disease-specific questionnaire, ThyPRO (80). The ThyPRO questionnaire is highly relevant to the experiences of patients with Graves' disease and is designed to

detect changes over time. This large non-randomized cohort study involving 1186 patients showed that quality of life scores were worse in patients with Graves' disease treated with RAI therapy, compared to ATDs or surgery at 6-10 years after treatment. The RAI therapy group had worse scores for goiter symptoms, hyperthyroid symptoms, tiredness, anxiety, depression, emotional susceptibility, impaired social life, impaired daily life, and impaired sex life than the ATD and surgery groups. This study had a larger number of participants and a longer duration of follow-up than previous studies, However, more patients in the RAI group had comorbidities that may have affected quality of life. If this finding is substantiated in future studies, RAI may become less desirable as a treatment option for patients with Graves' disease.

Thyroidectomy

Surgical thyroidectomy is an effective approach for the management of Graves' hyperthyroidism and is particularly suitable for some patients, such as those with a large goiter. Owing to the cumulative risk of recurrent thyrotoxicosis over time that is associated with subtotal thyroidectomy, the surgical approach for Graves' disease should be total thyroidectomy, meaning that lifelong hypothyroidism with the need for levothyroxine replacement is the inevitable outcome of a successful operation.

In a patient with Graves' disease, thyroidectomy should be considered in patients with the following features:

1. Large goiter.
2. Co-existing cytologically or sonographically suspicious or malignant thyroid nodule.
3. Intolerance or serious adverse reaction to ATDs.
4. High circulating TRAb concentration (e.g. >5 times upper limit of reference range).
5. Active thyroid eye disease.

Pre-operative preparation is necessary, usually with ATDs, to ensure that the patient is euthyroid at the time of surgery, in order to minimize the risk of bleeding from a vascular gland with uncontrolled hyperthyroidism or post-operative thyroid storm. In the case of urgent surgery in a hyperthyroid patient, preparation with iodine/iodide solutions (Lugol or SSKI) may be necessary (81). Oral cholecystographic contrast agents, ipodate or iopanoic acid are also effective in rapidly controlling thyrotoxicosis but are not freely available in many countries. In addition, there is data to support reduced blood loss during elective surgery following routine preoperative use of iodide preparations (81). In common with all operative procedures, risks include infection, bleeding, keloid or hypertrophic scar formation; the latter being of concern to patients where a good cosmetic outcome is seen as highly desirable. In addition, inadvertent removal, damage or devascularization of parathyroid glands may lead to transient hypocalcemia and more rarely permanent hypoparathyroidism in less than 2% of cases (82). It is important to optimize vitamin D status prior to surgery, as insufficiency may exacerbate postoperative hypocalcemia and render it refractory to treatment. Damage to the recurrent laryngeal nerve may result in change of voice quality or even vocal cord paresis. Inability to project the voice or shout may also result from damage to the external branch of the superior laryngeal nerve. Laryngeal nerve monitoring using a modified endotracheal tube containing sensing electrodes is used by many surgeons. The experience of the surgeon is a critical factor in complications following thyroidectomy, with a high-volume for thyroid surgery being a key predictor of a high-quality surgical outcome. A UK survey showed that surgeons performing more than 50 thyroidectomies annually had lower complication rates than those with less operative throughput (82).

Post-operative bleeding into the thyroid bed has an incidence of 1 to 2% of operations (83), and it can lead to asphyxiation through airway obstruction or neurological sequelae if there is compression of the neck vessels. Immediate decompression by removing

neck sutures or staples and manual evacuation of the hematoma followed by local pressure to control bleeding and airway management may be needed as an emergency at the bedside (see Figure 2 for 'SCOOP' protocol) (83). Although some centers routinely perform day case thyroidectomy surgery with good results (84), this rare risk of compressive post-operative hematoma cannot be entirely avoided, limiting its applicability. The American Thyroid Association has made recommendations about patients for whom day case surgery is inadvisable (85), including significant comorbidity, residing in a location remote from healthcare provision, an adverse social setting or lack of a willing caregiver.

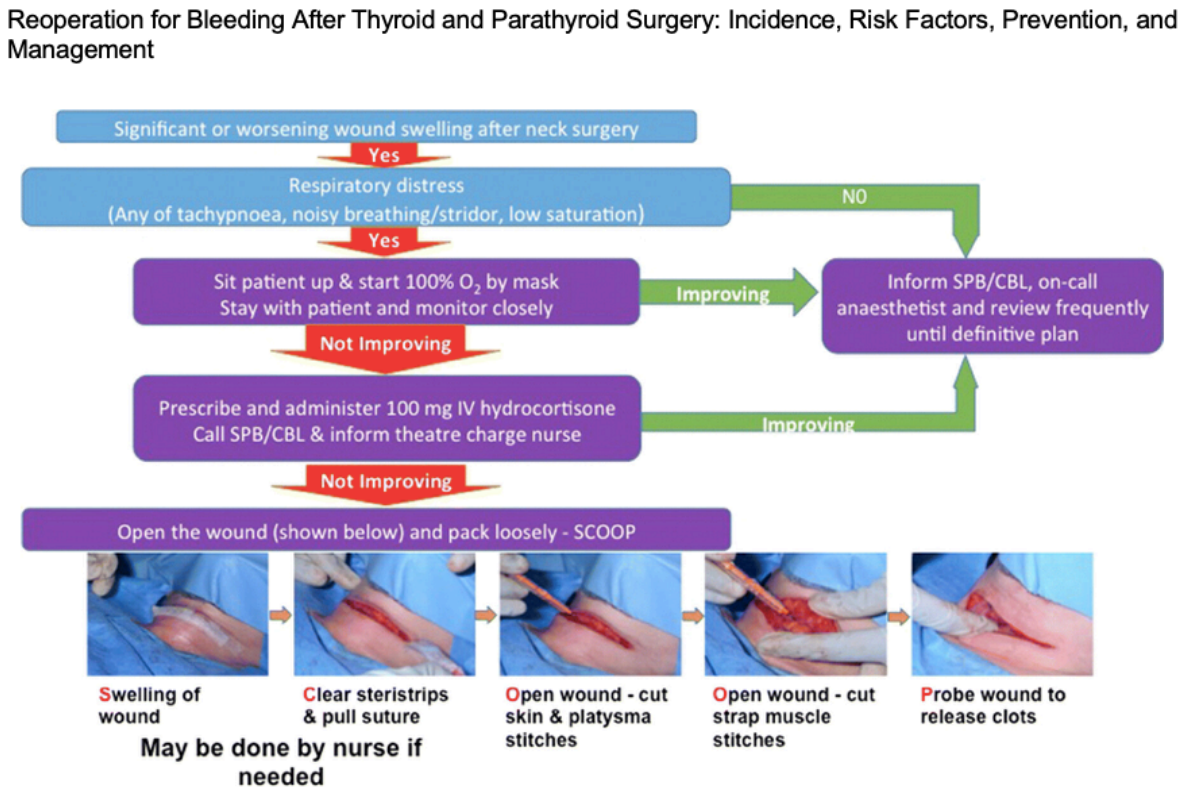

Figure 2. SCOOP post-thyroidectomy protocol.

Wound swelling associated with tachypnea, reduced oxygen saturation, stridor or noisy breathing should lead to should lead to emergency action (83).

Swelling of the thyroidectomy wound postoperatively with airway compromise.

Clear/Cut steri strips or sutures.

Open skin and /or platysma stitches

Open wound by cutting strap muscle stitches

Probe wound by finger or suction to release clots

Owing to patient concerns about having a visible scar in the anterior neck following thyroidectomy, different surgical approaches have been developed over recent years (86). Initial procedures included open or endoscopic lateral neck, submental, or axillary approaches. More recently, trans-oral approaches through the vestibular area have been developed and operating robotics employed. Apart from the usual

risks of thyroidectomy, tumor seeding to the operative access route is a potential limitation for these procedures in patients who have thyroid cancer, but this caution is not relevant to most patients with uncomplicated Graves' disease. These approaches are likely to increase in popularity in the future as surgical expertise with endoscopic and robotic approaches improves.

Immunomodulatory Approaches

Graves' disease is an autoimmune condition that arises because of the loss of immunological tolerance to the TSH receptor (87). It is characterized by the production of stimulatory autoantibodies, generated by plasma cells, which are terminally differentiated B lymphocytes. The pathological immune response involves not only B cells but also T lymphocytes and antigen-presenting cells within the thyroid and adjacent lymphoid tissues. Unlike type 1 diabetes, where beta-cell destruction is typically advanced at presentation, the symptoms of Graves' disease are due to hyperfunction and some patients achieve long-term remission with normal thyroid function following a course of ATD therapy. This suggests that immunological tolerance to thyroid antigens can, in some cases, be restored. ATDs such as thionamides also possess intrinsic immunomodulatory properties, including reduction of thyroid autoantibody levels, modulation of thyroid antigen structure, and inhibition of pro-inflammatory cytokine release and T lymphocyte activity (88). The combined use of modern immunomodulatory treatments and ATDs may therefore exert a synergistic effect on autoimmune activity. Therapeutic options available for patients with Graves' disease have remained largely unchanged for over 70 years, but recent advances in the understanding of interactions between B and T lymphocytes, and the autoantigen – antibody complex has enabled further insights into the immunopathology of Greaves' disease and opens the door to combination immunomodulatory strategies designed to increase remission rates and reduce long-term reliance on thyroid ablation or hormone replacement. Examples of these are shown in Figure 3.

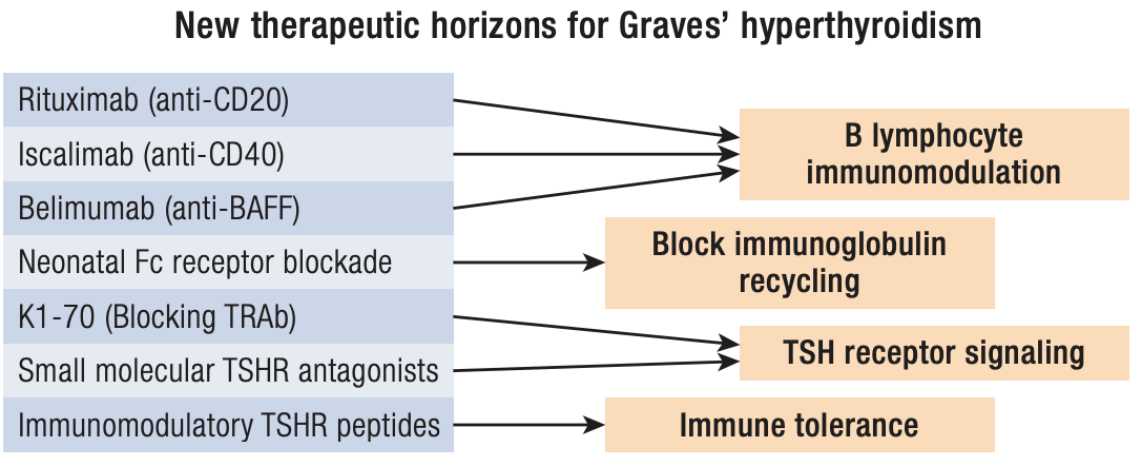

Figure 3. Novel treatment options in development for Graves' hyperthyroidism. Figure reproduced from ref. 99

B LYMPHOCYTE DEPLETION

Rituximab (RTX) is a monoclonal antibody that targets CD20, a surface protein expressed on B cells. Upon administration, RTX leads to B cell depletion through lysis in the circulation, thyroid, and lymphoid tissues, thereby interrupting autoantibody production and antigen presentation. The immunomodulatory effects are thought to arise through multiple mechanisms:

1. Prevention of new plasma cell generation.
2. Reduction in thyroid-specific antigen presentation.
3. Diminished T cell activation.

Importantly, mature plasma cells do not express CD20, and therefore existing memory antibody responses remain intact. This allows patients to retain immunity to previously encountered pathogens. RTX has an established safety profile in both adult and pediatric populations, with longstanding use in diseases such as rheumatoid arthritis and systemic lupus erythematosus. Although hypogammaglobulinemia is a possible side effect, it is rare and typically transient. Circulating B cell populations usually recover within 6 to 24 months post-treatment.

In adult patients with Graves' disease, RTX has demonstrated disease-modifying activity. Published case series and reports indicate that approximately 53% of thyrotoxic adults achieve euthyroidism following RTX therapy (89,90). Notably, many of these individuals presented with relapsed disease or severe orbitopathy, suggesting a potential role for RTX in more treatment-resistant phenotypes (90).

Graves' orbitopathy, a debilitating extrathyroidal manifestation of Graves' disease, occurs in 25–50% of affected adults. Graves' orbitopathy and Graves' disease share key immunopathogenic features, including the involvement of shared autoantigens. Two randomized controlled trials have evaluated RTX in Graves' orbitopathy: Salvi et al. reported a significant improvement in clinical activity scores in patients treated with RTX (91). By contrast, Stan et al. found no significant benefit, potentially due to longer disease duration among participants (92).

A recent pilot study evaluated the safety and efficacy of RTX in 27 adolescents and young adults (aged 12–20 years) with Graves' disease. Participants received a single dose of RTX in combination with standard ATD therapy. One year after stopping ATD, 48% of patients remained in remission, compared to the 20–30% typically observed over 1–3 years following standard therapy alone (93). The treatment was well tolerated, and no serious adverse events were reported.

IMMUNOGLOBULIN-DEPLETING APPROACHES

With TRAb having a central role in the pathogenesis of Graves' hyperthyroidism, methods to deplete these pathogenic antibodies are being actively investigated. The neonatal Fc receptor (FcRn) is responsible for recycling circulating Immunoglobulin G (IgG) in the circulation as well as transmitting IgGs across the placenta to the fetus. Blocking FcRn action using monoclonal antibody approaches leads to reductions in serum IgGs, including TRAb by around 70%, while leaving serum IgA and IgM concentrations unchanged. One FcRn blocker, batoclimab, has shown promise in Graves' orbitopathy during early phase trials (94). Similar compounds are already licensed for use in myasthenia gravis and other antibody-mediated autoimmune disorders.

DIRECT MODULATORS OF TSHR SIGNALING

There is growing focus on TSHR–specific treatment modalities as these have the practical advantage of offering a targeted, thyroid-specific approach, whilst minimizing disruption to the immune system.

Examples of specific TSHR modulation include the use of small molecule antagonists or antagonistic TSHR monoclonal antibodies, which lock the TSHR into an inactive conformation. One such antagonistic (blocking) TSHR antibody known as K1-70 has been used in two early-phase trials with promising results (95,96). In contrast, small molecule TSHR antagonists must be selective for the TSHR over the homologous LH/HCGR and FSHR to avoid reproductive toxicity, and such compounds have yet to be tested in human to our knowledge (97,98).

The introduction of novel therapeutics may lead to euthyroidism without the need for lifelong/definitive treatment and thus transform the treatment landscape in Graves' disease (99). The potential risks of immune compromise and cost implications mean that further work is needed in this area before these are routinely used in clinical care.

Minimally Invasive Approaches

Two principal minimally invasive techniques have been applied to the treatment of Graves' disease, namely thermal / radiofrequency ablation and thyroid arterial embolization. These procedures are claimed to have some advantages over traditional therapies for Graves' disease, especially thyroidectomy, based on speedier recovery, repeatability, better cosmetic outcome and greater cost-effectiveness (100,101). Experience is limited, however, and no current guideline recommends these treatments for Graves' disease.

THERMAL AND RADIOFREQUENCY ABLATION

Observational studies of 30-50 patients have shown a remission rate at 1-2 years of 57–96% but patients often required more than one procedure (101,102). Minor complications including pain, swelling, and hematoma were observed in up to 20% of patients.

THYROID ARTERIAL EMBOLIZATION

Small series of patients (n=16-27) receiving thyroid arterial embolization have been reported (103,104). The remission rate at 27 months to 3 years was 59-100%. No complications were reported by one study (103).

Minimally invasive approaches to the treatment of Graves' disease are feasible and seem to be safe. However, efficacy does not seem to be superior compared to other conventional treatments, and long-term outcome data are lacking. Their place in the routine management of patients with Graves' disease is currently unclear.

MANAGEMENT OF GRAVES' HYPERTHYROIDISM IN SPECIAL SITUATIONS

Subclinical Hyperthyroidism

Subclinical hyperthyroidism (SH), defined by a low serum TSH, in conjunction with FT3 and FT4 levels within the reference range, is more common in women than in men (female: male ratio = 1.5: 1) and its incidence increases with advancing age. The Colorado Thyroid Disease Prevalence Study reported that 1 to 2% of women over the age of 60 had SH (TSH <0.3 mU/l) (105) whilst the NHANESIII survey, using a TSH threshold of <0.4 mU/L, found that SH was even more common in advanced age, affecting 3% of people over the age of 80 (106). SH is heterogeneous from the biochemical point of view, with about three quarters of individuals having a serum TSH between 0.1 and 0.4 mU/L, termed grade 1 SH, and the remainder having a suppressed TSH concentration, below 0.1 mU/l (Grade 2 SH) (107). This is an important distinction as it predicts outcome. In a UK study of 44 patients who had Graves' disease confirmed by positive serum TRAb and serum TSH below reference range but normal free thyroid hormones (i.e. both grades of SH), 34% had developed overt hyperthyroidism within 3 years (108).

Approximately one third had persistent biochemical SH and TSH normalized in a third. Ultimate euthyroidism was most frequent in those with initial grade 1 SH. In contrast, a study of 110 Japanese Graves' disease patients with SH defined by TSH <0.1 mU/L (grade 2) showed that 63% had progressed to overt hyperthyroidism by the end of observation (109). Whether to treat SH in patients with positive TRAb is dependent on symptoms, co-morbidity, and risk of progression (4,5,107). In the presence of tachyarrhythmia or unexplained weight loss, treatment would be strongly favored, particularly if serum TRAb concentration was high (e.g. ≥5 IU/L), TSH was <0.05 mU/L and the patient was ≥65 years of age. However, in an asymptomatic patient with a TSH in the 0.1–0.4 mU/L range, observation with repeat measurement of serum free T3 and free T4 in 3 to 6 months would be proportionate to the risk, as spontaneous normalization of TSH may occur. If treatment is considered, low dose ATD are favored, as the chances of long-term remission are high (4,5,107).

Graves' Orbitopathy

Out of control thyroid function, either hyperthyroidism and hypothyroidism, in a treated Graves' patient is associated with severe Graves' orbitopathy and worse ophthalmic outcomes, if untreated (110). Therefore, rapid establishment and maintenance of euthyroidism is important and should be supervised by an endocrinologist. ATDs, thyroidectomy, and RAI are effective in achieving this goal. Evidence from randomized studies (111,112), supported by meta-analyses (113,114) indicate that RAI is associated with a small (approximately 15% over 24 months) risk of exacerbation of Graves' orbitopathy. This risk seems to be almost negligible for patients with inactive Graves' orbitopathy, provided a euthyroid status is preserved (115). However, in patients receiving RAI for relapse of hyperthyroidism after initial ATD, risk of orbitopathy may increase over an extended time to around 25% (116). Current consensus is to manage the hyperthyroidism of patients with Graves' orbitopathy with ATDs as the principal choice (117-119), unless there are contraindications (agranulocytosis, other significant side-effects). RAI is also an option, with or without cover from a course of oral steroids (prednisolone 0.16-0.5 mg/kg daily, tapering and withdrawing after 6-12 weeks) (111, 120) which prevents exacerbation of Graves' orbitopathy, especially in patients with moderate to severe eye disease of recent onset and with risk factors for progression. Thyroidectomy is also appropriate when the patient has a large symptomatic goiter, there are difficulties in achieving euthyroidism, or suspicion of malignancy. For most cases however, when ATDs are well tolerated, they can be continued beyond two years and until the thyroid eye disease is inactive.

Diagnosis and Treatment of Graves' Disease in the Young

Graves' disease is particularly challenging to manage in the young person. The diagnosis can easily be overlooked and the effects of thyroid hormone excess prior to treatment can have a long-lasting impact on education and neurodevelopment. Autoimmune diseases tend to be more severe in the young and the autoimmune process is more resistant to intervention (121). The severity of the underlying thyroid hormone excess at presentation is more profound than in adults and a course of ATD therapy is less likely to result in long term remission. Side-effects of ATDs are more likely to occur (18) and therapeutic options are more limited, particularly in the younger child.

BACKGROUND

The incidence of childhood hyperthyroidism appears to be increasing in some populations with figures ranging from 1.58 to 6.5 per 100,000 reported in Danish, Swedish, and Chinese populations (122-124). The peak incidence of Graves' disease in childhood occurs around 12-13 years of age and whilst there is a marked female preponderance in adolescence, the sex difference in very young children is less profound (121,122).

PRESENTATION

The young patient with Graves' disease can be referred to a variety of different health professionals including cardiologists, gastroenterologists, and psychologists. Many children do not demonstrate significant weight loss and issues such as anxiety can be misattributed to normal adolescent behavior. Patients frequently do not have a goiter or eye disease that might lead to an earlier presentation or referral. Clinical features such as disrupted sleep and poor concentration prior to diagnosis can disrupt learning and be profoundly detrimental to a child's education and neurocognitive development (125). Untreated Graves' disease can lead to rapid growth and tall stature.

BASELINE INVESTIGATIONS

Whilst the focus of this chapter is Graves' disease, children and adolescents can occasionally have other causes of hyperthyroidism such as a toxic nodule or McCune-Albright syndrome (MAS), so a thorough history and examination is important to aid in the differential diagnosis, for example asking about precocious puberty and the presence of café au lait patches if considering MAS and careful thyroid examination for palpation of any discrete nodules (see Table 3). Thyroid function tests (TSH, free T4 and free T3) as well as TRAb should be measured at presentation. The classical signature of Graves' disease is a suppressed serum TSH (below the assay threshold) and the presence of a raised FT3 concentration and elevated TRAb. There is little to be gained by imaging (ultrasonography or a radioisotope uptake scan) unless serum TRAb are absent or the goiter is found to have a nodule or nodules on examination. A low white cell count and raised ALT may be a feature of the underlying disease process. Checking these parameters at baseline will assist in the interpretation of future white cell counts or deranged liver function in the long term.

TREATMENT

ATD

First-line treatment of Graves' disease in the young is with the ATD methimazole or carbimazole. In mild to moderate thyroid hormone excess a starting dose of 0.15 mg/kg of methimazole or 0.25 mg/kg of carbimazole is appropriate. There is little to be gained by splitting the dose of carbimazole or methimazole into a twice per day or three times per day regimen. Once daily will suffice. Doses of 0.5 mg/kg or 0.75 mg/kg will stop thyroid hormone production in the majority of young patients and can be used even in the case of profound thyroid hormone excess at diagnosis. Propylthiouracil should not be used because of the risk of drug-induced liver failure (28,126). As with adults, beta blockers can be used to ease symptoms while ATDs reduce thyroid hormone concentrations down to normal levels. The preferred means of carbimazole or methimazole administration is with a dose titration strategy (18) although 'block and replace' is still used by some pediatricians if the biochemistry is particularly unstable, for example if hyperthyroidism keeps recurring as the dose of ATD is reduced.

Families should be informed that it takes 4-6 weeks for thyroid hormone concentrations to normalize. ATD side-effects are more likely in the young and an awareness of what to do in the event of sore throat or fever that signal possible agranulocytosis is crucial. In this scenario children should stop ATDs and have a full blood count checked as soon as possible. Only when agranulocytosis has been excluded can ATDs be recommenced. Excessive weight gain is not uncommon in young people with GD in the months post diagnosis and discussing ways of reducing this likelihood are important (127).

Until relatively recently many young people were simply treated with ATDs for 2-3 years before

stopping. Unfortunately, remission rates after this period of ATDs are only approximately 25%. Recent guidance suggests that treatment should ideally be for at least 3 years and there is evidence to suggest that longer courses of ATDs are associated with a greater likelihood of remission. As with adults, a persistently raised TRAb concentration is associated with an increased likelihood of relapse following ATDs. Many clinicians regard a raised serum TRAb titer as a reason for continuing ATD therapy or exploring the role of definitive treatment options. Patients who remain euthyroid for 12 months after ATDs are stopped should continue to have thyroid function monitored at least annually because of the future risk of relapse and also because of the long-term risk of autoimmune hypothyroidism.

Definitive Treatment

Definitive treatment with surgery or RAI will be required by many young people diagnosed with Graves' disease. This reflects a number of considerations including:

1. Troublesome side-effects (e.g. rash) linked to ATD therapy that do not settle down.
2. More serious but uncommon side-effects such as agranulocytosis.
3. Reluctance on the part of the young person to take ATDs. This is a relatively common concern that may in part reflect the relationship between resolution of the hyperthyroid state and weight gain.
4. Low likelihood of remission following a course of ATDs.
5. Early definitive treatment may be preferred in the case of children with learning difficulties who are unable to reliably report symptoms such as sore throat or fever.
6. Young people wanting a simpler treatment option than ATDs before they move away from home or progress into higher education.

Surgery

Surgical treatment of Graves' disease consists of total thyroidectomy and hence thyroid hormone replacement will be required after the procedure. Partial thyroidectomy is not recommended because of the likelihood of persistent or recurrent hyperthyroidism. Thyroidectomy needs to be undertaken by a surgeon with appropriate expertise who performs the operation regularly (see above), however, even with the most experienced surgeons, operative complications such as hypoparathyroidism occur more commonly in the young than in adults (128). Patients who have been thyrotoxic in the months leading up to surgery may be at particular risk of hypocalcemia postoperatively and it is important to optimize vitamin D status prior to the surgery.

Radioiodine (RAI)

In this context, the objective of RAI administration is thyroid gland ablation. RAI is less likely to result in hypothyroidism in patients with very large goiter and is not recommended in the very young (under 10 years of age) because of the relatively high radiation exposure to tissues elsewhere in the body. As with adults, glucocorticoid cover should be considered if there is significant, active Graves' orbitopathy. There may be particular logistical considerations when planning RAI therapy in young people, for example the presence of young siblings at home who will need to maintain a safe distance from the patient. Some centers administer a fixed activity of RAI although recent guidance has suggested that dosimetry with calculation of the administered RAI treatment is advantageous in young patients (2). A more refined approach to dose calculation has the potential to minimize the activity of RAI administered whilst maintaining efficacy in rendering the patient hypothyroid.

Summary

Managing Graves' disease in the young person is more challenging than in adults in almost every respect. There is, therefore, a pressing need for more innovative treatment strategies that will reduce the proportion of patients ending up on thyroid hormone replacement following radioiodine or surgery.

Preconception and Pregnancy

Detailed information concerning management of Graves' disease in pregnancy is discussed elsewhere (see chapter: Thyroid Regulation and Dysfunction in the Pregnant Patient). ATDs may rarely cause birth anomalies (129) and so the principles of care during pre-conception and pregnancy are to minimize fetal exposure to ATDs where possible, and to keep the patient euthyroid. Ideally, a patient with Graves' hyperthyroidism seeking future pregnancy should have definitive treatment with either RAI or thyroidectomy before the pregnancy, as the risks of ATD are eliminated and the pregnancy is carried with levothyroxine therapy only (130). If RAI is selected as the definitive treatment, a minimum interval of six months should elapse between its administration and the onset of pregnancy. In addition, with either definitive treatment, serum TSH should be optimized by adjustment of levothyroxine dose in the preconception period to achieve a TSH between 0.4–2.5 mU/L (131,132).

Not all patients will have anticipated pregnancy or will want definitive management. However, if pregnancy is anticipated in the near future, a patient stable on ATDs should be controlled with the lowest effective dose of ATD and changed from methimazole or carbimazole to an equivalent dose of propylthiouracil (PTU) (131,132). This is because, although the prevalence of birth defects is similar, the spectrum of congenital anomalies in fetuses exposed to methimazole or carbimazole tends to be more severe than in those exposed to PTU (129,130). Thus, if a patient has low or undetectable TRAb and stable detectable serum TSH for 6 months before pregnancy, then ATDs can be stopped in early pregnancy with frequent monitoring (132). If ATDs are continued in the first trimester, the dose may often be reduced, leading to discontinuation in the second or third trimester, owing to the natural waning of autoimmunity during pregnancy (133). In any event, serum TSH and free T4 should be monitored every 2 to 4 weeks during the first trimester and then every 4 to 8 weeks during the remaining pregnancy. It is important to understand that the reference range for serum thyroid hormones changes during pregnancy, and in particular that lower TSH levels are physiological in the first trimester.

TRAb can cross the placenta and stimulate the fetal thyroid, which is active from around 10-12 week's gestation. Therefore, women with previous definitive therapy and persisting detectable TRAb (particularly greater than 3-times the upper limit of the reference range) should have more intensive ultrasound monitoring of fetal heart rate, goiter and growth throughout the pregnancy (130,131). If fetal thyrotoxicosis is suspected, treatment of the mother with ATDs can be used to restore euthyroidism in the fetus.

If ATD use is necessary beyond the first trimester, the mother can be safely swapped back to methimazole or carbimazole, as fetal organogenesis is complete and these have the convenience of once daily dosing and a lower risk of hepatotoxicity. Graves' hyperthyroidism that has undergone drug-free remission during pregnancy may frequently undergo an aggressive relapse in the first year, and monitoring at 6 weeks post-partum is recommended. Breast feeding is permitted on lower doses of methimazole/carbimazole (≤20 mg daily) and propylthiouracil (≤400 mg daily), using a split daily dose taken immediately after feeding (131).

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