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Treatment Modalities in Thyroid Dysfunction

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1. Introduction

Thyroid dysfunction is a common condition mainly affecting women, with a male to female ratio of around 1:10. An organ-specific autoimmune response is the underlying cause in the majority and susceptibility to thyroid autoimmunity is believed to be influenced by an interaction between genetic predisposition and environmental factors, in addition to endogenous factors such as age and sex (Vanderpump 1995).

Autoimmune hyperthyroidism, or Graves' disease (GD), affects around 2% of the female population and is characterised by the presence of thyroid stimulating antibodies (TSAb), which mimic the action of thyroid stimulating hormone (TSH), resulting in uncontrolled thyroid hormone production. TSAb also contribute to extra-thyroidal manifestation of the disease, including thyroid eye disease (TED), although the exact mechanistic pathways are not entirely clear. At the other end of the spectrum, autoimmune hypothyroidism (AH) affects up to 5% of women and is characterised by the presence of thyroid peroxidase (TPO). These antibodies do not seem to have a direct functional role but are implicated in perpetuating the intrathyroidal inflammation and tissue destruction (Ajjan & Weetman 2008).

In this Chapter, we discuss the various therapies used in hyper- and hypothyroidism, and address management of special cases.

2. Aetiology of hyperthyroidism

GD is by far the commonest cause of hyperthyroidism accounting for around 80% of cases (Weetman 2000). It is frequently seen in multiple family members indicating a genetic predisposition, commonly seen in organ-specific autoimmune conditions.

The second commonest cause is a solitary toxic nodule or multinodular goitre accounting for 15-20% of cases (Orgiazzi & Mornex1990). Toxic multinodular goitres tend to occur insidiously in elderly patients with a longstanding nodular goitre. Toxic adenomas result from benign monoclonal proliferation producing a single autonomously functioning nodule, typically greater than 2.5cm in diameter. Goitres of any nature are more prevalent in iodine deficient areas and are more common in females (Reinwein et al 1988).

There are other rare causes for hyperthyroidism, which should be kept in mind when assessing the patient and these are summarised in Table 1.

Cause of hyperthyroidism	Frequency and aetiology	Diagnosis
Graves' disease	99%, thyroid stimulating antibodies	Clinical examination (Smooth goitre, extrathyroidal complications) Thyroid autoantibodies Thyroid uptake scan in difficult cases
Toxic nodule or toxic multinodular goitre	15%, activating mutations in TSH receptor and Gsα protein	Clinical examination Thyroid uptake scan
Thyroiditis	3%, autoimmune, viral or drug-related (amiodarone)	Clinical examination Thyroid uptake scan ESR
TSH-secreting tumour	<1%	Raised TSH and thyroid hormones Pituitary imaging
Exogenous thyroid hormone administration	Variable, excess ingestion of thyroid hormones	Clinical assessment
Hyperemesis gravidarum Choriocarcinoma	Rare, raised hCG	Clinical assessment Absence of thyroid autoimmunity Known pregnancy Imaging of the pelvis
Struma ovarii	Rare, ectopic ovarian thyroid tissue	Clinical assessment Thyroid/pelvic uptake scan Imaging of the pelvis
Thyroid hormone resistance	Rare, pituitary resistance to thyroid hormones	Clinical assessment Family history

Table 1. Hyperthyroidism: aetiology and diagnosis.

2.1 Diagnosis of hyperthyroidism

Main symptoms and signs of hyperthyroidism are summarised in Table 2. Careful history and examination will typically point towards a diagnosis of hyperthyroidism and its underlying cause. Biochemical confirmation is required and enables the clinician to monitor response to treatment. Levels of thyroid stimulating hormone (TSH) are suppressed (<0.03miu/l) together with elevated levels of circulating thyroid hormones, L-thyroxine (T4) and/or L-triiodothyronine (T3). Measurement of TSH and free T4 (FT4) is usually sufficient to

confirm a diagnosis of thyrotoxicosis, but FT3 levels should be measured when TSH levels are suppressed with normal FT4 levels as roughly 5% of all cases may only have elevated levels of T3 (Singer et al 1995).

The diagnosis of GD is usually based on clinical and biochemical thyrotoxicosis in the presence of a smooth goitre with or without extrathyroidal manifestation of the disease. In some cases, the cause of hyperthyroidism is unclear and additional biochemical and/or imaging tests may be needed.

The presence of thyroid autoantibodies supports the diagnosis of thyroid autoimmunity. Antibodies (Ab) against TPO are frequently checked in clinical practice, although these are only detected in 80% of individuals with GD (Ajjan & Weetman 2008). Antibodies against thyroid stimulating hormone receptor (TSHR) are detected in 95-99% of patients with GD (depending on the sensitivity of the test used) and therefore these are more informative than TPO-Ab in cases of uncertain aetiology (Ajjan&Weetman 2008; Matthews & Syed 2011).

Radioisotope uptake scans using 99mtechnetium or 131iodine, will show an increase in uptake and a diffusely enlarged thyroid in GD. Toxic MNG will show multiple nodules with increased uptake. A solitary nodule with increased uptake and suppressed function in the remaining, normal tissue is seen in a toxic adenoma (Cooper 2003). All forms of thyroiditis can be differentiated by low or absent uptake.

Symptoms	Frequency
Nervousness, irritability, heat intolerance, palpitation	>90%
Weight loss, increased appetite, fatigue, loose stool	>80%
Eye symptoms (TED)	>50%
Menstrual irregularities, insomnia, polyuria	>25%
Signs	**Frequency**
Hyperkinetic behaviour, fast speech, tachycardia, tremor, goitre, tachycardia or atrial fibrillation, moist skin	>90%
Thrill/bruit over the thyroid	>70%
Eye signs (in GD), thinning of hair, hyperreflexia	50%
Pretibial myxoedema and acropachy (in GD), onycholysis	5%

Table 2. Main symptoms and signs in Graves' disease. TED: thyroid eye disease, GD: Graves' disease.

2.2 Management of hyperthyroidism

There are three main treatment modalities for hyperthyroidism, which include medical therapy, radioactive iodine and surgery. In addition, supportive therapy is sometimes required to control symptoms. Treatment options for hyperthyroidism are summarised in Figure 1.

2.2.1 Medical

Control of hyperthyroidism. Anti thyroid drugs (ATD), known as thionamides, are commonly prescribed to control the excessive production of thyroid hormone and include carbimazole, its active metabolite methimazole and propylthiouracil (PTU). Use of these agents varies worldwide; methimazole and PTU are preferred in the USA, carbimazole is widely used

first line in the United Kingdom and Methimazole is preferred in the rest of Europe and Asia (Weetman 2000). Methimazole or Carbimazole is often preferred to PTU as it has a longer half life and is therefore given once a day whereas PTU needs to be taken 2 or 3 times a day (Franklyn 1994). They should generally be instituted in patients with a confirmed diagnosis of hyperthyroidism, but may not be necessary if definitive treatment is planned early and hyperthyroidism is mild (Weetman 2000). Thionamides can be used in the short term to induce euthyroidism prior to more definitive treatment such as radio-iodine or surgery or in the medium term in case of GD with the aim of inducing remission. Long term treatment is reserved for patients in whom definitive treatment is relatively contraindicated, such as elderly, frail patients

T4 and T3 molecules are formed within the thyroid gland by the coupling of iodotyrosine residues, which in turn have been formed from the binding of iodine and tyrosine within thyroglobulin, an action catalysed by TPO (Cooper 2005). The thionamides act by inhibiting the formation and coupling of these iodotyrosine residues and thus reduce T4 and T3 concentrations. Propylthiouracil also has the action of inhibiting the peripheral conversion of T4 to T3.

Carbimazole is usually commenced at a dose of 20-40mg once a day, depending on the severity of thyrotoxicosis. Regular monitoring of TSH and T4 is required every 4-6 weeks and the initial dose can be titrated as the thyroid function normalises and the patient becomes euthyroid. A drop in the T4 to low-normal levels or below the normal range indicates that a reduction in dosage or addition of levothyroxine is needed. The former scenario constitutes the "titration regime", whereas the latter is known as "block and replace regime". In the titration regime, the smallest dose of anti-thyroid drug is used to maintain thyroid function within the normal range. The levels of T4 and T3 will begin to reduce within 2-4 weeks of treatment, however the TSH may remain suppressed for significantly longer and hence TSH alone should not be used to guide and monitor treatment (British Thyroid Association guidelines [BTA] 2006, Bahn 2011).

If block and replace is used, which is usually reserved to individuals with GD, the patient is maintained on a high dose of carbimazole or propylthiouracil for 4-6 weeks and when the T4 levels fall to the normal range, Levothyroxine is commenced (usually 75-150 µg daily, according to patient weight) whilst continuing with the same dose of thionamide. Regular monitoring of TSH and T4 are required initially with alterations in the dose of thyroxine guided by T4 levels. Once established on a maintenance dose and TSH and T4 levels have normalised, the doses are unlikely to vary and so less frequent testing is possible (e.g. 6 monthly). Block and replace regimes should not be used in pregnant women (detailed below).

If thionamides are used to treat Graves' disease they can usually be discontinued after a course of treatment, ranging from 6-18 months, with approximately 50% of patients remaining in remission thereafter (Hedley et al 1989, Maugendre et al 1999). In most centres, titration regime is administered for 18 months, whereas block and replace is usually given for 6 months only (Abraham et al 2005). There does not appear to be a difference in remission rates between titration and block and replace regimes (Abraham et al 2005, Reinwein at al 1993). Higher rates of relapse typically occur with severe biochemical thyrotoxicosis at diagnosis, a large goitre, extrathyroidal complications, high anti-TSHR titres and in men (Vitti et al 1997). Thyrotoxicosis caused by nodular goitres does not

undergo remission and generally requires a more definitive treatment once the initial thyrotoxicosis has been controlled.
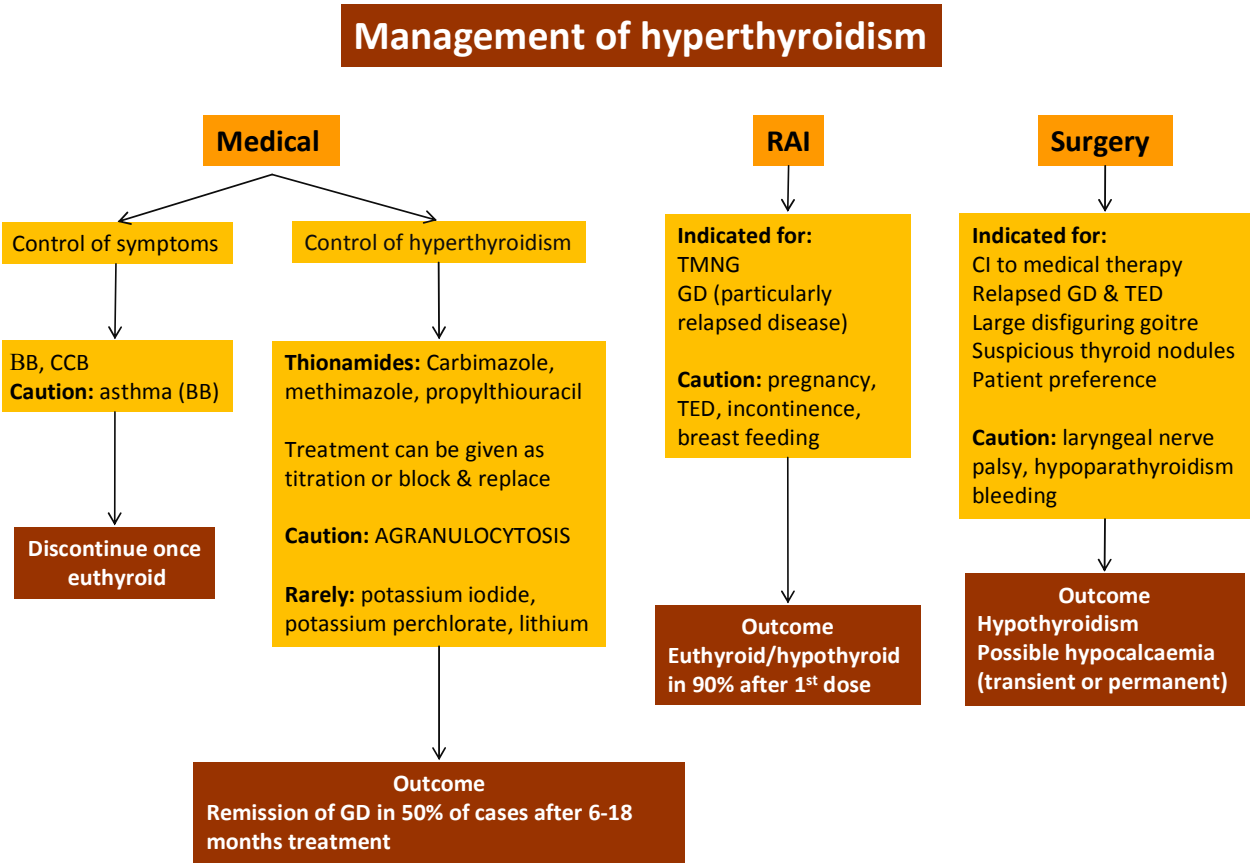

Fig. 1. Summary of the management of hyperthyroidism. BB: β-blockers, CCB: calcium channel blockers, GD: Graves' disease, TMNG: toxic nodular goitre, TED: thyroid eye disease, CI: contraindication.

Several side effects can be attributed to thionamide medication. Common adverse effects include nausea, gastrointestinal upset, headache, fever, rash, urticaria and arthralgia. Rarely, hair loss may occur as a result of carbimazole therapy, although this may also be a manifestation of thyrotoxicosis. More worrying but less frequent side effects include agranulocytosis, vasculitis, and hepatitis, with the latter being more of an issue with PTU (Cooper & Rivkees 2009). Agranulocytosis occurs in approximately 0.4-0.5% of cases. All patients are warned of this rare but serious side effect and asked to immediately report symptoms consistent with agranulocytosis such as severe sore throat, fever or mouth ulcers. Urgent full blood count is required in patients taking thionamide with such symptoms and treatment withheld until it is clear that white blood cells and neutrophil counts are normal. When such a complication develops, patients are admitted to hospital, given appropriate antibiotics and a haematology opinion is sought, particularly if they require granulocyte stimulating factor administration. Once a patient develops agranulocytosis to an antithyroid drug, it represents a contraindication to the use of other thionamides (Biswas 1991). However, in the presence of other adverse effects, swapping to another antithyroid medication is a possibility. For example, arthralgia induced by carbimazole does not necessarily occur with propylthiouracil treatment.

Supportive management. Some patients who present with significant thyrotoxic symptoms require supportive treatment whilst awaiting normalisation of thyroid hormone levels. Typically β-adrenergic blockers such as propranolol are used until thyroid function tests improve at which point they may be withdrawn (Franklyn 1994). Caution must be used in patients with a contra-indication such as heart failure and asthma. An alternative therapy would be a non-dihydropyridine calcium channel blockers such as diltiazem or verapamil

Other medical therapies. Treatments such as potassium iodide, potassium perchlorate and lithium are less conventional, but possible treatment options, particularly when agranulocytosis develops secondary to antithyroid drug treatment. When given in large enough quantities, potassium iodide blocks the synthesis and release of thyroid hormones from a thyrotoxic gland and results in an accumulation of iodide within the gland. A significant reduction in thyroid hormones can be seen as quickly as 2 days following administration, and is typically reserved for preparing thyrotoxic patients, who are unable to tolerate thionamide medication, for surgery. However, this treatment can only be given for a short period of time as the patient eventually "escapes" from the inhibitory effect of iodine (Philippou 1992).

Lithium acts by inhibiting the release of T4 & T3 and is generally used in similar circumstances to potassium iodide or in combination with a thionamide in patients who have needed recurrent doses of radioiodine as it is thought to help retention of I^{131} (Bal et al 2002, Bogazzi et all 1999). Potassium perchlorate is generally reserved for use in type 1 amiodarone induced thyrotoxicosis and requires similar monitoring to other anti-thyroid medication, with aplastic anaemia being the most serious side effect.

2.2.2 Radioactive Iodine (RAI)

Indications for RAI. This can be used as a primary treatment for hyperthyroidism or as a secondary option if anti-thyroid medication has failed to control hyperthyroidism. It is common practice for patients with GD to undergo a course of anti-thyroid medication initially. If this does not achieve long term euthyroidism, due to either the relapsing nature of the condition following withdrawal of ATD or treatment difficulties, then radioactive iodine is indicated as a definitive treatment due to long term morbidity and mortality associated with uncontrolled hyperthyroidism. Severe adverse events such as agranulocytosis and hepatic dysfunction caused by thionamides are also an indication for RAI (Royal College of Physicians [RCP] 2007). It is more commonly used in North America as a primary treatment in patients with GD (Solomon et al 1990), due to poor remission rates, and other factors including age, pre-existing medical conditions such as cardiovascular disease, availability of RAI and patient preference may influence this decision. RAI is recommended in patients with hyperthyroidism due to nodular goitres as antithyroid drugs do not result in long term cure of the disease.

RAI is successful in achieving long-term euthyroidism or hypothyroidism in approximately 90% of patients after a single dose of between 400-600MBq after 1 year (Regalbuto et al 2009). A minority will require a second dose and very rarely a third treatment with RAI.

Contraindications to RAI. Pregnancy and breastfeeding are absolute contraindications to RAI and pregnancy should be avoided for 6 months following treatment. Iodine is concentrated in milk and is able to cross the placenta, damaging the foetal thyroid. RAI should also be

avoided in patients who are unable to comply with the safety regulations after administration. Current treatment with amiodarone (or within the preceding 12 months) is another contraindication as this reduces the uptake of RAI into the thyroid, greatly reducing its efficacy as is suspicion of thyroid malignancy. Caution is needed in patients incontinent of urine, which represents a relative contraindication and insertion of a urinary catheter or urinary pads with appropriate disposal facilities are ways to circumvent the problem (RCP 2007). Another relative contraindication is individuals with active eye disease. If RAI treatment is necessary in TED patients then concurrent oral glucocorticoids are effective in reducing development or progression of TED (Bartalena 2011). Some centres, including ours, advocate starting block and replace one week after RAI for 6 months after which antithyroid drugs can be withdrawn and levothyroxine continued. This helps in avoiding fluctuation in thyroid function, which can be associated with worsening of TED (Tallstedt et al 1994).

Precautions after RAI treatment. Most of the radioactivity is taken up by the thyroid, whilst some is excreted in urine and sweat. It is important that patients are able to comply with the necessary restrictions following RAI treatment to limit the radiation exposure of other members of the public. These include limiting close contact (less than 1m) with people, especially children under 3 years of age and pregnant women. The exact duration of the limitations will vary depending on the dose received, and can be up to 28 days (RCP 2007). Patients should be instructed to flush the toilet twice after passing urine and to wash their hands carefully. They should not share towels or face cloths and ensure that cutlery is thoroughly cleaned. Following RAI patients should be issued with a card outlining the details of their treatment and should carry this for 4 weeks or up to 6 months if they are travelling by plane as some airport security devices are able to detect levels of radioactivity this long after RAI (RCP 2007).

Follow up and monitoring. Careful follow up after RAI is essential to detect alterations in thyroid status. Patients treated with ATD and who are biochemically euthyroid prior to RAI are unlikely to require subsequent ATD unless the risk of recurrent hyperthyroidism is deemed unacceptable such as in the elderly or those with cardiovascular co-morbidity (RCP 2007). Patients should be warned that there is a risk of an increase in hyperthyroid symptoms in the first 1-2 weeks after treatment which often respond to β-blockers. Thyroid function tests (TFT's) should be performed around 6 weeks after RAI. Hypothyroidism within the first 6 months of RAI may be transient and thyroid replacement medication should only be commenced if there is a continual rise in TSH levels and falling freeT4 levels Aizawa et al 1997). If patients require re-commencement of ATD following RAI this should be gradually withdrawn over 3 to 5 months. If a patient remains euthyroid 6 weeks post RAI then further thyroid function tests should be performed at 12 weeks, 6, 9 and 12 months. In those who remain hyperthyroid 6 months post RAI, a second dose should be considered (RCP 2007). Annual TFT's are subsequently required to monitor for late onset hypo-, or hyperthyroidism (BTA 2006).

2.2.3 Surgery

Patient selection. Thyroid surgery, in various guises, has been performed since the 1860's as a treatment of goitres (Sawyers 1972). In the modern age there are a number of indications for thyroidectomy; relapse of GD following a course of ATD is one and patients who are unable to undergo RAI, i.e., pregnant women, those with small children who are unable to comply

with restrictions, and those with severe ophthalmopathy can be offered surgery as are those who decline RAI. Similarly, patients who are hyperthyroid due to nodular goitre may be offered surgery as a definitive treatment due to the same reasons. Other indications include thyroid malignancy or uncertainty regarding thyroid malignancy and to alleviate compressive or respiratory symptoms due to large goitres (BTA 2006). Another indication for surgery is a cold nodule in a patient with GD, due to the relatively high risk of malignancy in such nodules (Abraham-Nordling et al 2005).

Preparation of patient for surgery. Euthyroid patients undergoing thyroid surgery require no special preparation prior to surgery. If they have had previous thyroid or parathyroid surgery, cervical disc operations or have a hoarse voice then direct or indirect laryngoscopy is recommended to identify previous recurrent laryngeal nerve palsy (Moorthy et al 2011). Thyrotoxic patients should be rendered euthyroid with ATD prior to surgery. Lugol's Iodine was used to be given pre-operatively, which along with reducing thyroid hormone secretion is also thought to reduce thyroid blood flow. However, this is now less common and provided the patient is euthyroid, such a treatment is not usually required (Feek et al 1980).

Post-operative complication. With careful pre-operative preparation and meticulous surgical technique, mortality from thyroid surgery should be <1% and similar to that of general anaesthesia alone (Weetman 2000). Complications do occur to varying degree and include thyroid storm, wound haemorrhage, hypoparathyroidism and recurrent laryngeal nerve injury. The incidence of thyroid storm as a result of thyroid surgery is now very low due to improved pre-operative treatment with ATD and post-operative management. Wound haemorrhage although rare, (occurring <1%) can be very serious and life threatening especially if there has been arterial bleeding causing tracheal compression. Any sign of wound haemorrhage causing respiratory compromise requires urgent intervention Schwartz et al 1998). The occurrence of hypoparathyroidism post-operatively can be either permanent or temporary and is rarely due to mistaken removal of all four parathyroid glands, but rather interruption to their blood supply (Pattou et al 1998). In the hands of experienced surgeons performing a total thyroidectomy, the risk is thought to be between 0-3% (Schüssler-Fiorenza et al 2006). New techniques such as auto transplantation of parathyroid glands during surgery are effective at reducing these rates further (Testini et al 2007). Injury to the recurrent laryngeal nerve is also thought to be around 1-2% and is also higher when surgery is performed for thyroid malignancy. Some return of function to the vocal cords can be expected within the first few months and possibly up to 12 months. Beyond this time it is likely that injury will be permanent.

2.3 Special cases of hyperthyroidism

2.3.1 Amiodarone induced thyrotoxicosis

Treatment of amiodarone induced thyrotoxicosis (AIT) can be challenging, due in most part to the degree of overlap between type1 and type 2 AIT. The first step in the treatment of either case is to discontinue amiodarone if it is safe to do so, for which a cardiology opinion is usually sought. The attending physician attempt to distinguish whether the patient has type 1 or type 2 AIT (summarised in Table 2). Type 1 AIT is due to increased production of thyroid hormones, and so treatment with a thionamide should result in lowering of thyroid hormone levels. Occasionally potassium perchlorate can be added or substituted if there is

no response. If successful the dose of thionamide is tapered and the thyroid function tests are monitored. If there is little to no response from first line treatment for type 1 AIT, this may raise the possibility that type 2 AIT is the predominant aetiology. Type 2 AIT is more of an inflammatory response to the drug itself leading to an increase in release of thyroid hormone rather than excessive production. Main treatment involves glucocorticoids, usually prednisolone at a dose of 0.5-1.0 mg/kg/day which is tapered over several months according to response. If hyperthyroidism persists despite these measures, in both type 1 and 2 AIT, then referral for thyroidectomy should be considered as RAI is unlikely to be of benefit due to reduced uptake secondary to amiodarone therapy. In clinical practice, it may be difficult to differentiate between type 1 and type 2 AIT, and sometimes both may occur together. Therefore, a pragmatic approach is frequently adopted by treating for both types of AIT simultaneously using antithyroid drugs and steroids.

2.3.2 Thyroid storm

Although thyroid storm is becoming increasingly less common due to improved diagnosis and treatment of hyperthyroidism, it remains a potentially life threatening emergency that requires urgent attention in an intensive care setting. Early supportive measures are important including fluid resuscitation, correcting electrolyte imbalances, supplemental oxygen, active cooling, and sedation if delirium is difficult to manage. Other treatments are based on clinical findings, such as broad spectrum intravenous antibiotics if infection is suspected and treating dysrhythmia or heart failure. More focused therapy includes ATD and typically PTU is preferred as it helps to lower T3 levels quicker that carbimazole due to its added effect of preventing peripheral conversion of T4 to T3 (Cooper & Rivkees 2009). PTU is given 6 hourly initially and usually oral administration is sufficient. Nasogastric tube may be required in individuals too ill to swallow and the drug can be administered intravenously if there are concerns over drug absorption. Unless contraindicated, propranolol is used to settle tachycardia and anxiety. Once ATD have been instituted, potassium iodide can be added, usually 1 hour after ATD and continued at a dose of 100 mg every 12 hours. The use of glucocorticoids is generally accepted, especially if there is a suspicion of concomitant adrenal insufficiency and may have the additional benefit of lowering T3 levels by preventing peripheral conversion of T4 to T3 (Bahn 2011). In extreme circumstances if there has not been a satisfactory response to treatment, procedures such as dialysis and plasma exchange can reduce levels of thyroid hormone, but in practice are very rarely required (Alfadhi & Gianoukakis 2011).

	Type 1 AIT	Type 2 AIT
FH of thyroid autoimmunity	Possible	Usually absent
Goitre	Yes	No
Thyroid antibodies	Yes	No
Vascularity of thyroid gland assessed by ultrasound	Increased	Decreased
Raised inflammatory markers (IL-6, CRP)	No	Yes

Table 2. Differentiation of type1 and type 2 amiodarone-induced thyrotoxicosis (AIT). FH: family history, IL: interleukin, CRP: C-reactive protein.

2.3.3 Pregnancy

Patients who are receiving treatment with ATD should receive pre-conceptual advice with a view to optimal preparation prior to pregnancy. This includes ensuring they are euthyroid prior to conception and altering medication to PTU which is felt to be superior to carbimazole during pregnancy, especially in the first trimester due to reduced incident of aplasia cutis (Bowman et al 2011). Current evidence suggests that following organogenesis, carbimazole or methimazole should be re-introduced due to a possible increased risk of hepatitis with PTU (Lazarus 2011). Those on a block and replace regime should also be swapped to PTU alone as thionamides will cross the placenta but levothyroxine will not, thus increasing the risk of foetal goitre and hypothyroidism (Weetman 2000). Pregnant patients taking ATD should have frequent TFT's throughout pregnancy (monthly) and the dose reduced to the lowest possible to maintain euthyroidism with T4 at the upper limit of the reference range (Lazarus 2011). Doses of ATD are reduced in the latter stages of pregnancy, and not infrequently stopped altogether as the condition undergoes remission. If hyperthyroidism is secondary to GD (or patient has had previous definitive treatment such as surgery or RAI) then TSH receptor antibodies should be measured as high titres can indicate intrauterine or neonatal thyrotoxicosis (Laurberg et al 1998). TSHR antibodies should not be checked in euthyroid patients previously treated with antithyroid drugs only.
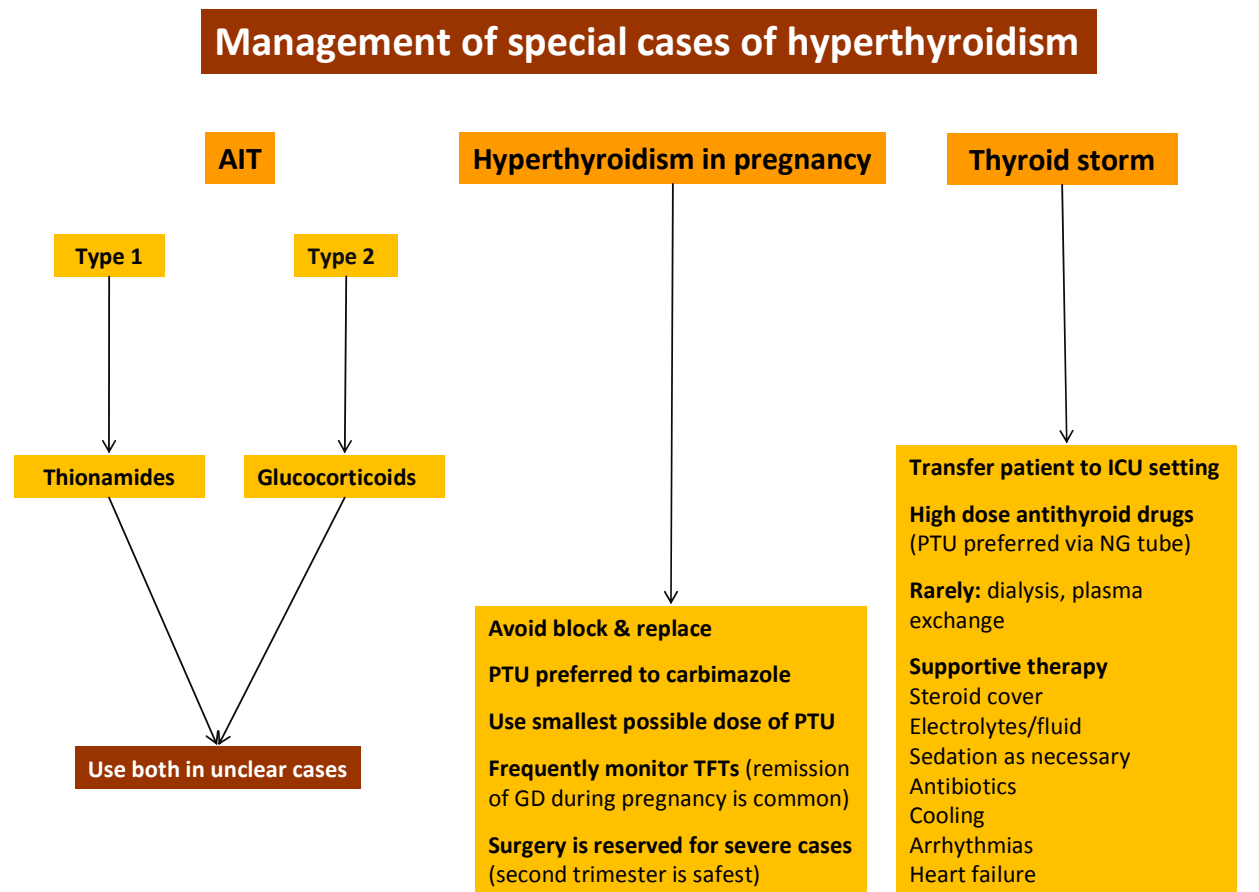

Fig. 2. Management of special cases of hyperthyroidism. AIT: amiodarone induced thyrotoxicosis, GD: Graves' disease, PTU: propylthiouracil, NG: nasogastric, TFT's: thyroid function tests. ICU: intensive care unit.

All euthyroid patients who have previously received treatment for hyperthyroidism should have TFT's checked in each trimester and importantly after delivery as there is an increased risk or recurrence post-partum. If surgery is required, due to allergy or adverse effect of ATD, it is safest to be performed in the second trimester.

2.3.4 Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a low TSH level, which is below the reference range (<0.1-0.4 mU/l), in the presence of a normal T4 and T3 concentration. It has become an increasingly problematic clinical entity following the introduction of new and more sensitive serum TSH assays. Patients usually exhibit non-specific symptoms or have no symptoms at all. There remains much debate regarding the correct management of such patients, with a lack of firm evidence to support treatment at present. The ultimate goal of treating these patients early (with the same treatment options as discussed above) is to prevent progression to overt hyperthyroidism, to reduce the risk of developing atrial fibrillation (AF) and ostoeporotic fractures and reduce mortality (Vanderpump 2011). A serum TSH level of between 0.1 and 0.4mU/l carries a very low risk of progression to overt hyperthyroidism, and so treatment need only be considered for those with a persistently suppressed TSH, especially in the presence of cardiovascular disease (Bahn 2011). Given the lack of supporting evidence advocating treatment, a pragmatic approach may be required, balancing the morbidity of hyperthyroid treatment against the risks of developing conditions such as AF, ostoeporotic fractures and overt hyperthyroidism (Vanderpump 2011).

3. Aetiology of hypothyroidism

The causes of hypothyroidism can be differentiated into primary thyroid failure or secondary central hypothyroidism caused by pituitary or hypothalamus failure. In clinical practice most cases are primary in nature, due to chronic autoimmune thyroiditis, which can be goitrous (Hashimotos thyroiditis) or non-goitrous (atrophic thyroiditis). Iatrogenic hypothyroidism is usually caused secondary to treatment of hyperthyroidism. Transient hypothyroidism may be seen following a post-partum thyroiditis or viral induced sub-acute thyroiditis as the thyroid begins recovery after a destructive phase in which stored thyroid hormone is released (Franklyn 1994). Causes of primary hypothyroidism are summarised in Table 3.

3.1 Diagnosis of hypothyroidism

Symptoms of hypothyroidism are numerous and are often also found in patients who are euthyroid, whilst some hypothyroid patients will complain of no symptoms at all. Clinical signs are also very variable, but if present give a strong suspicion of the disease. However the absence of signs cannot be relied upon to exclude a diagnosis. Thyroid function testing is vital to make a diagnosis and include the measurement of TSH and T4 levels. The presence of TSH >10mU/l and free T4 levels below the normal reference range indicate overt hypothyroidism and requires treatment with thyroid replacement hormone. Subclinical hypothyroidism is classified by TSH level above the normal reference range with normal T4. The majority of patients (>95%) with hypothyroidism due to thyroid autoimmunity have detectable TPO antibodies, which aid the diagnosis and help to differentiate from other causes of low thyroid hormone levels. The main clinical symptoms and signs of hypothyroidism are summarised in Table 4.

3.2 Management of hypothyroidism

Treatment of individuals with hypothyroidism is relatively easy and consists of replacement with thyroid hormones. In frank hypothyroidism the decision to start treatment is straightforward but in subclinical disease, criteria to start treatment are more complex (detailed below). Management of hypothyroidism is summarised in Figure 3.

Cause of hypothyroidism	Aetiology	Permanent?
Primary Myxoedema	Autoimmune	Yes
Hashimotos thyroiditis	Autoimmune	Yes
Silent Thyroiditis	Autoimmune	No
Postpartum thyroiditis	Autoimmune	No (30% may develop permanent hypothyroidism)
Subacute thyroiditis	Viral	No
Post-surgery	Iatrogenic	Yes
Following RAI	Iatrogenic	Yes
Drug induced	Iatrogenic	Reversible if drug discontinued
Iodine deficiency or excess		Reversible

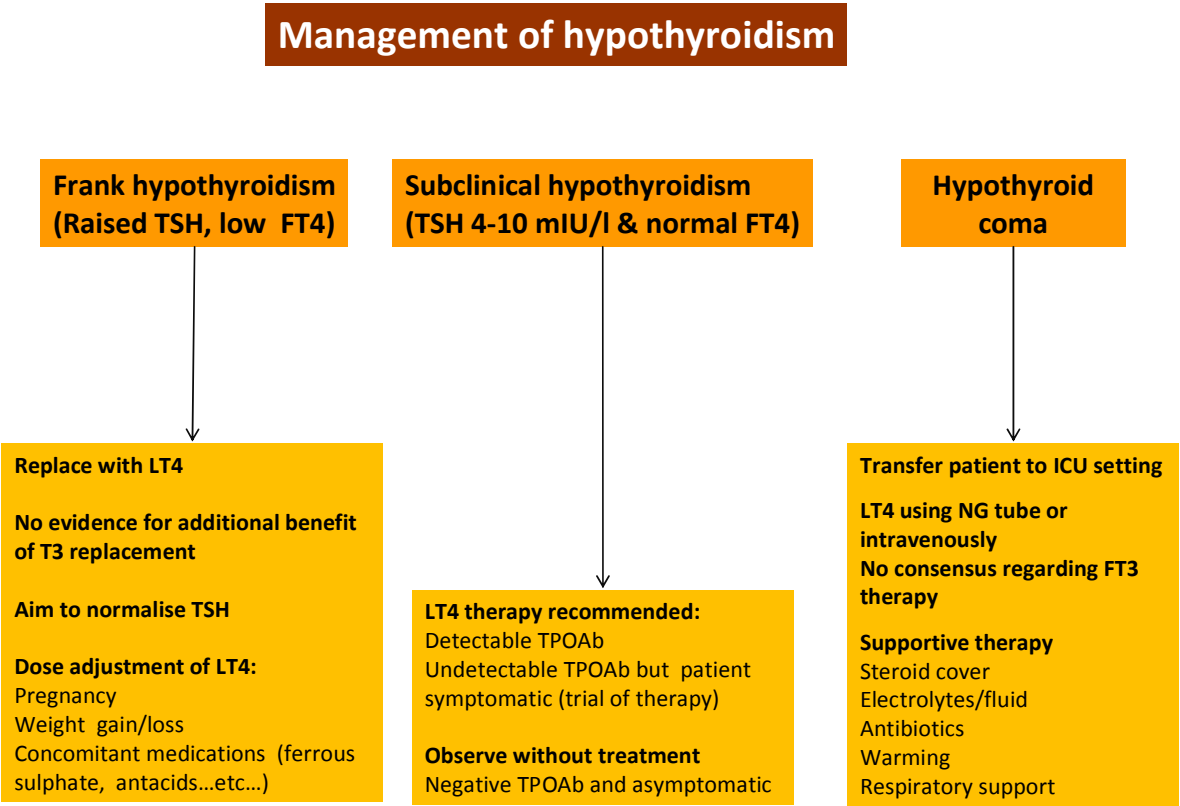Table 3. Causes of primary hypothyroidism.

Fig. 3. Management of hypothyroidism. LT4: levothyroxine, TSH: thyroid stimulating hormone, TPOAb: thyroid peroxidise antibodies, ICU: intensive care unit.

3.2.1 Levothyroxine replacement

In non-elderly individuals with no history of cardiovascular disease, levothyroxine can be commenced at a dose of 50-100mcg daily, otherwise low doses are started initially (25 mcg evey day or every other day). It is estimated that most individuals require roughly 1.4-1.6 mcg/kg and so frequently doses will need to be titrated further, which can be done in increments of 25-50 mcg. Free T4 and TSH should be measured 8-12 weeks after commencing levothyroxine and after a change in dose. Until patients are on a stable dose of thyroxine, TSH and T4 should be checked together, after which annual check of TSH is sufficient. Controversy remains as to what value of TSH should be the target in hypothyroid patients treated with levothyroxine (Wartofsky & Dickey 2005). There does appear to be a lack of evidence supporting improved patient well being from maintaining TSH at the lower end of the reference range (BTA 2006), however many physicians continue to advocate this along with a lowering of the upper limit of the reference range for TSH to 2.5mu/L, given that >95% of euthyroid individuals have a TSH between 0.4mU/l to 2.5 mU/L (Gursoy et al 2006). A pragmatic approach which our centre follows is to aim for a TSH in the lower reference range by adjustment of levothyroxine dose if a patient remains symptomatic. The suppression of TSH is certainly not recommended due to fears of osteoporosis and atrial fibrillation (BTA 2006).

Assuming that a patient's weight remains stable, with no alterations to their medication or change in co-morbidities, the dose of levothyroxine should in theory remain stable. There are several factors that require alterations in doses such as pregnancy, malabsorption and medication.

Any state that produces intestinal malabsorption, such as coeliac disease, may lead to reduced uptake of thyroxine and hence a need to increase thyroxine dose. It is important to be weary of individuals who suddenly need an increase in thyroxine and who complain of gastrointestinal symptoms. Many medications can interfere with the absorption of thyroxine, such as ferrous sulphate, calcium carbonate, proton pump inhibitors, orlistat and cholestyramine (BTA 2006). Patients prescribed these medications should be advised to take them at least 2-4 hours apart from their thyroxine. In rare circumstances, TSH levels remain raised despite replacement therapy, usually due to compliance issues that the patient typically denies. Provided malabsorption is ruled out, a large dose of supervised levothyroxine replacement (1 mg/week) can be attempted, which fixes the problem in the majority (Grebe et al 1997).

Symptoms	Frequency
Weakness, lethargy, slow speech and dry/coarse skin	>90%
Cold intolerance, facial oedema, coarse hair	>80%
Weight gain, constipation, hair loss, memory problems	>60%
Anorexia, impaired hearing, dyspnoea, menorrhagia	>30%
Emotional instability, chest pain, dysphagia	10%
Signs	**Frequency**
Dry/coarse skin, facial oedema, thick tongue	>80%
Bradycardia, skin pallor, slow relaxing reflexes	>65%
Pericardial effusion	30%
Ascites, pleural effusion, carpal tunnel syndrome	<10%

Table 4. Main symptoms and signs in autoimmune hypothyroidism

3.2.2 T3 replacement therapy

The use of tri-iodothyronine, either alone or in addition to levothyroxine remains controversial (Escobar-Morreale et al 2005). LT-3 has a much shorter half life than T4 and so repeated doses are needed throughout the day, and this can also impair measurement of free T3. Measurement of free T4 when T3 is used alone is of no benefit, and similarly to T4 treatment, the aim is for TSH within the normal range. There is currently no consistent evidence that combination therapy of T4 and T3 is superior to T4 treatment alone, and therefore this therapy is not generally advocated (BTA 2006).

3.3 Special cases of hypothyroidism

3.3.1 Myxoedema coma

Myxoedema coma is a very rare complication of untreated hypothyroidism but is associated with significant mortality. Patients with severe long standing hypothyroidism suddenly become unable to maintain homeostasis, usually due to a precipitating event such as infection, heart failure, stroke, gastrointestinal bleeding or medications (mainly sedatives and analgesics). Prompt treatment with intravenous levothyroxine is required, initially with a loading dose, followed by smaller maintenance doses which can be given orally if the patient is able. No consensus exists as to whether T3 treatment should commence at the same time, or indeed if T3 alone is all that is required (Kwaku & Burman 2007). Caution is needed in the elderly, or those with cardiovascular disease due to increased risk of myocardial infarction and tachyarrhythmia. Concurrent use of intravenous glucocorticoids are usually required during initiation of thyroxine treatment due to the potential for evoking an adrenal crisis in the first few days as the hypothalamic-pituitary-adrenal axis is usually impaired in severe hypothyroidism. Other supportive measures include blankets to warm the patients slowly, cautious use of intravenous fluid to treat hypotension and a low threshold for broad spectrum antibiotics if infection is thought to be implicated. Consideration should be given early to intubation and mechanical ventilation if deemed appropriate, especially in a comatose patient.

3.3.2 Pregnancy

During pregnancy, it is common for thyroxine requirements to increase by roughly 50%, and it is essential therefore that all pregnant ladies on thyroxine are reviewed regularly during pregnancy so that dose alteration can be made. It is recommended that TSH is maintained at the lower end of the reference range during pregnancy, with the free T4 at the upper range of normal (Lazarus 2011). It is particularly important during the first trimester, before the foetal thyroid is formed, that normal maternal levels of T4 are maintained as they play a vital role in foetal neurological development (Williams 2008). TSH and T4 should be checked pre-conceptually, at antenatal booking, within each trimester and 4-6 weeks post-partum, at which point the dose of thyroxine can usually be reduced to pre-pregnancy levels (Lazarus 2011).

3.3.3 Subclinical hypothyroidism

This relatively common clinical scenario can cause management confusion. It is recommended that replacement therapy is started in those with TSH between 4 and 10

mIU/L and positive TPO antibodies as these individuals usually progress to overt hypothyroidism. In those with similar TSH levels, symptoms of hypothyroidism but negative TPOAb, a 6 months trial of replacement therapy is advocated with reassessment as to whether this therapy is needed. In asymptomatic individuals with negative TPOAb, simple observation with repeat TFT's is probably all that is required (BTA 2006).

4. Conclusion

Thyroid dysfunction can represent a wide spectrum of disease and the consequences of under treatment are evident with the two extremes of thyroid storm and myxoedema coma. Treatment options of both hypo- and hyperthyroidism are generally well established but are not perfect and there remain several unanswered questions regarding both forms of management, such as the optimal range of TSH with thyroxine replacement, the duration of ATD for GD, and whether to treat subclinical disease. Ongoing research into such areas is likely to provide further insight into the conditions and new therapies. Even with an expansion of the evidence base, clinical experience is likely to remain an invaluable asset in many instances. Regardless of treatment, lifelong follow up is required to maintain euthyroidism.

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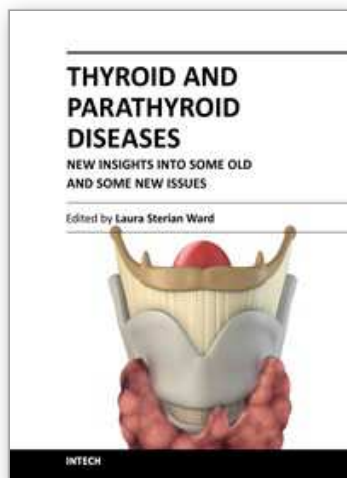
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