Management of Disorders of Thyroid Function

Written by Dr Julie Martin-Grace, Research Registrar in Endocrinology, Beaumont Hospital & RCSI/Beacon Hospital StAR MD Programme

Written by Dr Carla Moran, Consultant Endocrinologist & Associate Professor, UCD School of Medicine

Overview

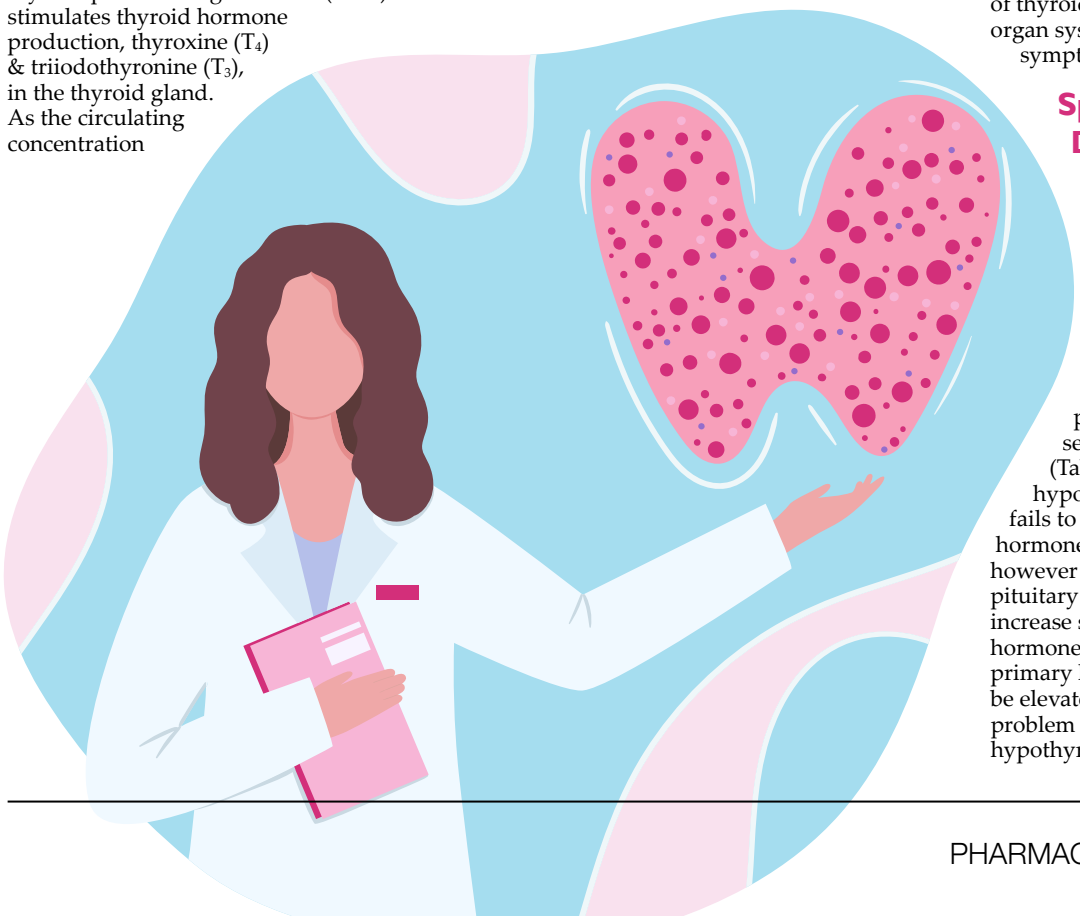
Diseases of the thyroid gland are common and affect up to 10% of people over their lifetime.[1] The most common problem is reduced thyroid hormone production (hypothyroidism), which is often due to an autoimmune disease called Hashimoto's Thyroiditis. Graves' disease is the most common cause of increased thyroid hormone production (hyperthyroidism) and is also autoimmune in nature. Thyroid disease predominantly affects females and often arises during child-bearing years. Both conditions are treated with medication (Thyroxine in the case of hypothyroidism and anti-thyroid drugs such as carbimazole or propylthiouracil for most causes of hyperthyroidism), but some patients with hyperthyroidism will require more definitive treatments such as surgery or radio-iodine treatment.

Introduction

The thyroid gland consists of two lobes which lie below the strap muscles in the anterior neck, joined in the midline by a band of tissue known as the thyroid isthmus. In healthy adults, the thyroid weighs between 10-20 g.[2] The thyroid is made up of follicles, which consist of a single layer of epithelial cells that surround a central lumen filled with clear colloid, surrounded by a network of capillaries.[3]

The regulation of thyroid function is tightly controlled by the hypothalamic-pituitary-thyroid axis due to a classical endocrine negative feedback loop. Thyroid stimulating hormone (TSH, or thyrotropin) is released by the anterior pituitary in response to thyrotropin-releasing hormone (TRH) and stimulates thyroid hormone production, thyroxine (T_4) & triiodothyronine (T_3), in the thyroid gland. As the circulating concentration of thyroid hormone rises, TSH secretion is suppressed by negative feedback to the anterior pituitary gland. thereby ensuring T_4/T_3 levels remain within a controlled range.[3]

Iodine is an important component of thyroid hormone (TH) production. Iodide is transported into the thyroid follicular cells, where it undergoes oxidation and organification in the colloid lumen to produce T_4 and a small amount of T_3. T_4 and T_3 are then secreted into the circulation, where the majority of TH is bound to plasma proteins.[3] T_4 is made only in the thyroid gland itself, but the majority of T_3, the active form of the hormone, is converted from T_4 to T_3 outside the thyroid gland, predominantly in the liver and kidney. T_3 then binds to thyroid hormone receptors present in cell nuclei, which in turn bind to specific regulatory sequences in DNA and mediate the actions of thyroid hormone by affecting the transcriptions of these TH target genes.[3] Thyroid hormone affects almost every organ in the body; it is essential for normal brain development and growth in childhood, and in adulthood maintains healthy brain function, regulates the metabolic rate, affects cardiac chronotropic and inotropic drive, and regulates cholesterol metabolism and skeletal muscle health. Therefore, disorders of thyroid function can affect multiple organ systems, producing a wide range of symptoms and clinical signs[4] (Table 1).



Spectrum of Thyroid Dysfunction

Disorders of thyroid function are classified as either primary or secondary, depending on whether the problem lies in the thyroid gland itself (primary) or the hypothalamus or pituitary gland (central or secondary). This distinction helps to explain the different patterns of thyroid function tests seen in different clinical scenarios (Table 2). For example, in primary hypothyroidism, the thyroid gland fails to produce sufficient thyroid hormone, so circulating levels of T_4/T_3 fall, however the hypothalamus and anterior pituitary will function normally, and increase secretion of TSH to boost thyroid hormone production. Therefore, in severe primary hypothyroidism, TSH level will be elevated, and T_4/T_3 levels low. If the problem is the pituitary gland itself (central hypothyroidism), both TSH and T_4/T_3 will

	Hypothyroidism	Thyrotoxicosis
Symptoms	Fatigue/lethargy Cold intolerance Menorrhagia Constipation Weight gain Dry skin and hair Myalgia	Palpitations Hyperactivity/irritability Emotional lability Heat Intolerance Amenorrhoea or lighter menstrual bleeding Increased appetite Weight loss Increased bowel frequency
Signs	Often none Goitre may be present If severe: Pale, cool skin Periorbital oedema Slow relaxing reflexes Loss of hair at eyebrows	Fine tremor Tachycardia/Atrial Fibrillation Warm, sweaty palms Proximal muscle weakness Eyelid retraction/lag Brisk reflexes Goitre may be present

Table 1. Symptoms and signs associated with hypothyroidism and thyrotoxicosis

be low. In primary hyperthyroidism, excess thyroid hormone is secreted by the thyroid gland, switching off TSH secretion, and therefore TSH levels will be undetectable.

Hypothyroidism

Primary hypothyroidism is a relatively common condition, particularly amongst women.[5] While the exact prevalence of hypothyroidism in Ireland is not known, thyroid hormone replacement therapy (levothyroxine) was the third most commonly prescribed drug on both the GMS and DPS schemes in Ireland in 2020.[6] Central hypothyroidism is rare, and almost always occurs in conjunction with anterior pituitary hormone deficiency.[7] Both primary and central hypothyroidism are treated with thyroid hormone replacement, predominantly levothyroxine.[8]

Subclinical Hypothyroidism

Subclinical hypothyroidism (SHypo) is a biochemical diagnosis, which over time can progress to overt hypothyroidism, particularly in individuals with positive anti-thyroid antibodies.[9] TSH levels are elevated, but thyroid hormone levels (T_4/T_3) remain in the normal reference range, and therefore SHypo does not always require treatment. Both European and US guidelines advise treating SHypo in patients under 70 years of age only if TSH >10 mIU/l (a typical reference range for TSH is 0.27-4.2mU/L). If symptoms suggestive of hypothyroidism are present, a trial of thyroid hormone replacement can be considered.[10, 11] SHypo should be treated with thyroid hormone replacement in pregnant women and women considering a pregnancy.[12]

Treatment of Hypothyroidism

The first-line treatment for both primary hypothyroidism, central hypothyroidism, and subclinical hypothyroidism (where appropriate) is thyroxine (T_4) monotherapy, in the form of levothyroxine.[8, 13, 14] T_4 is then converted to active T_3 in peripheral tissues under the normal physiological pathway.[3] The goal of therapy is three-fold; to improve symptoms, normalise serum TSH in the case of primary and subclinical hypothyroidism (or achieve a free T_4 concentration within the upper reference interval for central hypothyroidism[7, 8]) and avoid overtreatment.[14] A dose of 1.6µg/kg/day is generally sufficient to treat primary hypothyroidism, however in elderly patients or those with known ischaemic heart disease, thyroid hormone replacement should be commenced at a low dose, and up-titrated over several months to avoid adverse effects.[3] Pregnant women require higher doses of thyroxine and close monitoring of thyroid function and should increase their daily dose by 20-30% as soon as pregnancy is confirmed. This can be achieved by doubling their regular dose on two days per week.[12, 15] Levothyroxine should be taken on an empty stomach, and patients should not eat, or drink any fluids other than water (including caffeinated beverages) for at least 30 minutes. They should also avoid taking medications such as calcium supplements or iron at the same time, to avoid interfering with absorption.[14] Thyroxine has a half-life of approximately 7 days, therefore clinicians should ideally wait for 6-12 weeks between dose adjustments and rechecking thyroid function testing.[14, 16] Overtreatment with thyroid replacement therapy carries a risk of atrial fibrillation and osteoporosis[17], and therefore it is important to monitor serum TSH annually once a patient is established on replacement therapy.[16]

There is little evidence to suggest that treatment with combination therapy of T_4/T_3 offers an advantage over T_4 monotherapy 18, and therefore is not recommended routinely by either the British Thyroid Association (BTA), American Thyroid Association (ATA) or the European Thyroid Association (ETA) guidelines. However, combination therapy may be considered as a trial approach in patients on a case-by-case basis. Such patients should be adherent to T_4 therapy and have consistently achieved target TSH measurements but experience persistent symptoms that may be due to hypothyroidism, without any other cause for symptoms identified.[13, 14, 19] Combination therapy is not recommended in women who are pregnant or seeking fertility in the short to medium term. The use of thyroid hormone extract is not recommended in any setting, and especially not in pregnancy.[14, 19, 20]

Thyrotoxicosis

Thyrotoxicosis is the term used to describe the clinical findings that arise when bodily tissues are exposed to excess amounts of thyroid hormone (Table 1 & 2). Hyperthyroidism is used to describe thyrotoxicosis which occurs due to overproduction of thyroid hormone by the thyroid gland itself (e.g. Graves' disease, toxic multinodular goitre, toxic adenoma), however thyrotoxicosis can also occur due to inflammation or destruction of the gland (thyroiditis, which causes the release of large amounts of pre-formed thyroid hormone into the circulation), or exogenous use of thyroid hormone in excessive doses. It is important to identify the underlying cause of thyrotoxicosis, as the treatment and long-term outcomes will differ.

Graves' disease is caused by the production of anti-TSH receptor antibodies (TRAb).

	Primary Hypothyroidism	Subclinical Hypothyroidism	Central Hypothyroidism*	Primary Hyperthyroidism	Subclinical Hyperthyroidism	Central Hyperthyroidism
TSH	↑	↑	↓/↔	↓↓	↓/↓↓	↑/↔
fT4/fT3	↓	↔	↓	↑	↔	↑

Legend: TSH thyroid stimulating hormone, fT4 free T_4, fT3 free T_3, ↑above upper end of reference range, ↔within reference range, ↓below lower reference limit ↓↓ Undetectable. * Pattern also seen with non-thyroidal illness.

Table 2. Patterns of thyroid function tests in primary and central thyroid disorders

These antibodies bind to the TSH receptor on the surface of thyroid follicular cells and activate the receptor, causing excessive TH production. The level of TRAb usually falls with time and ATD therapy, and so thyrotoxicosis due to Graves' Disease remits in up to 40% following 12-18 months of medical therapy. If remission does not occur, or the patient experiences a relapse, definitive management is required, which may entail radioactive iodine therapy, total thyroidectomy or long-term medical management with ATD.[21]

Toxic multinodular goitre (many thyroid nodules with autonomous TH production) or toxic adenoma (a single adenoma with autonomous TH production) can also cause thyrotoxicosis, however in such patients spontaneous remission does not occur, and therefore ATD therapy is used to normalise thyroid function as a bridge to definitive management.

Thyroiditis is usually managed symptomatically, with anti-inflammatory treatment, if required, for neck pain, and beta-blockade for palpitations during the thyrotoxic phase. Although thyroiditis is self-limiting, many patients experience hypothyroidism following the thyrotoxic phase, which is usually, but not always, transient. Importantly, anti-thyroid drugs should be avoided, since they are ineffective (the thyrotoxicosis is due to the release of stored TH, not production of new TH) and any ensuing hypothyroidism will be worsened by using such medications.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism (SHyper) is a biochemical diagnosis. It is usually due to toxic adenoma or toxic multinodular goitre. TSH is low or suppressed but thyroid hormone concentrations (both T_4 and T_3) remain within the reference range and can be divided into grade 1 (TSH is below the lower reference limit but remains detectable) or grade 2 (TSH is fully suppressed). Grade 2 SHyper is associated with increased risk of fractures, atrial fibrillation, heart failure and increased mortality in older adults, and therefore should be treated in patients over 65 years. Treatment should also be considered in patients <65 years with persistent grade 2 SHyper and symptoms or known heart disease22. Of note, patients with suppressed TSH, normal FT4 and raised T3 have a condition called T3 toxicosis, which is often also caused by toxic adenoma or toxic multinodular goitre, but notably these patients are treated as having thyrotoxicosis, not SHyper.

Treatment of Thyrotoxicosis and Subclinical Hyperthyroidism

There are two main components of the medical management of thyrotoxicosis; β-adrenergic blockade for symptomatic relief, particularly for patients with a resting tachycardia, and the use of anti-thyroid drugs to block the production of thyroid hormone. Non-selective β-adrenergic blockers are useful to control the adrenergic symptoms associated with thyrotoxicosis (palpitations, tremor etc). When used in high doses, non-selective β-adrenergic blockers such as propranolol (30-40mg three times daily) can also inhibit the peripheral conversion of T_4 to active T_3.[21, 23]

Anti-thyroid drugs (ATD) such as thionamides (propylthiouracil, carbimazole and methimazole) are used to normalise thyroid function in hyperthyroidism, by inhibiting the synthesis of thyroid hormone within the thyroid. There are two different approaches to their use, a dose-titration approach or block and replace approach. The dose-titration approach, whereby a patient is commenced on a high dose of ATD, and the dose gradually reduced depending on thyroid function tests every 4-8 weeks, until a steady state is achieved, has the advantage of using the lowest possible ATD dose but requires frequent monitoring to guide dose modification. The block and replace approach, whereby a patient receives a high ATD dose daily, with replacement thyroxine being added once the FT4 level is normal, requires less frequent monitoring but requires higher cumulative doses of ATD, increasing the potential risk of adverse events.[24] There is little difference in efficacy between the two regimes, however during the Covid-19 pandemic, the block and replace regime was recommended for newly diagnosed patients.[25]

Carbimazole, which is decarboxylated to the active drug methimazole in the liver, and propylthiouracil, both inhibit the de novo synthesis of thyroid hormone, and at high doses propylthiouracil can also inhibit the peripheral activation of T_4 to T_3. Up to 5% of patients treated with thionamides will experience a mild skin rash, which can be managed with antihistamine therapy alone and usually subsides. If the reaction is severe, the patient can be changed to an alternative ATD. Agranulocytosis is a rare (1-3/1000) but potentially serious side effect of both carbimazole and propylthiouracil. All patients commenced on thionamides should be counselled regarding this risk and given written advice regarding possible symptoms of agranulocytosis (severe sore throat, mouth ulcers, fever, flu-like illness). If these symptoms occur, patients are advised to stop taking the medication immediately and present within 24 hours for a full blood count. If the white cell count is normal, the patient can restart the ATD. As the onset of agranulocytosis is often abrupt and unpredictable, monitoring using full blood count is not recommended.[21]

Hepatotoxicity is reported in association with both carbimazole and propylthiouracil.[26] Carbimazole is associated with a cholestatic pattern however propylthiouracil has been reported to cause fulminant hepatic failure, which is often fatal.[27] Carbimazole is therefore recommended as first line ATD therapy in non-pregnant adults by both the ATA and ETA. Patients commenced on ATD therapy are recommended to have thyroid function testing performed every 4-6 weeks while the dose is being titrated, and every three months once a maintenance dose has been achieved.[16]

Women of childbearing age should be counselled regarding the risks of conceiving while being treated for thyrotoxicosis. Thyrotoxicosis in pregnancy increases the risk of complications for both mother and fetus, and ATD cross the placenta and are associated with an increased risk of birth defects.[28] Women who conceive during treatment for hyperthyroidism should be treated with propylthiouracil in the first trimester (due to the risk of methimazole embryopathy during fetal organogenesis) and may be switched back to carbimazole in the second and third trimester to attempt to reduce the risk of hepatotoxicity.[21, 28]

Conclusion

Disorders of thyroid dysfunction are common in the community and cover a broad spectrum of presentations ranging from overt hypothyroidism to thyrotoxicosis. Correct administration of thyroxine is essential to optimise absorption and pharmacists have a role in conveying this message to patients. Anti-thyroid drugs are generally safe and well tolerated, however patients should be counselled regarding the rare, but serious potential risk of agranulocytosis. Pre-pregnancy counselling is an important component of the care of women of child-bearing age treated for all disorders of thyroid function, to optimise pregnancy outcomes for both the mother and infant.

References available upon request