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REVIEW

Shifting the paradigm in the management of conditions affecting the thyroid gland

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Abstract

Disorders of the thyroid gland are frequently encountered in the clinical practice setting and typically fall into one of two categories, namely hypothyroidism (i.e. deficient levels of circulating thyroid hormone), or hyperthyroidism (or thyrotoxicosis) that involves abnormally high levels of thyroid hormone in the bloodstream. This article provides a high-level overview of thyroid function, the two major pathophysiological abnormalities of the thyroid gland, as well as treatment modalities aimed at managing patients with thyroid pathology.

Keywords: thyroid gland, thyroxine, triiodothyronine, iodide, hypothyroidism, hyperthyroidism, goitre, thyroid storm

Overview of thyroid pathophysiology

The thyroid gland forms part of the peripheral endocrine system (i.e. those endocrine glands that are situated *outside* the central nervous system). It is characteristically shaped like a bowtie (or butterfly), with the central isthmus joining together its two lateral lobes. It is situated in the midline, anterior to the larynx and trachea, and at the level of the C5 to T1 vertebrae. The highly vascular thyroid gland secretes two blood-borne thyroid hormones that regulate the rate of the body's basal metabolism (including energy levels and body temperature), as well as calcitonin that opposes the net effect of parathyroid hormone (PTH) on plasma calcium levels, in the regulation of calcium metabolism. The thyroid hormones also play a vital role in normal growth and development and are able to augment the functions and effects of the sympathetic nervous system.[1-5]

The two thyroid hormones, which are secreted by the follicular cells, are triiodothyronine (T_3) and thyroxine (tetraiodothyronine or T_4), which are both synthesised from tyrosine and iodine. Tyrosine is a non-essential amino acid that is synthesised in the body, and the iodine is derived from the diet. In the body, the negatively charged iodide ions (I^-) are actively transported from the bloodstream, via the follicular cells, into the colloid of the thyroid gland against a steep concentration (electrochemical) gradient by the sodium-iodide-symporter.[1-5]

About 90% of the secreted T_4 is converted to T_3 in peripheral target tissues outside of the thyroid gland. This process of activation mainly takes place in the liver and kidneys. T_3 is significantly more potent than T_4. Thyroid hormone secretion is regulated via the hypothalamic-pituitary-thyroid gland axis. Thyroid-stimulating hormone (TSH) from the anterior pituitary gland regulates the secretion of T_3 and T_4 into the bloodstream. In turn, TSH-secretion is regulated by thyroid-releasing hormone (TRH) from the hypothalamus. Both T_3 and T_4 are capable of exerting negative or inhibitory feedback upon the release of TRH and TSH. Refer to Figure 1.[1-5]

Figure 2 illustrates the peripheral metabolic pathways of thyroxine (T_4).

Abnormal secretion of the thyroid hormones

There are two main categories of abnormal thyroid gland functioning, namely hypothyroidism (i.e. insufficient thyroid hormone secretion) and hyperthyroidism (i.e. an excessive secretion of the thyroid hormones).

Hypothyroidism

Hypothyroidism refers to low plasma levels of the thyroid hormones due to their inadequate production or secretion by the thyroid gland. Inadequate levels of circulating thyroid hormone during foetal development and early infancy will result in a condition known as cretinism. Three underlying mechanisms may result in the hyposecretion of thyroid hormone:

- Inadequate dietary intake of iodine, which is probably the most common cause of hypothyroidism worldwide.
- A secondary insufficiency due to deficient levels of TRH and/or TSH.
- As a result of primary gland failure of the thyroid itself.[1,5]

Hyperthyroidism

The condition is also referred to as thyrotoxicosis, and is the result of excessive, or hypersecretion of thyroid hormone. Hyperthyroidism is most commonly caused by an autoimmune condition known as Grave's disease. The other two causative mechanisms of hyperthyroidism are:

- Thyroid tumours that secrete excessive amounts of thyroid hormone.
- A secondary excess due to abnormally high levels of TRH or TSH.[1,5]

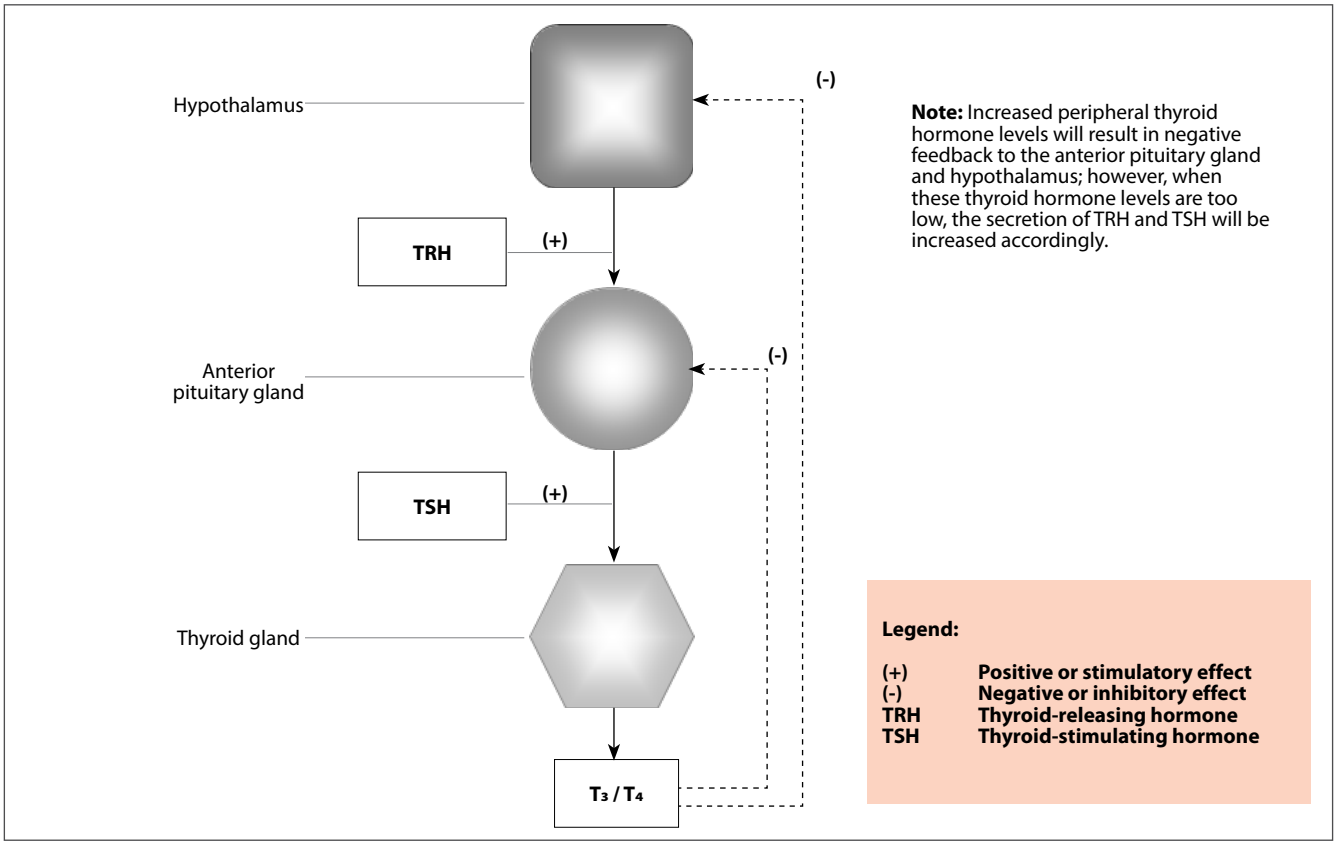

Figure 1. Simplified diagram of the hypothalamic-pituitary-thyroid gland axis

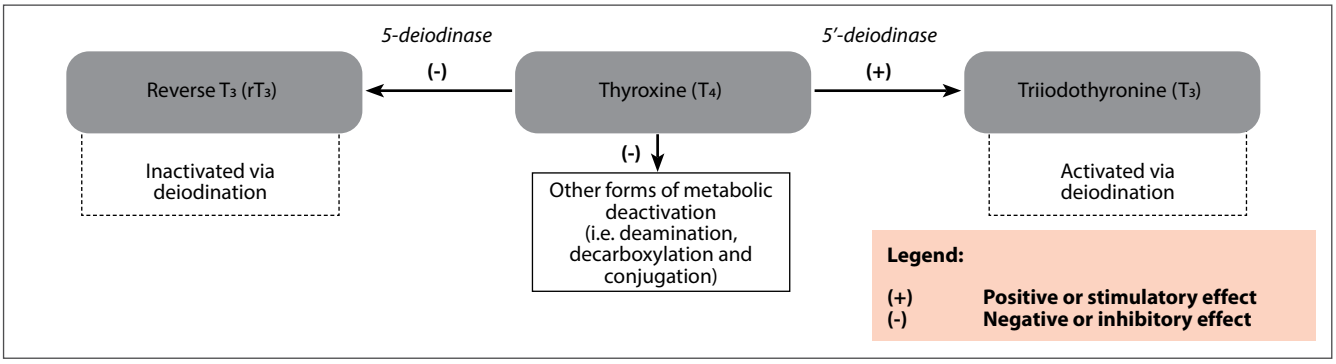

Figure 2. The peripheral metabolism of thyroxine (adapted from Katzung *et al*)[3]

Laboratory diagnosis of thyroid disorders

Thyroid function tests may be performed, which will typically include the levels of TSH, free T_4, as well as T_3 in the bloodstream. In hypothyroidism, the levels of T_3 and T_4 will be low, with a compensatory increase in the level of TSH. The reverse is found in thyrotoxicosis, where the TSH-level will be decreased, and the free levels of the thyroid hormones conversely increased.[1,5]

However, the desired TSH-level is a homeostatic concept and cannot be adjusted to a fixed range. The homeostatic control may shift from feedback, where TSH is inversely related to T_4, towards tracking where TSH becomes positive. Pituitary TSH cannot be accurately interpreted as a reliable image of thyroid function, because the TSH-to-T_4 correlation is frequently inverted or broken by common conditions such as obesity, aging and levothyroxine (LT_4) treatment. The relationships between thyroid hormones, TSH and the engaging elements of the homeostatic control system are dynamic, individual and adaptive. This paves the way for a paradigm shift in the diagnostic use of the TSH measurement.[6]

The current paradigm of thyroid diagnosis

The modern paradigm of thyroid function testing was shaped by two events, namely the methodological advances in the accurate measuring of pituitary TSH and the negative feedback mechanism by thyroid hormones on TSH.[6] If TSH serum levels displayed a more accurate mirror image of associated thyroid hormone status than thyroid hormones themselves, this would have provided clinicians with an ideal diagnostic tool.[6] Since the 1980s, TSH measurement gained a primary role in thyroid function testing, introducing new definitions of hyper- or hypothyroidism, facilitating cost-effective diagnostic screening, and providing biochemical treatment targets. Multiple epidemiological studies associated TSH serum concentrations

with clinical outcomes, which led to a highly questionable paradigm as a parameter in current guidelines for diagnosis and management of thyroid diseases.[6] Recent clinical studies have revealed fundamental concerns with the interpretation of TSH concentrations and documented poor improvement in the quality of life of patients receiving treatment for hypothyroidism in accordance with the current TSH-based criteria.[6]

Shifting the paradigm

The key question to ask is whether a patient's thyroid hormone status is always accurately reflected by the TSH concentration. Thyroid hormones, predominantly T_4, regulate pituitary TSH levels through negative feedback (refer to Figure 1). The primary physiological role of TSH is to elevate the hypothyroid to the euthyroid state. Without adequate glandular stimulation by TSH, as is apparent in secondary hypothyroidism, the primary hormone output by the thyroid gland remains subtherapeutic. On the other hand, in thyroid health, TSH will raise thyroid hormone production to its physiological state, as well as enhance the formation of T_3 and its conversion from T_4.[6]

A so-called TSH-T_3 shunt is incorporated into the homoeostatic management of the thyroid-pituitary axis. The shunt enables T_3 stability against glandular T_4 variations in output, and its absence may result in T_3 production inconsistency in athyreotic patients. This homeostasis loop still operates within the euthyroid TSH range.[6]

Pathophysiological challenges, other than thyroid disease, may also disturb TSH and thyroid hormone equilibria, requiring setpoint modification of the hypothalamic-pituitary-thyroid axis. Aging, weight gain or loss, and alterations in body composition, frequently shift the control mode from negative feedback towards tracking T_4 rather than opposing it. It is clinically important to identify this reversal in TSH-T_4 correlation; however, it may be misinterpreted as hypothyroidism when the diagnostic tests solely rely on TSH measurements.[6]

Appropriateness versus normality

Range consideration is a different concept from the appropriateness of a TSH-level.[6] In secondary hypo- or hyperthyroidism, TSH-levels may often be inadequate, although residing within a normal range, yet abnormally decreased in relation to the low T_4 level.[6] Major statistical issues arise due to the high-individuality index of TSH and its relative variation with thyroid hormones, because the concept of statistical hypothesis testing demands the sample to be representative of the population.[6] For some individuals, the same TSH value may indicate perfectly normal thyroid health, for others declining T_4 concentrations with thyroid failure and a negative association between the two hormones, and for others a homoeostatic shift towards a positive TSH-T_4 correlation.[6] Consequently, we cannot merely rely on adjusting TSH-levels to within an acceptable population range and then expect autoregulation of the thyroid hormone to adequately supply tissue with T_3.[6]

There are two primary concerns with this popular assumption regarding the ability of the patient's pituitary gland.[6] Firstly, this frequently leaves patients dissatisfied, since their quality of life is not ultimately restored with LT_4 treatment to that seen in healthy individuals despite their TSH-levels residing within the reference range.[6] Secondly, TSH concentrations for patients receiving LT_4 treatment are different to those of untreated persons.[6] The clinical treatment response to LT_4 is diverse and influenced by several treatment-related and unrelated factors.[6] Because of low-conversion efficiency in some patients, the TSH equilibrium may be shifted below the reference range of a healthy population. This poses a significant treatment dilemma to clinicians.[6]

Toward an individualised treatment strategy

Given the significant changes in thyroid management related to LT_4 medication, physicians can no longer dismiss patient complaints regarding clinical hypothyroid and biochemical euthyroid states.[6] Advancements in the understanding of the diverse aspects of pituitary control suggest replacing the current diagnostic paradigm with a more inclusive approach.[6] The proposed paradigm should take into account all three thyroid parameters, clinical signs and symptoms, and their interrelationships.[6] The appropriateness of the particular levels relative to each other, the specific condition and the previous healthy thyroid state plays a more important part in categorising than do conventional reference ranges.[6]

Unfortunately, fixed-range considerations for TSH-levels do not apply to patients receiving LT_4 since every patient on LT_4 may not tolerate or require a suppressed TSH. There is no easy solution, but a paradigm shift could be the first step, where treatment adequacy is judged on an individual basis together with a combination of biochemical and chemical outcomes.[6] Table I provides a summary of the differences between the current thyroid-stimulating hormone (TSH) paradigm and the newly-proposed relational paradigm.[6]

Pharmacology of thyroid drugs

Introduction

Drug therapy used in the management of thyroid conditions has been utilised for more than a century. Antithyroid drugs are used in the management of hyperthyroidism, whilst drugs used to restore normal thyroid hormone concentrations in body tissue, are used in the management of hypothyroidism. The latter is aimed at providing symptomatic relief, and in newborns to prevent neurological deficits (i.e. cretinism), as well as to reverse the biochemical abnormalities associated with hypothyroidism.[7]

Non-pharmacological management

Non-pharmacological measures can also be used in the management of hypo- and hyperthyroidism. Hyperthyroidism may either be managed by conservative treatment (i.e. antithyroid drugs) or by reduction or ablation of the thyroid tissue (e.g. radioactive iodine, thyroidectomy).[10] In the management of hyperthyroidism, the surgical removal of the hypersecreting thyroid is an option in patients with clinical symptoms that include:[8]

- Large thyroid (> 80 g)
- Severe ophthalmopathy
- Decreased response to antithyroid drugs

Table I. A comparison between the current thyroid-stimulating hormone (TSH) paradigm and the newly-proposed relational paradigm[6]

Current TSH paradigm	New relational paradigm
Normality-based approach	Homoeostatic equilibria
Univariate normal distribution	Multivariate distributions
Population-based range	Setpoint, joined TSH–T_4 pairs
Low degree of individuality	High-individuality index
TSH is reflective of thyroid hormone status	TSH is interlocked with T_4 and T_3
The reference range is fixed across individuals and conditions	The setpoint is genetically determined and adjustable to various conditions
The parameters are treated as singularities, even when interpreted in combination	The parameters are interpreted in relation to each other
Interpreting ranges	Reconstructing setpoints
Levels are interpreted as being within the reference range or outside its limits	Levels are interpreted as relatively appropriate or inappropriate
A TSH within its reference range in a healthy population indicates euthyroidism	The population-based TSH reference range is too wide to reliably define euthyroidism in a person
A high TSH indicates overt or subclinical hypothyroidism with rare exceptions	A high TSH originates from diverse physiologies
The setting of reference ranges and their interpretation is a simple process	The derivation of conjoined homeostatic equilibria constitute an intricate process
Subclinical thyroid disease entities are solely based on laboratory measurements and do not correspond to treatable clinical entities	The clinical change or challenge is considered primary mounting a defensive reaction that may alter the setpoint or transfer function
TSH is frequently interpreted without sufficient consideration of the clinical situation	The interpretation of TSH is tied to the clinical presentation
The TSH reference range is universally suitable to judge treatment success	A TSH-level is inadequate as a measure of treatment success and LT_4 dose adequacy
The suitable TSH range remains unchanged in LT_4-treated patients	The suitable TSH range is shifted in LT_4-treated patients

Following a thyroidectomy, hyperthyroidism may be persistent post-surgery in 0.6 % to 17.9 % of patients suffering from Graves's disease, and especially in children. Complications of surgery most frequently include hypothyroidism, and less commonly hypoparathyroidism and vocal cord abnormalities.[7,8]

The management of hypothyroidism will depend on the levels of thyroid-stimulating hormone (TSH) and the presenting symptoms of the patient. Refer to Figure 3 for an overview of the management of hypothyroidism.[9]

Hyperthyroidism

Methimazole, carbimazole, and propylthiouracil (PTU) are relatively simple molecules known as thionamides, and contain a sulfhydryl group and a thiourea moiety within a heterocyclic structure; these drugs are also the mainstay of antithyroid-drug therapy.[7,10,11] Collectively they are referred to as the antithyroid drugs (ATDs). Their main mechanism of action is through the blockade of thyroid hormone synthesis by inhibition of thyroid peroxidise. This enzyme catalyses iodide oxidation, iodination of tyrosine residues into thyroglobulin, and coupling of iodotyrosines (monoiodotyrosine (MIT) and diiodotyrosine (DIT)) to form the thyronines, tetraiodothyronine or thyroxine (T_4) and triiodothyronine (T_3). An additional effect of PTU is to inhibit monodeiodination of thyroxine to triiodothyronine.[7,10,11] They also have immunosuppressive actions, which are useful in the management and treatment of Graves's disease.

Antithyroid drugs are used in two ways:[7]

- The primary treatment for hyperthyroidism.
- Used in preoperative preparation before radiotherapy or surgery.

The following conditions may be managed with antithyroid drugs: Graves' disease, toxic adenoma, and toxic multinodular goitre. In the case of toxic adenoma and toxic multinodular goitre, ATDs are used as a tool to prepare the patient for more definitive treatment. Antithyroid drugs are used as the primary

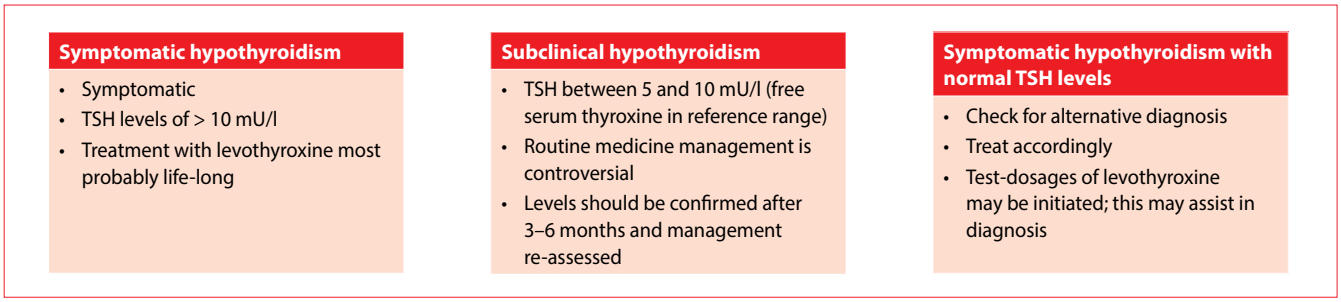

Figure 3. Overview of the management of hypothyroidism

treatment option in pregnant patients, as well as in children and adolescents.[10,11]

When prescribed for Graves' hyperthyroidism, these drugs are used to induce a remission, which is defined as having normal thyroid hormone levels for one year after drug treatment has been stopped.[10,11]

In the management of hyperthyroidism, and when patients are fully compliant with the medicines prescribed, the ATDs may be highly effective. The choice of drug to be used is based on a decision made between the prescriber and the patient. However, methimazole has the advantage of a once-daily dosing regimen and serum thyroxine and triiodothyronine levels decrease more rapidly in patients treated with this drug. The risk of agranulocytosis is also lower with methimazole, and when used in moderate dosages may improve compliance and makes this drug preferable to propylthiouracil.[7,10]

Once a patient has been started on treatment of ATD, follow-up testing of thyroid function should be undertaken every four to six weeks, until the thyroid function is stable or until the patient is diagnosed as being euthyroid (i.e. having normal thyroid function). Clinically most patients improve considerably after four to twelve weeks; drug dosing can be reduced to maintain normal thyroid function. Administering the incorrect dosage, or not monitoring the dosage, can produce hypothyroidism or even goitre. Treatment with ATDs will normally last for 12 to 18 months.[7]

Side-effects experienced with ATDs

Antithyroid drugs are associated with side-effects that may range from being minor, to being potentially life-threatening or even lethal. Methimazole has dose-related side-effects, whereas propylthiouracil side-effects seem to be less associated with the actual dosage. The milder side-effects are usually self-limiting and are observed in less than 5% of cases; these side-effects seem to be noticed during the initial phases of treatment when the daily dosage administered is higher than usual.[10,11]

When more severe side-effects are experienced with one agent, another thionamide can serve as a substitute; however, cross-sensitivity has been described in as much as 50% of patient cases.[7,10,11] Side-effects should be evaluated and if serious the drug should be discontinued. Side-effects of the ATDs are listed in Table II and have been provided in the form of a checklist, which may be utilised by the pharmacist in the practice setting.[10,11]

β-blockers

β-adrenergic blockers are used in symptomatic management of hyperthyroidism due to Graves' disease or toxic nodules awaiting surgery. They are used to reduce the sympathomimetic symptoms induced by hyperthyroidism, such as palpitations, anxiety and tremors, and should be discontinued once the patient becomes euthyroid. All β-blockers may be used in the management of hyperthyroidism; atenolol and nadolol may improve compliance as they only necessitate a once-daily dosing routine. β-blockers should still be used with caution in patients with asthma and heart failure as co-morbid conditions.[10]

Table II. Side-effects of the antithyroid drugs

Body system	Side-effect	Frequency (and drug involved)	Experienced by the patient (✓ or ✗)
Blood	Mild leukopenia	Relatively frequent	
	Agranulocytosis	Uncommon	
	Aplastic anaemia	Very rare	
	Thrombocytopaenia	Very rare	
	Pancytopenia	Very rare	
Skin	Skin rash	Very common	
	Urticaria	Very common	
	Itching	Very common	
	Generalised rash	Very rare	
	Alopecia	Very rare	
Hepatic (liver)	Hepatocellular necrosis	Rare (PTU)	
	Cholestasis	Very rare (MMI)	
Collagen	Arthralgia	Common	
	SLE-like syndrome	Very rare (PTU > MMI)	
	Vasculitits	Very rare (PTU)	
Embryopathy	Choanal atresia, esophageal atresia, cardiac defects, aplasia cutis	Very rare (MMI)	
	Situs inversus ± dextrocardia, unilateral kidney a/dysgenesis, cardiac outflow tract defect	Very rare (PTU, uncertain)	
Miscellaneous	Loss of taste	Rare (MMI)	
	Hypothrombinaemia	Rare (PTU)	
	Insulin auto-antibodies	Very rare	

[MMI = methimazole; PTU = propylthiouracil; SLE = systemic lupus erythematosus]

Radioactive iodine (RAI)

Recurrent hyperthyroidism and Graves' disease may be treated with radioactive iodine. RAI is used as it causes destruction of thyroid tissue with the end-goal of achieving a patient with either euthyroid or hypothyroid levels. Sodium iodide 131 (^{131}I) is the RAI of choice in the treatment of Graves' disease and toxic autonomous nodules. RAI is a colourless and tasteless liquid. Dosing regimens and the contact-time following the administration of RAI is not well established; however, low dosages may be more convenient for the patient.[10,11]

Iodides

Iodine is a temporary solution that inhibits the release of thyroid hormones for only a few days or weeks (one to two weeks), and for this reason its usefulness is limited to the preparation of patients with Graves' disease for surgery, as well as to treat patients suffering from a thyrotoxic crisis. The inhibitory effect is achieved via the blocking of hormone release, by interfering with hormone biosynthesis through competing with intrathyroidal iodide use. This decreases the size and vascularity of the thyroid gland. Preparations are available as either a saturated potassium iodide solution (SSKI) or as a Lugol's solution.[10,11]

Hypothyroidism

When hypothyroidism is left untreated it can result in cardiac failure, psychosis, and coma.[12] Thyroxine-replacement therapy is highly effective and has been used in its rudimentary form since 1891.[12] The major indications for thyroid-replacement therapy remain:[13]

- Hypothyroidism
- Cretinism
- Thyroid-stimulating hormone (TSH) suppression therapy in patients suffering from thyroid cancer

Levothyroxine (T_4; L-thyroxine) is a synthetic thyroid hormone and remains the drug of choice for thyroid-replacement therapy as it is chemically stable, not expensive, and with uniform potency.[14] Dosages of levothyroxine (LT_4) can be related to bodyweight (dosed at 1.8 µg per kg in adults, 0.5 µg per kg in older adults) and is dosed at higher levels in infants and young children.[14] When therapy is initiated it should be at the lower end of the calculated dose; i.e. for a 70 kg adult, 125 µg per day.[15] To initiate therapy at 25–50 µg per day and titrating upwards is unnecessary and prolongs the desired response to treatment.[14,15] Dosages should be titrated using serum thyrotropin concentrations and should be undertaken four to six weeks after a new thyroxine dosage has been prescribed. Thereafter, this should be done annually, or whenever a patient presents with persistent symptoms of either hypo- or hyperthyroidism.[14]

The target level of treatment is determined by the following:[15]

- The patient expressing a sense of well-being, with signs and symptoms decreasing in frequency and severity
- TSH-levels at the lower end of the reference range (0.4 to 2.5 mU/l)

It is important to avoid a fully-suppressed TSH (< 0.1 mU/l); each patient should be assessed using TSH-levels and symptoms, and dosed individually.[15] Patient counselling when initiating the therapy should include the advice as listed in Table III.

Side-effects experienced with levothyroxine therapy

Side-effects experienced with thyroid-replacement therapy are related to excessive thyroid hormone action and may include the following:[6,11,15]

- Symptomatic thyrotoxicosis
- Subclinical thyrotoxicosis (with an increase in bone loss)
- Atrial tachyarrhythmias
- Heart failure
- Angina pectoris
- Myocardial infarction

Patients who were previously diagnosed with underlying ischaemic heart disease may exacerbate myocardial ischaemia once euthyroidism has been established.[11,15] Synthetic products very rarely produce allergic or idiosyncratic reactions, as were previously experienced with the natural or animal-derived products.[5]

Hyperthyroidism may lead to a decrease in bone density due to hyper-remodelling of the cortical and trabecular bone, which could result in an increased likelihood of bone fractures.[5] Acute sympathomimetic symptoms and hair loss have also been experienced after thyroxine treatment has been initiated.[12]

Table III. Patient advice when initiating levothyroxine therapy[15]

Patient advice	Experienced by the patient (✓ or ✗)
It may take a week or more for you to start feeling better. Levothyroxine has a half-life of seven days.	
If you miss one dose, the effect might not be noticeable (due to the long half-life); take as soon as you remember.	
Other symptoms (e.g. muscle stiffness/weakness and mental effects may take several months to resolve once the chemical imbalance has been corrected).	
Levothyroxine should be taken on an empty stomach, it will maximise absorption.	
Treatment will be life-long, and dose adjustments will only be made according to hormone (thyroid) levels. Hormone levels should be taken once a year.	
The following drugs should be avoided or taken with caution when taking levothyroxine therapy: Drugs that will **prevent absorption** of levothyroxine (e.g. calcium salts, ferrous sulphate, aluminium hydroxide, cholestyramine). Drugs that **increase the clearance** of levothyroxine, in other words drugs that will cause a decrease in levothyroxine levels (e.g. phenytoin, carbamazepine, phenobarbitone and rifampicin).	

Conclusion

The thyroid gland plays a vital role in the maintenance of a normal basal metabolism in the human body. Abnormalities in thyroid hormone levels could, therefore, have far-reaching effects on various body systems, organs and tissues. Such abnormalities typically fall into one of two categories, namely hypo- or hyperthyroidism, and require effective treatment to either replace the deficient levels of thyroxine in the bloodstream, or to antagonise the excessive levels of circulating thyroid hormone. Patients who are using such therapies in the long-term will require additional monitoring and support from the multidisciplinary team, including the pharmacist.

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