Clinical review: hyper- and hypothyroidism

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Abstract

Thyroid disorders can range from a slightly enlarged thyroid gland, that needs no treatment, to life-threatening thyroid cancer. The most common thyroid problems involve the abnormal production of thyroid hormones. Thyroid function disorders can generally be grouped into two classes, namely hyperthyroidism and hypothyroidism. The proper treatment of hyper- and hypothyroidism depends on recognition of the signs and symptoms of the disease and determination of the aetiology. In hyperthyroidism, treatment consists of thionamides, iodine therapy, thyroidectomy, radioactive iodine and/or beta blockers. For hypothyroidism, treatment consists of substituting the deficient hormone, mostly with levothyroxine. The pharmacist’s role in both hyper- and hypothyroidism is supportive, assisting the patient to reach a euthyroid state.

Introduction

Thyroid disorders can range from a slightly enlarged thyroid gland, that needs no treatment, to life-threatening thyroid cancer. The most common thyroid problems involve the abnormal production of thyroid hormones. Thyroid function disorders can generally be grouped into two classes:

- **Hyperthyroidism (thyrotoxicosis):** Overactivity of the thyroid gland leads to high levels of thyroid hormones and the speeding up of the metabolism. The heart rate and blood pressure may increase, heart rhythms may be abnormal, and patients may sweat excessively, feel nervous and anxious, have difficulty sleeping, and lose weight without dieting. Graves’ disease (toxic diffuse goitre) is the most common cause of hyperthyroidism.

- **Hypothyroidism (myxoedema):** Underactivity of the thyroid gland leads to inadequate production of thyroid hormones and a slowing of metabolism. The facial expressions become dull, the voice is hoarse, speech is slow, the eyelids droop, and the eyes and face become puffy. Patients with hypothyroidism usually need to take thyroid preparations for the rest of their lives.

The thyroid gland is located across the trachea and is shaped like a butterfly. It produces thyroxine, a hormone that regulates the metabolic activity of the body. Too much thyroxine increases the metabolism, causing weight loss, temperature elevation, nervousness and irritability. Too little thyroxine slows the metabolism down, deepens the voice, causes weight gain and water retention, and retards growth and mental development in children. Both conditions also alter hair and skin growth, bowel function and menstrual flow. Table I compares the signs and symptoms of hypo- and hyperthyroidism. Interestingly, the thyroid gland can be enlarged whether it is making too much hormone or too little, or sometimes even when it is functioning normally. The term “goitre” refers to an enlarged thyroid gland and it may cause the neck to appear visibly swollen and can interfere with normal breathing and swallowing.

The thyroid is controlled by the pituitary gland, which secretes thyroid-stimulating hormone or thyrotropin (TSH) in response to the blood thyroxine level. The thyroid gland uses iodine (mostly from the diet, e.g. seafood and salt, or medicine) to produce thyroid hormones. The two most important thyroid hormones are thyroxine (T₄) and triiodothyronine (T₃). The hormone with the most biological power is T₃. Once released from the thyroid gland into the blood, a large amount of T₄ is converted into T₃, the active hormone that affects the metabolism of cells in the body. These hormones regulate the body’s metabolism and affect processes such as growth and other important functions in the body.

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Table I: Signs and symptoms of hypo- and hyperthyroidism

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry, coarse hair</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Loss of eyebrow hair</td>
<td>Bulging eyes</td>
</tr>
<tr>
<td>Puffy face</td>
<td>Sweating</td>
</tr>
<tr>
<td>Enlarged thyroid (goitre)</td>
<td>Enlarged thyroid (goitre)</td>
</tr>
<tr>
<td>Slow heartbeat</td>
<td>Rapid heartbeat</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Constipation</td>
<td>Frequent bowel movements</td>
</tr>
<tr>
<td>Brittle nails</td>
<td>Soft nails</td>
</tr>
<tr>
<td></td>
<td>Warm, moist palms</td>
</tr>
<tr>
<td></td>
<td>Tremor of fingers</td>
</tr>
</tbody>
</table>

Further signs and symptoms

<table>
<thead>
<tr>
<th>Arthritis</th>
<th>Difficulty sleeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold intolerance</td>
<td>Heat intolerance</td>
</tr>
<tr>
<td>Depression</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Irritability</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>Infertility</td>
</tr>
<tr>
<td>Heavy menstrual periods</td>
<td>Scant menstrual periods</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Muscle aches</td>
<td></td>
</tr>
</tbody>
</table>

The goal of therapy is to correct the imbalance, with the fewest side-effects and the lowest incidence of medically induced hypo- or hyperthyroidism. Hyperthyroidism and hypothyroidism are discussed separately below.

Hyperthyroidism

Hyperthyroidism is also known as thyrotoxicosis. It is characterised by hypermetabolism and elevated serum levels of free thyroid hormones. There is enlargement of the thyroid gland and exophthalmos (bulging eyes). Aetiological diagnosis influences prognosis and therapy.

The presenting symptoms of hyperthyroidism vary according to the age of the patient, duration of illness, magnitude of hormone excess and presence of comorbid conditions. Typical symptoms include tachycardia, fatigue, weight loss and tremor. The clinical presentation is different in younger and older patients.

Diagnosis

Diagnosis is based on clinical examination and thyroid function tests. Physical examination may reveal thyroid enlargement, tremor, hyperactive reflexes or an increased heart rate. The systolic blood pressure may be elevated. Subclinical hyperthyroidism is defined as a mild form of hyperthyroidism that is diagnosed by abnormal blood levels of thyroid hormones, often in the absence of any symptoms.

Blood tests measuring the levels of thyroid hormones typically show:

- TSH is low.
- T₃ and free T₄ are high

The following tests may also be of benefit in hyperthyroidism:

- Serum cholesterol and triglycerides.
- Serum glucose.
- Radioactive iodine uptake.
- T₃ resin uptake that measures the level of proteins that carry thyroid hormone in the blood.
- Vitamin B₁₂ (in rare cases).

Aetiology

There are various reasons why a person may suffer from hyperthyroidism:

- Graves’ disease is the most common cause of hyperthyroidism, accounting for 60-80% of all cases. It is an autoimmune disease caused by an antibody that stimulates TSH receptors, causing the gland to synthesise and secrete excess thyroid hormones. An infiltrative ophthalmopathy accompanies Graves’ disease in approximately 50% of patients.

- Toxic uni- or multinodular goitre and adenomas: These are nodules that develop in the thyroid gland and secrete thyroid hormones, upsetting the body’s normal chemical balance.
• Thyroiditis: Subacute thyroiditis is caused by inflammation of the thyroid gland and produces an abrupt onset of thyrotoxic symptoms as excess hormone leaks from the inflamed gland. It often follows a viral illness and results in temporary hyperthyroidism that generally lasts for a few weeks, but may persist for months. Lymphocytic and postpartum thyroiditis are further transient inflammatory causes of hyperthyroidism. Postpartum thyroiditis may occur in 5-10% of females within the first three to six months after delivery.

• Treatment-induced hyperthyroidism includes, for example, iodine-induced hyperthyroidism which may occur after the intake of excess iodine in the diet, exposure to radiographic contrast media or medicine. Amiodarone-induced hyperthyroidism can be found in up to 12% of treated patients, especially those in iodine-deficient areas. Thyroid hormone-induced hyperthyroidism may also be caused by the intentional or accidental ingestion of excess amounts of thyroid hormone. Some patients may use thyroid hormones to achieve weight loss.

• Tumours: Rare causes of hyperthyroidism include metastatic thyroid cancer, ovarian tumours that produce thyroid hormone, trophoblastic tumours and TSH-secreting pituitary tumours.

Treatment

Treatment depends on the cause and severity of the disease, the patient’s age, goitre size, comorbid conditions and treatment preferences. Treatment includes pharmacotherapy, radioactive iodine and surgical treatment (Table II). Establishing the cause is of critical importance before treatment can be recommended.

Table II: Summary of treatment options for thyrotoxicosis

<table>
<thead>
<tr>
<th>Aetiological diagnosis</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>Pharmacological therapy</td>
</tr>
<tr>
<td></td>
<td>Radioactive iodine</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Toxic nodular goitre</td>
<td>Radioactive iodine</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Destructive thyrotoxicosis, e.g. subacute granulomatous thyroiditis, postpartum thyroiditis</td>
<td>Symptomatic treatment</td>
</tr>
</tbody>
</table>

Antithyroid medication

Thiouracils and sulphur-containing imidazole derivatives (thioamides: propylthiouracil and carbimazole) interfere with thyroxine synthesis in the thyroid gland and are used mainly to prepare patients for surgery or irradiation, or in the long-term management of hyperthyroidism associated with Graves’ disease. Propylthiouracil is not available in South Africa. Approximately 40-50% of females and 20% of males with Graves’ disease will remain in remission after 12 months of antithyroid medication.

Iodine therapy

This is administered as aqueous iodine oral solution BP (Lugol’s solution) or potassium iodine solution. It is particularly valuable preoperatively and in the management of thyrotoxic crisis. It is usually combined with other antithyroid agents. It rapidly blocks the conversion of T4 to T3 and inhibits hormone release from the gland while rendering it less vascular and easier to operate on.

Radioactive iodine

Patients with toxic uni- or multinodular goitres who do not respond to antithyroid medicine may require radioactive iodine (sodium iodine or 131I), which concentrates in the thyroid gland and destroys thyroid tissue, and thus stops excess production of hormones. It is also used in the management of malignant neoplasms of the thyroid and for thyroid isotope scans. It is a safe and effective oral treatment usually administered in a capsule form. It is contraindicated during pregnancy and when breastfeeding. Side-effects include transient neck soreness, flushing and decreased sensation of taste, radiation thyroiditis (in a small percentage of patients), and potential exacerbation of ophthalmopathy.

Surgery

During thyroidectomy, all or part of the thyroid gland may be removed. The thyroid mass is therefore reduced. It is the treatment of choice for patients who are pregnant, children who have had major adverse reactions to antithyroid drugs, toxic nodules in patients younger than 40 years, and for patients with large goitres causing compressive symptoms. It may also be considered for patients who are noncompliant, refuse radioactive iodine or fail antithyroid drugs, and in patients with severe disease who could not tolerate recurrence. It may also be done for cosmetic reasons. If the thyroid is removed by surgery or destroyed with radiation, the patient will have to take thyroid hormone replacement medicine for the rest of his or her life.

Symptomatic treatment

Beta blockers (such as propranolol) are effective in controlling some symptoms of hyperthyroidism, such as rapid heart rate, sweating and anxiety, until the hyperthyroidism is treated. There is no effect on the underlying disease, radioactive iodine uptake or thyroid function tests. Beta blockers are useful at the start of therapy with other agents, preoperatively, for the management of a thyrotoxic crisis, and short-term therapy in pregnancy. Doses of propranolol up to 80 mg three times daily can be used. Beta blockers should be used with caution in older patients and patients with pre-existing heart disease, chronic obstructive pulmonary disease or asthma.

Hypothyroidism

Hypothyroidism results from a deficiency of thyroid hormones. It is usually a primary process in which the thyroid gland produces insufficient amounts of thyroid hormone. Rarely it may also be caused by inadequate secretion of either TSH from the pituitary gland, or thyrotropin-releasing hormone from
the hypothalamus (secondary and tertiary hypothyroidism respectively).

Hypothyroidism is biochemically characterised by an elevated TSH and a decreased free T₄. Symptoms are usually vague and non-specific. Cold intolerance, constipation, dry skin, low heart rate, hoarse voice and impaired mental performance are common. In its most extreme form, heart failure and coma may occur. Hypothyroidism in children can cause mental retardation. Hypothyroidism caused by iodine deficiency is said to be the single most prevalent cause of mental retardation in children in some parts of the world.

**Diagnosis**

Physical examination may reveal a diminished thyroid gland, although sometimes the gland is normal or even enlarged (goitre). The examination may also reveal:

- Brittle nails.
- Coarse facial features.
- Pale or dry skin, which may be cool to the touch.
- Swelling of the arms and legs.
- Thin and brittle hair.

A chest X-ray may show an enlarged heart. Laboratory tests to determine thyroid function include serum TSH and T₄ levels. Further laboratory tests may also reveal anaemia on a full blood count, increased cholesterol, liver enzymes and prolactin, and low sodium. The most important early and late symptoms of hypothyroidism are given in Table III.

**Table III: Symptoms of hypothyroidism**

<table>
<thead>
<tr>
<th>Early symptoms</th>
<th>Late symptoms (if left untreated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to cold</td>
<td>Decreased sensation of taste and smell</td>
</tr>
<tr>
<td>Constipation</td>
<td>Hoarseness</td>
</tr>
<tr>
<td>Depression</td>
<td>Puffy face, hands and feet</td>
</tr>
<tr>
<td>Fatigue and slowing down</td>
<td>Slow speech</td>
</tr>
<tr>
<td>Heavier menstrual periods</td>
<td>Thickening of the skin</td>
</tr>
<tr>
<td>Joint and muscle pain</td>
<td>Thinning of the eyebrows</td>
</tr>
<tr>
<td>Pale and dry skin</td>
<td></td>
</tr>
<tr>
<td>Thin, brittle hair and fingernails</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
</tr>
<tr>
<td>Unintentional weight gain</td>
<td></td>
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</tbody>
</table>

Subclinical hypothyroidism is defined as a mild form of hypothyroidism. It will be treated in certain circumstances, for example in pregnancy, if there is female infertility associated with the subclinical hypothyroidism, or in case of high total or low-density lipoprotein (LDL) cholesterol levels.

**Aetiology**

The causes of hypothyroidism are varied:

- Thyroiditis: Inflammation of the thyroid gland causing thyroid hormone to leak out. At first it leads to raised hormone levels in the blood (leading to hyperthyroidism for a month or two), then most patients experience hypothyroidism before the thyroid is completely healed.
- Hashimoto’s thyroiditis (Hashimoto’s disease or lymphocytic thyroiditis) is a progressive autoimmune disease of the thyroid gland with degeneration of its epithelial elements and replacement by lymphoid and fibrous tissue.
- Congential hypothyroidism, or hypothyroidism that is present at birth, occurs when a thyroid is not fully developed or does not function properly. It can lead to mental retardation and growth failure.
- Thyroidectomy: The thyroid gland or parts of it may be surgically removed or chemically destroyed as treatment for hyperthyroidism.
- Irradiation: Radioactive iodine, a common treatment for hyperthyroidism, gradually destroys the cells of the thyroid, eventually leading to hypothyroidism. People with Hodgkin’s disease and other lymphomas, as well as head and neck cancers, are treated with radiation, which may damage the thyroid.
- Too much or too little iodine in the diet. Worldwide, iodine deficiency is by far the most prevalent cause of hypothyroidism.
- A pituitary disorder.
- Iatrogenic causes, e.g. after previous treatment for hyperthyroidism, or other medication (such as amiodarone, lithium, interferon alpha and interleukin 2).

**Treatment**

Treatment constitutes substituting the deficient hormone with levothyroxine (L-thyroxine) sodium. It is a synthetic thyroid hormone derivative of T₄, and it normalises blood levels of TSH, T₄ and T₃.

The dose is dependent on the underlying cause and weight of the patient (usually 1.8 µg/kg for autoimmune hypothyroidism and 2 µg/kg after thyroidectomy). In the elderly and in patients with cardiovascular morbidity, it is advised to start more slowly (25 µg, with dose adjustments based on TSH every four to six weeks). There are no differences in the quality of life between a fast and slow titration schedule. Thyroid hormone dose is adjusted on the basis of TSH (not T₄), aiming for a TSH in the normal range. The average maintenance dose is 100 µg to 150 µg daily. If conditions such as pregnancy, surgery or other drugs alter hormone levels, the patient’s thyroid needs will have to be reassessed. Some dietary changes, e.g. an increase in soy product consumption or a high-fibre diet, can also change the absorption of thyroid medicine. L-thyroxine should be taken either in the morning on an empty stomach or in the evening at bedtime.

L-thyroxine is slowly assimilated by body organs, and it therefore usually takes up to six weeks before symptoms improve in adults. However, many patients experience symptom improvement after two to three weeks of treatment. The rate at which specific symptoms improve varies:
• Weight loss, reduction in puffiness and improved pulse rate usually occur early in treatment.
• Improvements in anaemia and skin, hair, and voice tone may take a few months.
• High LDL levels decline very gradually. High-density lipoprotein (HDL) levels are not affected by treatment.
• Goitre size declines very slowly, and some patients may need high-dose thyroid hormone (suppressivethyroid therapy) for a short period.

Levothyroxine reduces blood pressure in about half of hypothyroid patients with hypertension, although antihypertensive medication may still be needed.

Several drugs, such as biliary salts, iron, antacids, calcium carbonate, aluminum hydroxide and sucralfate, interfere with thyroxine uptake. It is therefore advised to take these medicines two to four hours apart from thyroxine. Phenytoin, carbamazepine, phenobarbital and rifampicin lead to an increased clearance of thyroxine, therefore the thyroxine requirement increases.

Life-long therapy is required, even if symptoms disappear, unless the diagnosis is transient viral thyroiditis. Initially, hormone levels will be monitored regularly, and thereafter at least annually. Since treatment is an ongoing process and many factors can cause changes that require modifying the thyroxine dosages, continuous monitoring for over- or underdosing is required. If left untreated for long periods of time, hypothyroidism may lead to myxoedema coma.

Liothyronine (triiodothyronine or T₃) is rarely used orally for maintenance therapy. Most patients respond well to T₄ alone, which is converted in the body into T₃. T₃ is indicated for myxoedema coma. After initial therapy, these patients are treated with thyroxine. The use of liothyronine may be useful in patients with the rare condition of 5'-deiodinase deficiency.

Thyroid dysfunction during and after pregnancy
Maternal thyroid hormone metabolism changes considerably during pregnancy. There is an increase in iodine demand as a result of placental transport to the foetus. Daily intake during pregnancy and lactation should therefore be at least 250 µg.

A lack of thyroid hormones at an early age can lead to the development of congenital hypothyroidism or cretinism, characterised by mental retardation and dwarfism (stunted growth). An infant with hypothyroidism is usually inactive and quiet, has a poor appetite and sleeps for excessively long periods of time.

Thyroid emergencies

Thyroid storm
Thyroid storm is a rare clinical syndrome characterised by a life-threatening thyrotoxicosis. It manifests as hyperthermia, severe tachycardia with or without cardiac failure, severe agitation and mental disorientation, culminating in stupor and coma. Mortality is high and patients should be monitored in an intensive care unit. Treatment should be supportive and thyroid-specific. Carbimazole, iodine, propranolol and glucocorticoids are used in treatment.

Myxoedema coma
Myxoedema coma is a severe state of hypothyroidism that presents with multisystem organ failure and altered mental status, respiratory insufficiency and hypothermia, besides other common hypothyroid symptoms. It is commonly precipitated by an acute event, e.g. an infection, myocardial infarction, or hypothermia with a background of long-standing untreated (or insufficiently treated) hypothyroidism. Treatment should be in an intensive care unit.

Conclusion
The proper treatment of hyper- and hypothyroidism depends on recognition of the signs and symptoms of the disease and determination of the aetiology. The goal of therapy is to achieve euthyroidism with the fewest side-effects and the lowest incidence of either hypo- or hyperthyroidism. The pharmacist has an important supportive role to play in the treatment of thyroid disorders.

References