The pharmacological management of hypothyroidism

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Abstract
Hypothyroidism is a condition characterised by the biochemical and clinical manifestations of deficient thyroid hormone concentrations. Worldwide, the most common cause of this condition is iodine deficiency. In cases where iodine deficiency is not the cause, the most common causes of hypothyroidism are Hashimoto's thyroiditis, thyroidectomy and radioactive iodine treatment. Apart from thyroid gland pathology (primary hypothyroidism), hypopituitarism (secondary hypothyroidism) should also be considered. Autoimmune hypothyroidism occurs at a mean annual rate of 4 per 1 000 women and 1 per 1 000 men. The onset of hypothyroidism is usually insidious, and patients may only become aware of symptoms after optimal thyroid hormone replacement. Typical signs include a puffy face, oedematous eyelids, non-pitting pretibial oedema, dry, brittle hair, alopecia, thinning of the outer third of the eyebrows, pallor and retarded nail growth. Goiter is sometimes the presenting symptom in Hashimoto's thyroiditis, but typical symptoms like fatigue, dry skin, hair loss, constipation, cold intolerance and weight gain may also be present. The aim of therapy is to improve symptoms, normalise serum thyroid-stimulating hormone (TSH), reduce the goiter size and to avoid overtreatment.

Keywords: hypothyroidism, pharmacological management, deficient thyroid hormone concentrations

Spectrum and diagnosis of hypothyroidism

Subclinical hypothyroidism
The prevalence of subclinical hypothyroidism varies from 4–20% within the adult population. This condition is identified by an abnormal thyroid function test in the absence of obvious symptoms. An elevated TSH with normal triiodothyronine (T3) and thyroxine (T4) levels is the hallmark of subclinical hypothyroidism. Although it may be associated with cardiovascular disease and a substantial number of patients progress to primary hypothyroidism, treatment is not always indicated.

Primary hypothyroidism
In this condition, the thyroid gland is unable to produce sufficient thyroid hormone to meet the body's requirements. The diagnosis is based on an elevated TSH level associated with T3 and T4 levels below the normal reference range. Unless the primary hypothyroidism is reversible or transient, all patients with this condition must receive replacement therapy.

Central (secondary) hypothyroidism
This condition is due to pathology of the pituitary gland or hypothalamus causing impaired release of TSH and/or thyrotropin-releasing hormone. A low TSH in the setting of a low or inappropriate TSH level is suggestive of central hypothyroidism. Potential causes are surgery, trauma, tumours and infiltrative disorders of the pituitary gland or hypothalamus.

Who must be treated?
All cases of primary and central hypothyroidism require treatment, except if the hypothyroidism is transient. Conversely, based on TSH levels, the approaches listed in Table I are recommended for managing subclinical hypothyroidism.

<table>
<thead>
<tr>
<th>Table I: Treatment for subclinical hypothyroidism</th>
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<tbody>
<tr>
<td>TSH</td>
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<tr>
<td>TSH ≥ 10 mIU/L</td>
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<tr>
<td>TSH 7–9.9 mIU/L</td>
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<tr>
<td>TSH of above upper limit of normal to 6.9 mIU/L</td>
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Pharmacology of available treatment options

Levothyroxine
Levothyroxine is a synthetic levorotatory isomer of thyroxine and has been the gold standard for treatment since the 1960s. In South Africa, levothyroxine sodium is available as tablets for oral administration. Approximately 80% of this compound is absorbed in the stomach and small intestine and absorption can be improved by taking it on an empty stomach. The tablet is taken daily and has a long t1/2 of seven days. Owing to this long t1/2, it does not have much of an effect on TSH and T4 levels when a dose is skipped.
Table II: Factors affecting levothyroxine treatment

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
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<tbody>
<tr>
<td>Impaired absorption</td>
<td>• Proton pump inhibitors and aluminium containing antacids&lt;br&gt;• Bile acid sequestrants&lt;br&gt;• Calcium carbonate and iron salts&lt;br&gt;• Lactose intolerance&lt;br&gt;• H. pylori infection&lt;br&gt;• Atrophic gastritis&lt;br&gt;• Celiac disease&lt;br&gt;• Foods like soy bean, papaya and grapefruit</td>
</tr>
<tr>
<td>Increased metabolism</td>
<td>• Rifampicin&lt;br&gt;• Carbamazepine&lt;br&gt;• Phenytoin&lt;br&gt;• Sertraline</td>
</tr>
<tr>
<td>Impairment of the peripheral conversion of T₄ to T₃</td>
<td>• Amiodarone</td>
</tr>
<tr>
<td>Uncertain mechanism</td>
<td>• Oestrogen&lt;br&gt;• Pregnancy&lt;br&gt;• Some of the statins and tyrosine kinase inhibitors used to treat certain malignancies</td>
</tr>
<tr>
<td>Decreased dosage requirements</td>
<td>• Older than 65 years&lt;br&gt;• Androgen therapy in women</td>
</tr>
<tr>
<td>Decrease in TSH without an effect on T₄ and T₃</td>
<td>• Metformin</td>
</tr>
</tbody>
</table>

Table II describes several factors that may influence therapy with levothyroxine.¹⁰,¹¹

Autoimmune gastritis is a potential cause that needs to be considered when thyroxine replacement doses exceed the theoretical requirements in patients treated for autoimmune thyroiditis.¹³

In South Africa, levothyroxine is available as tablets of different strengths. Some of these are also scored, and dose titration increments of 12.5 mcg are possible. Soft gel and liquid formulations are designed to improve bioavailability, but in a recent trial, the evidence for using these formulations was weak, and further studies are needed.¹⁴

Liothyronine

Daily production of T₃ by the thyroid gland is inadequate for the demands of the body. Approximately 80% of the produced T₄ is disposed of by the peripheral conversion of T₄ to T₃ by deiodination.¹²,¹₅,¹₆ Of both the active thyroid hormones, T₃ is the more active due to a 10-fold greater affinity of the cell nucleus for T₃.¹²,¹₅

Liothyronine sodium is a salt of T₃ and is available as a tablet in South Africa. In contrast to levothyroxine, this salt is absorbed almost completely after oral ingestion. The shorter t₁/₂ of 18–24 h of this compound makes it necessary to administer liothyronine sodium more than once a day and treatment with this compound may cause transient elevations of the serum T₃ above the normal range.⁵,¹¹

Treatment of hypothyroidism

Levothyroxine monotherapy

Monotherapy with levothyroxine is the preferred form of treatment for hypothyroidism and is recommended in various published meta-analyses as well as national and international guidelines.²⁻⁴,¹⁷⁻²¹

Levothyroxine/Liothyronine combination therapy

Combination therapy is a controversial topic. Although the majority of studies are in favour of levothyroxine monotherapy,⁴,¹⁸ a subpopulation of approximately 10–15% of optimally treated patients with residual symptoms of hypothyroidism is recognised.¹²⁻²¹ The various explanations for these residual symptoms are as follows:

• The basal metabolic rate in patients treated with levothyroxine is approximately 10% slower than that of normal controls despite TSH levels in the normal range. This might be the result of lower free T₃ levels causing relative tissue hypothyroidism.²⁶,²⁷
• The peripheral conversion capacity of T₄ to T₃ is a heterogenous process, with 20% of patients on levothyroxine that do not achieve adequate free T₃ concentrations while they are in the normal reference range for TSH.²¹,²₈
• In rats, it has been shown that the T₄ to T₃ conversion process is inhibited by T₄. The inhibition is more pronounced in the peripheral tissues and less pronounced in the hypothalamus. The preservation of T₃ production in the hypothalamus may be responsible for normal suppression of TSH in contrast to the low T₃ and increased T₄:T₃ ratio in the peripheral tissues.²⁹
• Failure of randomised controlled trials to prove superiority of levothyroxine/liothyronine combination therapy may be a result of the inadequate design of these trials.³⁰

Residual hypothyroidism symptoms should not immediately be attributed to inadequate thyroid hormone treatment and other potential causes (such as endocrine disorders, autoimmune disorders, haematological conditions, end-organ damage, nutritional deficiencies, metabolic syndromes, concomitant drugs or lifestyle) for these symptoms should be excluded.²¹,²₅,³¹

Suggested candidates for treatment with combined levothyroxine/liothyronine therapy are (i) patients with persistent hypothyroidism symptoms after thyroidectomy or ablative therapy with radioiodine.²⁻¹⁰,³¹ despite optimal levothyroxine therapy and (ii) patients on optimal levothyroxine treatment that experience persisting symptoms and who have a serum T₃ level at or below the lower limit of the T₃ reference range.³

Levothyroxine/liothyronine combination therapy is not recommended either in pregnant women or in patients with cardiac dysrhythmias, and should be stopped if patients do not experience an improvement in their symptoms after three months of treatment.¹²⁻¹⁰,³¹
Initiation of therapy

Levothyroxine monotherapy

The levothyroxine monotherapy replacement dose varies in patients with different aetiologies of hypothyroidism and is dependent on the residual functionality of the thyroid tissue. In post thyroidectomy patients without any residual thyroid tissue functionality, a full replacement dose can be calculated based on BMI rather than weight-based dosing, due to a tendency to overdose overweight and underdose normal weight patients. The mean euthyroid dose stratified according to BMI is given in Table III.

The average full replacement dose is 1.6 mcg/kg/day and may be prescribed for patients under the age of 65 years without a history of ischaemic heart disease. On this dose, it takes about four weeks for the free T₄ (FT₄) concentration to normalise. Where there is still residual thyroid function, in older patients or if there is a history of ischaemic heart disease, a lower dose of 25–50 mcg per day should be initiated and adjusted over time. Although the FT₄ normalises faster when the full replacement dose is given, there is no difference in the time it takes for symptoms and quality of life to improve when a full replacement approach is compared to a low starting dose adjusted over time.

Levothyroxine/liothyronine combination therapy

The ultimate goal of combination therapy is to improve the residual hypothyroidism symptoms in patients with a normal TSH. Liothyronine is three to four times more potent than levothyroxine which means that 12.5 mcg liothyronine plus 50 mcg levothyroxine is equal to 100 mcg thyroxine. The secretion ratio of T₃/T₄ with an average of 16:1 (13:1–20:1), and the potency of liothyronine must be taken into account when the dose of the different components of the combination therapy is calculated. The calculation of the components are as follows:

- To calculate T₃: Daily dose of T₄ that normalises TSH divided by 17 (to approach the physiological T₃/T₄ ratio of 16:1).
- To calculate T₄: Subtract 3xT₃ from T₄ (daily dose).
- In South Africa, it is almost impossible to prescribe the physiologically correct dose of liothyronine since the only liothyronine preparation currently available is Tertroxin 20 mcg tablets. These tablets are scored so that a minimum dose of 10 mcg can be given, which is still too much in most patients.

One can also use Table IV to convert levothyroxine monotherapy to levothyroxine/liothyronine combination therapy.

<table>
<thead>
<tr>
<th>Table III: Mean euthyroid dose stratified according to BMI</th>
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<tbody>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>≤ 24.99</td>
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<tr>
<td>25.00–29.99</td>
</tr>
<tr>
<td>30.00–34.99</td>
</tr>
<tr>
<td>≥ 35.00</td>
</tr>
</tbody>
</table>

Appropriate administration of thyroid replacement medication

Absorption of levothyroxine is affected by many factors, as mentioned earlier, and it has been shown that non-fasting regimens are associated with an increase in both the level and variability of TSH. An interesting study that evaluated the optimal timing of administration of levothyroxine found that there was no difference in the absorption between morning, noon and bedtime administration of levothyroxine. From the above, we can deduct that taking levothyroxine in the fasting state is more important than the time of day that it is taken. To prevent impaired absorption due to food, the levothyroxine must be taken 60 minutes before breakfast in the fasting state and at least 3 hours after supper when taken at bedtime.

No specific administration regimen has been suggested for liothyronine.

Monitoring and adjustment of therapy

Levothyroxine monotherapy

After initiation of levothyroxine therapy, patients can expect an improvement in their symptoms within two weeks. However, in severe cases, recovery can take months. The TSH level is used as a parameter to adjust levothyroxine therapy. It is recommended that the TSH is collected before the morning levothyroxine is taken. The TSH level must be measured every six weeks and the levothyroxine adjusted accordingly. Depending on the TSH value, the levothyroxine is adjusted in increments of 12.5–25 mcg. Downward adjustment is necessary for a low TSH and an increase in dose is required for an elevated TSH level. After optimal replacement with levothyroxine is achieved, the TSH level should be measured every 6–12 months.

The goal in secondary hypothyroidism is to maintain the FT₄ in the upper half of the reference range. However, in older patients or patients with comorbidities at risk of treatment complications, a lower FT₄ value can be accepted. The FT₄ should, like the TSH, be measured every 4–8 weeks until an optimal dose of levothyroxine is reached. Thereafter, the FT₄ should be measured every 6–12 months to monitor therapy.

Levothyroxine/liothyronine combination therapy

Monitoring of combination therapy should be done by measuring TSH, FT₄ and free T₃ (FT₃), and calculating the FT₄/FT₃ ratio on serum collected before the morning dose.
The aim is to achieve normal values for all the markers. If adjustment of therapy is necessary, it is suggested that only one of the components be adjusted, preferably liothyronine. An alternative approach is to measure only the TSH and FT₄ since FT₃ values fluctuate too much during the day and is actually a reflection of the interval since the last dose of liothyronine. The markers should be repeated every six weeks until the patient is euthyroid, after which it must be followed up every 6–12 months.

**Special patient groups**

**The elderly**

TSH levels, as well as thyroid antibodies, increase as people age. Owing to the increase in the TSH concentration, elderly patients can still be euthyroid with a TSH value above the upper limit of normal. The presence of anti-thyroid antibodies does not predict development of thyroid disease in the elderly.

Older people (> 65 years) are more susceptible to the adverse effects of thyroid hormone overreplacement, and treatment with levothyroxine should be initiated with low dosages and gradually titrated upwards, bearing in mind that a slightly elevated TSH might be appropriate.

**Coronary heart disease**

Although thyroid hormone replacement therapy has a positive inotropic and chronotropic level on the myocardium and can lead to angina in patients with severe ischaemic heart disease, symptoms may actually improve or, in asymptomatic patients, initially not appear when treatment is initiated. Owing to the risk of angina in this patient group, it is recommended that patients should be started on low doses of levothyroxine followed by a gradual increase in dose. The use of β-adrenergic blocking drugs make optimal treatment possible in most patients.

**Pregnancy**

The fetal thyroid gland only starts contributing to the thyroid hormone requirements of the fetus during the second half of gestation and the fetus is therefore dependent on the mother’s thyroid hormones for normal neurological development. Hypothyroidism in pregnant women, even when mild and still asymptomatic, can adversely affect their children’s neuropsychological development. Elevated TSH levels during pregnancy can also lead to the following adverse obstetric outcomes:

- Increased caesarean section rate in both overt and subclinical hypothyroidism.
- Increased rate of fetal death.
- Increased rate of spontaneous pregnancy loss.
- Increased risk of placental abruption and preterm delivery.

Subclinical and overt hypothyroidism should be managed on an urgent basis and replacement therapy in overt hypothyroidism should be managed by initiating full replacement therapy.

The following is a general guide to levothyroxine dosing:

- TSH: > 4 mIU/L with a low T₄: approximately 1.6 mcg/kg/day
- TSH: > 4 mIU/L with a normal T₄: approximately 1.0 mcg/kg/day
- TSH: 2.6–4 mIU/L low dose initiation

Levothyroxine requirements during pregnancy increases by approximately 30–50%.

**Goals of levothyroxine replacement during pregnancy are:**

- TSH less than 2.5 mIU/L prior to conception; however, some experts prefer a preconception TSH of < 1.2 mIU/L.
- TSH of less than 2.5 mIU/L or in the lower half of the trimester-specific reference range during the pregnancy.

The TSH should be measured every 4–6 weeks and the levothyroxine adjusted accordingly.

**Oestrogen therapy**

Oestrogen therapy may increase the need for levothyroxine in thyroid hormone replacement patients and the TSH concentration should be measured 6–12 weeks after initiation of oestrogen therapy. Dosage adjustments may also be required in young women on thyroid replacement therapy when an oral contraceptive is prescribed.

**Surgical patients**

Post-surgical patients that are unable to eat for a few days should receive replacement therapy via the parenteral route.

**Conclusion**

The spectrum of hypothyroidism consists of subclinical hypothyroidism, primary hypothyroidism and secondary hypothyroidism. It is important to diagnose and adequately treat this biochemical abnormality since it is associated with an increased risk for the development of ischaemic heart disease and other conditions. Subclinical hypothyroidism does not always need to be treated, but primary and secondary hypothyroidism should be managed with thyroid hormone replacement therapy. Levothyroxine is the mainstay of treatment but combination therapy with levothyroxine/liothyronine is indicated in a small percentage of patients. Combination therapy is still controversial and should be reserved for patients where other causes of persistent hypothyroidism symptoms have been excluded. Combination therapy should be stopped if symptoms are still present after three months of optimal therapy. The dose of the initiation of therapy will depend on the residual amount of functioning thyroid tissue. A full replacement dose is given after surgical removal of the thyroid gland but patients with residual thyroid function are started on lower dosages and titrated upwards until euthyroid. In elderly patients and patients with ischaemic heart disease, low-dose replacement therapy is initiated due to the risk of adverse effects of overreplacement of thyroid hormones. Pregnant women and women planning on falling pregnant should be carefully monitored and optimally supplemented to avoid the fetal and obstetric complications associated with hypothyroidism.