Chapter 64

Hypothyroidism: Treatment Issues

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INTRODUCTION

The thyroid gland, which is situated in the neck, produces two important hormones: thyroxine (T4) and triiodothyronine (T3). The predominant thyroid hormone secreted by the gland is T4; only a small amount of T3 is produced by the thyroid gland. In the peripheral tissues, T3 is the active form of hormone. All the circulating T4 needs to be converted into T3 for its action in peripheral tissues. Deficiency of thyroid hormones is called hypothyroidism, and this can affect the function of virtually every system in the body.

Thyroid hormone production by the thyroid gland is controlled by thyroid-stimulating hormone (TSH) produced from the pituitary gland, which in turn is controlled by TSH-releasing hormone (TRH) production by the hypothalamus. A small amount of T3 and a large amount of T4 are directly secreted by the thyroid gland into the bloodstream; in the blood T4 is more protein bound than T3. Thyroxine-binding globulin (TBG) is the major hormone binding to thyroid hormones and albumin is a minor binder. In the peripheral tissues, T4 is deiodinated to form T3 by enzymes called deiodinases.

ETIOLOGY OF HYPOTHYROIDISM

Hypothyroidism can be classified into primary, secondary and tertiary forms. Primary hypothyroidism is due to abnormalities intrinsic to the thyroid gland, while secondary hypothyroidism is due to pituitary disease which impairs TSH production and tertiary hypothyroidism is due to hypothalamic, i.e. TRH deficiencies. Thyroid-stimulating hormone is the major hormone stimulating thyroid hormone production, and whenever the thyroid gland fails, the production of thyroid hormone becomes suboptimal. Due to the positive feedback from low thyroid hormone level, the TSH concentration rises and this characterizes primary hypothyroidism. Sometimes the rise in TSH can stimulate the thyroid gland to keep thyroxine in the normal range, a condition called subclinical hypothyroidism. But when the thyroid gland fails completely and the high TSH is unable to keep thyroid hormone level in the normal range, overt primary hypothyroidism occurs. In certain situations, like in pituitary damage, the secretion of TSH becomes low, and this TSH hyposecretion leads to secondary failure of the thyroid gland. This is called secondary hypothyroidism. Thyroid-stimulating hormone deficiency can be due to pituitary disease or hypothalamic disease due to a low TRH production. In practice, it is not important to distinguish between secondary and tertiary hypothyroidism, as the management rarely differs. Table 1 lists the various causes of hypothyroidism.

<table>
<thead>
<tr>
<th>Primary Hypothyroidism</th>
<th>Secondary Hypothyroidism</th>
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<tbody>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Hypothalamo-pituitary lesions</td>
</tr>
<tr>
<td>Postpartum thyroiditis</td>
<td>Tumors</td>
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<tr>
<td>Iodine deficiency</td>
<td>Radiation</td>
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<tr>
<td>Post-thyroidectomy</td>
<td>Surgery</td>
</tr>
<tr>
<td>I-131 therapy</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Drugs: e.g. lithium</td>
<td>Trauma</td>
</tr>
<tr>
<td>Rare causes</td>
<td>Transient central hypothyroidism</td>
</tr>
<tr>
<td>Viral thyroiditis</td>
<td>Recovery from primary thyrotoxicosis</td>
</tr>
<tr>
<td>Rare infections</td>
<td>Withdrawal of thyroid hormone therapy</td>
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<tr>
<td>Tuberculosis</td>
<td>Resolving Thyroiditis</td>
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<td>P. Carinii</td>
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CHRONIC AUTOIMMUNE THYROIDITIS OR HASHIMOTO’S THYROIDITIS

In the classic form of the disease described by Hashimoto, the thyroid gland is enlarged due to lymphocytic infiltration. The gland is described as being “rubbery”. Hypothyroidism is due to autoimmune damage to the thyrocytes. Typically, there is an elevated titer of antibodies to thyroid antigen; among them, the most striking increase is seen in the levels of antibodies to thyroperoxidase (TPO) or anti-TPO antibodies as they are called. However, in many cases of chronic autoimmune thyroiditis, the gland is not enlarged. This is termed as atrophic thyroiditis and is due to extensive fibrosis of the gland; it is believed to be an end-stage of chronic autoimmune thyroiditis. In a small proportion of subjects, antibodies that block the TSH receptor also lead to hypothyroidism.

CLINICAL FEATURES OF HYPOTHYROIDISM

In severe cases of hypothyroidism, the diagnosis is readily apparent to the clinician. The patient often complains of weight gain, and facial puffiness. There is also a history of intolerance to cold weather, and constipation. There is weight gain despite a relative lack of appetite. The skin becomes dry, and hair loss occurs. The patient is slow in thought, speech and action. In women, menorrhagia is the most common menstrual irregularity, but almost any type of menstrual disturbance is seen with hypothyroidism. The voice is coarse and thick. Often, there is a history of excessive snoring and daytime somnolence. On examination, a rubbery goiter may be present in many cases of thyroiditis, but goiter is absent in atrophic thyroiditis. Classically, the ankle jerks relax slowly after contraction. Sometimes,
hearing disturbances may be an associated clinical feature; this may be due to either sensorineural deafness or conductive deafness due to thickening of the ear drum/middle ear effusions. Cardiomegaly and pericardial effusions are occasional findings.

In children and adolescents, presentation may be more atypical. Children may present with growth failure, declining academic performance, delayed dentition, pubertal delay, menstrual irregularities, or even rarely, precocious puberty. The presentation is more complex in neonates, and any newborn/infant with the following features must undergo thyroid function testing: hoarse cry, prolonged jaundice, mottled skin, umbilical hernia, constipation, poor feeding and failure to achieve milestones. In contrast to primary hypothyroidism, subjects with secondary hypothyroidism behave a little differently. Features of fluid retention are less striking, and weight gain is not prominent. The skin appears pale.

LABORATORY INVESTIGATIONS

The diagnosis of primary hypothyroidism is confirmed by measuring the T4 and TSH levels (Table 2). Hypothyroidism is characterized by a low T4 and a high TSH level. When the TSH is high, but the T4 is normal, this condition is described as subclinical hypothyroidism. Most of the subjects with subclinical hypothyroidism will go on to develop complete or overt thyroid failure. Triiodothyronine is not routinely measured in the diagnosis of hypothyroidism. This is because, in milder forms of hypothyroidism, the increased TSH stimulates the selective production of T3 and this may result in a high normal T3. However, in severe varieties of hypothyroidism, the T3 is also low. Free hormone estimations (which estimate the concentration of thyroid hormones that are not bound to circulating proteins) are advantageous as they measure the metabolically active component, and also because they are not affected by conditions which increase or decrease the levels of thyroid-hormone binding proteins. The diagnosis of chronic autoimmune thyroiditis is essentially clinical, but is supported by the following findings: high levels of anti-TPO antibodies or a fine-needle aspiration study of the enlarged gland showing features of lymphocytic thyroiditis.

Diagnosis of Neonatal Hypothyroidism

Ideally, serum TSH and T4 are estimated from an eluate of whole blood collected on filter paper by a heel prick between 4th day and 6th day of life. Before the 4th day, TSH and T4 levels are physiologically elevated. If only one test is feasible, then TSH-based screening is superior, because, though T4 estimations have also been used for screening, about 20–90% hypothyroid subjects may have T4 in the low-normal range, and if the cut-off for T4 is raised, then this would result in more subjects being recalled for subsequent TSH testing. Triiodothyronine estimations are usually normal, and should not be used for screening. If the screening blood TSH is more than 40 mU/L then immediate treatment is required after collecting samples for confirmation. If TSH is 20–39 mU/L then the child is called for periodic retesting, but treatment is not indicated unless rising levels are documented, because the overwhelming majority of these children have normal thyroid function when tested many weeks later. Usually, isolated rise in TSH levels subside over 3–9 months.

### TABLE 2 Interpreting thyroid function test results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subclinical (Primary) Hypothyroidism</th>
<th>Overt Primary Hypothyroidism</th>
<th>Secondary Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>TSH</td>
<td>High</td>
<td>High</td>
<td>Low/Normal</td>
</tr>
</tbody>
</table>

Chapter 64 Hypothyroidism: Treatment Issues

Thyroid hormone actions are very important, and even the correction of mild-thyroid dysfunction can have a positive impact on health. In many cases, hypothyroidism is suspected early, but sometimes it is diagnosed only when obvious symptoms and signs occur, e.g., goiter, weight gain, cold intolerance, or constipation. The treatment of choice is levothyroxine (LT4), which is one of the most widely prescribed drugs.

The dose of LT4 depends upon the age, and also the body weight. The desirable initiating dose in healthy adults is 1.7 µg/kg/day. For the elderly or in subjects with heart disease, one should start with 12.5–25 µg/day and increase the dose by 12.5 µg every 6 weeks. In the elderly, the final dose required may be less than 1 µg/kg/day.

Thyroxine has a narrow therapeutic range. In other words, even a small change in T4 levels can have significant effects. Therefore, even small changes in LT4 can cause changes in the clinical well-being, and also result in large changes in TSH levels; TSH is the preferred test for monitoring. Thyroid-stimulating hormone normalization may take about 8–12 weeks. Levothyroxine has a half-life of 7 days, which means that the T4 levels too could normalize by about 6 weeks. Thyroid-stimulating hormone is the most sensitive indicator of T4 effect, as TSH level rises significantly in response to a minor decline in T4 which stimulate the TSH-producing cells in the pituitary. While interpreting thyroid function tests, it is important to remember that several non-thyroidal illnesses and drugs can alter free and total hormone levels. Several drugs can interfere with LT4 absorption. This includes cholestyramine, ferrous sulfate, sucralfate and aluminum hydroxide. Other agents like the antitubercular drug rifampicin and anticonvulsants can accelerate the metabolism of L-thyroxine; hence dose adjustments may be needed in these situations. In practice, frequent retesting is important, because monitoring can also prevent overtreatment with LT4, which is associated with bone loss, atrial fibrillation and thyrotoxicosis.

The required dose of LT4 might also depend upon the etiology of hypothyroidism. Subjects with chronic thyroiditis or total thyroidectomy may need higher L-thyroxine doses as compared to subjects with Graves’ disease who have undergone iodine (I-131) therapy or surgery; in the latter situation, some residual functional thyroid tissue might be present. It has been argued that T4 alone replacement is unphysiological, as both T4 and T3 are thyroid hormones. Moreover, T3 is the more active hormone, and so, it has been argued that both T4 and T3 need to be replaced. To address the controversy issue of “perfect” thyroid hormone replacement, a recent study compared the use of a combination of T3 and LT4 (i.e. T3 + T4) versus isolated LT4 therapy; the results show no definite advantage of the combination therapy. In fact this study showed that such treatment increases the risk of subclinical hypothyroidism due to fluctuations in the steady state free T3 serum concentrations. Both T4 and T3 preparations are commonly available, and in the body, T4 needs to be converted into T3 for tissue action. The issue of combination therapy is still controversial, and for the present, LT4 alone is the treatment of choice.

For neonatal hypothyroidism, therapy is begun at a high dose of 50 µg/day (10–15 µg/kg/day) for replenishing diminished reserves, and after a week, is reduced to 37.5 µg/day. After 6 months, the daily dose is decreased to 6–8 µg/kg and later, 5 µg/kg between 1 year and 12 years. Testing should be performed weekly for a month, followed by monthly for 6 months, then every 3 months up to 2 years of age, and annually thereafter. Thyroxine is best given once daily to the neonate; the tablets crushed in breast milk and fed 30 minutes prior to feeds. If a dose is missed, then it is better to take another dose the next day rather than skip the tablet altogether. Thyroxine levels reach 10 µg/dL in about 2 weeks, but TSH usually normalizes only by 4 weeks of therapy.
Endocrinology

Treatment considerations in secondary hypothyroidism are the same, but if associated cortisol deficiency is suspected, then LT4 therapy must be instituted only after achieving a eucortisolemic state. Similar considerations are important in cases of suspected polyglandular autoimmune disease, where hypoadrenalinism and hypothyroidism can coexist.

Myxedema Coma

This is a life-threatening complication of hypothyroidism, and refers to severe coma following severe, untreated thyroid failure. Precipitating factors include: cold exposure, general anesthesia, infections, or stress. Clinical features, in addition to classic hypothyroid features, are hypventilation, bradycardia, hyperthermia and carbon dioxide narcosis. The treatment is to replace T3 or T4 or a combination intravenously. Where intravenous preparations are not commonly available, as in most of India at the time of writing the chapter, LT4 is given at a bolus dose of 600 µg orally or through the Ryle’s tube, followed by 100–200 µg/day. Steroid therapy with intravenous hydrocortisone too is desirable, as it can cover for a sudden increased metabolic demand incurred by the starting of thyroxine therapy, and also cover for any coexisting adrenal insufficiency. Usually, positive pressure ventilation is required and broad-spectrum antibiotic therapy based on cultures is also needed. Mortality however remains high, at about 50%. Therefore the condition must be suspected and treated early on.

Subclinical Hypothyroidism

When the free thyroxine (FT4) is normal and the TSH is high, this state is termed subclinical hypothyroidism. As a rule, there must be no history of thyroid dysfunction or therapy. Clinical evidence of thyroid dysfunction is often scant or lacking. In this situation, if the TSH is more than 10 mU/L, thyroxine therapy is indicated. In cases where the TSH is above normal (usually this means above 5 mU/L) but below 10 mU/L, a variety of criteria indicate the need to therapy (Table 3). The evidence in favor of treating these disorders with thyroxine is not very well established, but available literature suggests that at least a trial of therapy is warranted. There are three principal reasons for starting therapy in subclinical hypothyroidism: firstly, to avert the symptoms of eventual thyroid failure. Secondly, to reverse the effects of mild thyroid deficiency on many organ systems and relieve subtle signs and symptoms caused by T4 deficiency, thus improving the patient’s quality of life; this is controversial. Finally, as in Table 3, therapy is indicated in specific scenarios. The dose required for treating subclinical hypothyroidism may be only about 50–75 µg/day.

Table 3 | Subclinical hypothyroidism: indications for therapy

- Positive anti-thyroid antibodies
- Goiter
- Dyslipidemia
- Depression
- Infertility
- Pregnancy
- Obesity
- Carpal tunnel syndrome
- Unexplained hyponatremia
- Menstrual irregularities
- Short stature

Pregnancy, Fertility and Hypothyroidism

In general, there is an increased need for thyroid hormones during pregnancy. Also, patients with a previous history of unexplained infertility or frequent miscarriages must have a sensitive TSH measurement before and during pregnancy. In pregnancy, the preferred initiating dose did not alter. During pregnancy, the follow-up is to be more intensive, i.e. every 4–6 weeks, to keep FT4 within normal limits. In pregnancy, given the increase in TBG, it is better to monitor with FT4, rather than total T4 levels. Due to increased demand, dosage of LT4 may need to be increased by about 30–50% during pregnancy, in order to keep the FT4 within normal limits. There is now accumulating evidence to suggest that universal screening should be done to detect hypothyroidism before pregnancy. For the present the following three groups should be screened prior to pregnancy: (1) women more than 35 years, (2) those with a family history of thyroid disorders or (3) those with coexisting autoimmune disorders. After delivery, the prepregnancy dose can be resumed.

Hypothyroidism, Dyslipidemia and Cardiovascular Risk

More than 90% of subjects with primary hypothyroidism have increased levels of cholesterol and/or triglycerides. On the other hand, about 13% of all subjects with lipid abnormalities have thyroid disease. The degree of dyslipidemia has generally correlated well with the severity of thyroid failure. Dyslipidemias should be screened for hypothyroidism. Subclinical or overt hypothyroidism if associated with dyslipidemia warrants LT4 therapy. In addition to lipid modulation, both subclinical and overt hypothyroidism can reduce cardiac function. Both changes in systolic time (ST) intervals as well as ST-T changes have been reported: these cardiac alterations are reversible with LT4 therapy. Lipid abnormalities in subclinical hypothyroidism are reversible with LT4 therapy; treatment even improves carotid intima-media thickness, a marker of atherogenic risk.

BIBLIOGRAPHY