Management of Hypothyroidism in Adults

Nikhil Tandon

Screening for Hypothyroidism

Routine screening for hypothyroidism in asymptomatic persons

A few expert panels have suggested that screening may be beneficial in high-risk patients such as in elderly women. Widespread screening is unlikely to be cost-effective and given the non-specific symptoms of hypothyroidism, many patients will nevertheless be tested. However, asymptomatic screening should not be confused with this practice.

Screening is recommended for the following high risk groups:

- All newborn infants (mandatory in many states)
- Downs syndrome
- Pregnant women with or without goiter
- Have a strong family history of thyroid disease
- A personal history of thyroid dysfunction
- Have an autoimmune disease, such as Type 1 Diabetes
- Are taking lithium
- Have Depression
- Have elevated lipid levels
- Are found to have a thyroid nodule

The American Thyroid Association (ATA) recommends routine screening at 35 years of age and subsequently after every 5 years. The recommendations of other professional bodies such as The American Association of Clinical Endocrinologist (AACE), American Academy of Family Physicians (AAFP), and The American College of Physician (ACP) vary with each other and with those of ATA. Patients in the high-risk category are:

- Those aged over 60.
- Those with a history of thyroid disease, thyroid surgery or radiation to the neck
- Those with a history of heart disease, particularly with atrial fibrillation
- Those with other autoimmune diseases.  

Management of Hypothyroidism

Management of adult hypothyroidism requires therapy

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Thyroxine treatment</th>
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<tr>
<td>Healthy adult patients with hypothyroidism</td>
<td>require thyroid hormone replacement in a dosage of 1.7 μg per kg per day</td>
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<tr>
<td>Elderly</td>
<td>1μg per kg per day may require up to 4μg per kg per day</td>
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<tr>
<td>Children</td>
<td>Levothyroxine therapy should be started at a dosage of 0.075 mg per day and should be titrated against increasing serum TSH levels with small gradual increments.</td>
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<tr>
<td>In young patients without risk factors for cardiovascular disease</td>
<td>Thyroid hormone replacement therapy should be started at a dosage of 0.025 mg per day, which should be gradually increased by 0.025 to 0.050 mg every four to six weeks until TSH levels are normalized.</td>
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<td>In patients at risk for the cardiovascular compromise</td>
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Thyroxine supplementation therapy is recommended to be administered as a single daily dose, half-an-hour to one hour prior to breakfast (Table 1). A minimum gap of 4 hours should be maintained between administration of thyroxine and drugs that are known to interfere with its absorption.

The rapidity with which normal thyroid hormone levels should be restored is dictated by several factors, notably, the age of patient, the duration and severity of the hypothyroidism, and the presence or absence of other co-morbid conditions, specifically cardiac disease. In healthy young adults, the complete replacement dose of 1.6 to 1.8μg levothyroxine/kg ideal body weight can be started immediately. The etiology of hypothyroidism may also influence the replacement dose, such that patients with total thyroidectomy or severe primary hypothyroidism have slightly higher requirements than do patients who become hypothyroid after radioiodine or surgical treatment for Graves’ disease, who may retain some residual thyroid function. In the absence of any functioning thyroid tissue, the complete daily replacement dose in women and men ranges from 100 and 150μg and between 125 and 200μg respectively. Full replacement doses should not be administered initially to patients over the age of 60, to patients who have a history of coronary artery disease, or to patients with long-standing severe hypothyroidism. This cautious approach is advisable to prevent precipitation of angina in people with underlying coronary heart disease or agitation and anxiety which can occasionally occur in patients with long-standing severe hypothyroidism exposed to the complete replacement dose. In such patients, the dose should be titrated, starting with 25μg a day and increased by increments of 25μg at 8-week-intervals until serum TSH falls to normal. If however, angina is precipitated while increasing thyroxine dose, the dose should be reduced to the highest dose tolerated by the patient, and a further attempt made to increase the dose again only after another 4 weeks.

After initiating therapy, the dose should be monitored by assessing serum TSH (with or without serum T4) after at least 2 months, the minimum time required for the pituitary-thyroid

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Professor, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi
loss, the other features which improve are appetite, constipation, usually minimal and late in the course of response. After weight mobilization of fluid. Weight loss consequent to decrease in fat is replacement is usually diuresis and weight loss, due to

<table>
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<th>Is there a need for documenting thyroid hormone replacement?</th>
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<tr>
<td>Yes: Start levothyroxine, 0.025 to 0.05 mg per day.</td>
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<tr>
<td>No: Start levothyroxine 0.075 mg per day</td>
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TSH level (if primary hypothyroidism) or free T4 level (if secondary hypothyroidism) to be monitored every 6 to 8 weeks; adjust dosage of levothyroxine until laboratory tests are normal.

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<th>Does the patient still have lethargy or memory problems?</th>
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<tr>
<td>Yes: Consider adding triiodothyronine, 0.0125 mg per day (although long-term effects are not known).</td>
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<tr>
<td>No: Continue to monitor TSH or T4 levels annually</td>
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axis to re-set after introducing therapy or making a dose adjustment (Table 2). If the serum TSH is within the normal range, ideally keeping a serum TSH target of approximately 2-3 mIU/L, the same dose of thyroxine can be continued. In the event that the serum TSH is either elevated or suppressed, there will be need for a modest increase or decrease in dose respectively. The dose should ideally not be increased or decreased by more than 12.5 or 25μg, and serum TSH again measured after two months to assess adequacy of the dose.

Once the patient attains a biochemical euthyroid state, serum TSH should next be measured after 6 months. This is required because at initiation of therapy, due to the hypothyroid state, the administered thyroxine may be still be metabolized slowly and appear adequate for the patient’s requirements. Once euthyroidism is restored, thyroxine metabolism may increase and the same dose be rendered sub-optimal. Once a stable thyroxine dose is achieved, monitoring needs to be carried out on an annual basis. While this strategy works for most patients with hypothyroidism, patients with post-ablative hypothyroidism may continue to have a decline in thyroid reserve over the years, necessitating semi-annual or even annual dose changes till the effect of the radio-iodine plateaus. Sometimes a similar evolution of declining thyroid reserve over a period of time may also be observed in patients with Graves’ disease who have had a sub-total thyroidectomy.

Some experts also estimate serum T4 (total or free) to monitor therapy. If this is being done, care should be taken that the blood sample should be collected prior to receiving the day’s dose of thyroxine. Invariably if the serum TSH levels are in the mid to low normal range, serum T4 levels will be in the mid to high normal range. For obvious reasons, the main role of serum T4 is when monitoring thyroxine replacement in a patient with central hypothyroidism.

Clinical response: The earliest clinical response to thyroxine replacement is usually diuresis and weight loss, due to mobilization of fluid. Weight loss consequent to decrease in fat is usually minimal and late in the course of response. After weight loss, the other features which improve are appetite, constipation, hoarseness of voice, and much later the cold intolerance and fatigue.

Treatment failures: The commonest cause for an inadequate response is poor compliance, which is not unusual with any chronic therapy. Most patients when questioned appropriately will accept the missing of doses. If the index of suspicion for non-compliance is high, it sometimes helps to confront the patient with the question – “How many doses did you miss last month – half or one-third or one-fourth?” than to ask “Did you miss any dose in the last month?” The following observations are clues for non-compliance: unexpectedly high thyroxine requirement, normal free T4 with elevated TSH, erratic and inexplicable serial thyroid function test readings. It sometimes helps to ask the patient to take a week’s supply of medicine in a separate pill-box, which will allow easy ascertainment of missed doses. Any extra pills left in the container can actually be taken on the last day of the week, to ensure that the patient receives his or her weekly dose. Weekly dosing or end of week catch up dosing while sub-optimal remains an acceptable alternative in patients who have been seen to be habitual non-compliers. If despite these measures TSH levels do not reach the target value, co-existing conditions or treatment which may interfere with either thyroxine absorption or metabolism should be checked.

Special situations

Pregnancy: A special situation which needs discussion in detail is the thyroxine replacement in pregnancy, which is probably related maximally to the increase in serum TBG. Patients on thyroxine replacement should report to their physician the moment pregnancy is confirmed, to allow a bi-monthly monitoring of TSH levels, and appropriate dose adjustments. The mean increment in the required daily thyroxine dose is 50µg; which is usually apparent by the end of the first trimester, though may be delayed to as late as the 6th month of gestation in some women. A similar up-titration of thyroxine dose may be required in women who are on estrogen preparations including the oral contraceptive pill.

Hypocortisolemia: In the event there is co-existence of thyroid hormone deficiency and glucocorticoid deficiency it is important to replace glucocorticoid before starting thyroxine. This is so because thyroxine therapy may lead to an increased metabolism, and thereby an increased demand, of cortisol, potentially increasing the likelihood of precipitating an adrenal crisis.

Central hypothyroidism: This should be dealt with similar to the patient with co-existent hypocortisolemia, in that the glucocorticoid replacement should be initiated prior to thyroxine replacement. Monitoring of therapy should be done with serum T4 levels instead of serum TSH levels, for which the sample should be collected prior to ingesting the morning dose of thyroxine.

Ischemic heart disease: As discussed above, while thyroxine therapy improves myocardial function and reduces peripheral vascular resistance, it also increases the myocardial oxygen demand. This may precipitate angina, which has been reported in 2% of patients in large series of hypothyroid individuals being initiated on thyroxine replacement. Hence, patients with preexisting angina should ideally undergo a cardiac evaluation prior to initiating thyroxine therapy. As already detailed above, therapy in such individuals should be started at 25µg/day or even less and increased no faster than at 4 weekly intervals.

Patients unable to take oral thyroxine: If patients are unable to take oral thyroxine for prolonged periods of time, intravenous thyroxine can be given in a dose approximately 70% of the oral.
Tissue-level unresponsiveness to thyroid hormone is rare, and is caused by mutation in the gene that controls a receptor for T3, rendering it unable to bind with the hormone. Only 300 families have been identified with this genetic mutation.

Such patients have adequate levels of thyroid hormones that are ineffective, leading to persistent elevation of TSH and continuation of symptoms. For further evaluation and proper management, such patients should be referred to an endocrinologist.

Drugs that potentially alter thyroid hormone replacement requirements

- Increase replacement requirements

Drugs that reduce thyroid hormone production

- Lithium
- Iodine-containing medications
- Amiodarone

Drugs that reduce thyroid hormone absorption

- Sucralfate
- Ferrous sulfate
- Cholestyramine
- Colestipol
- Aluminium-containing antacids
- Calcium products

Drugs that increase metabolism of thyroxine

- Rifampin
- Phenobarbital
- Carbamazepine
- Warfarin
- Oral hypoglycaemic agents

Increase thyroxine availability and may decrease replacement requirements

Drugs that displace thyroid hormone from protein binding

- Furosemide
- Mefenamic acid
- Salicylates

Potential adverse effects of treatment: Regular monitoring of serum TSH levels to ensure mid-normal serum TSH values ensures that life-long replacement therapy with thyroxine is safe and free from adverse events. In the event that thyroxine is being given in suppressive doses, as used after carcinoma thyroid surgery, there are several potential adverse effects especially involving the skeletal and cardiovascular system. A TSH value of ≤ 0.1mU/L, has been identified as a risk factor for the development of atrial fibrillation, and is also associated with left ventricular hypertrophy and enhanced risk for ischemic heart disease. Sub-clinical thyrotoxicosis consequent to an inappropriately high dose of thyroxine, especially in post-ablated post-menopausal patients with Graves’ disease has been associated with bone loss.

Treatment of Myxedema Coma: Myxedema coma is a severe life-threatening situation which is more often reported in winter in the setting of sepsis, cerebrovascular accidents, congestive heart failure or inappropriate drug therapy e.g. overzealous diuretic use for hypertension and edema resulting in hyponatremia, sedatives, and anti-depressants. The common clinical manifestations, in addition to the peripheral features of severe hypothyroidism include respiratory depression, bradycardia, hypotension, decreased intestinal motility, hyponatremia, altered sensorium, infections and hypothermia. These are specifically listed here because they need individual attention to ensure recovery of a patient from myxedema coma. All patients must be admitted to the intensive care unit and ventilatory support initiated. Most patients need ventilatory support for at least 24-48 hours, and during this period frequent measurement of arterial blood gases is mandatory. The endotracheal tube should be retained till the patient is fully conscious. In case the patient is not intubated care of the upper airway should be performed with diligence. In case of hyponatremia, fluid restriction and judicious use of small volume of saline or dextrose saline is usually adequate if serum sodium is > 120mEq/L. If serum sodium falls < 120mEq/L, hypertonic saline followed by intravenous furosemide to promote water diuresis may be needed. Warmth should be ensured but this
Table 3: Conditions requiring adjustment of thyroxine for hypothyroidism.

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<tr>
<th>Conditions requiring adjustment of the replacement dose of thyroxine for hypothyroidism.</th>
<th>Proposed Interventions</th>
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<tbody>
<tr>
<td>Increased dose requirement</td>
<td>Change in dose till the malabsorption syndrome is rectified</td>
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<tr>
<td>Decreased intestinal absorption of T4</td>
<td>Treat primary condition</td>
</tr>
<tr>
<td>Malabsorption (e.g. celiac disease); short bowel syndrome</td>
<td>Alter time of high fiber supplement</td>
</tr>
<tr>
<td>Atrophic gastritis, infection with H pylori</td>
<td>Alter time of ingestion of iron, aluminium</td>
</tr>
<tr>
<td>Dietary fiber supplements; bran</td>
<td>Increase dose</td>
</tr>
<tr>
<td>Drugs: aluminium hydroxide (used as an antacid), ferrous sulfate, calcium carbonate, omeprazole (and other proton pump inhibitors)</td>
<td>Decrease dose</td>
</tr>
</tbody>
</table>

Increased need for T4

- Weight gain
- Pregnancy
- Increased clearance of T4
- Phenobarbital, phenytoin, carbamazepine, rifampicin, valproate, imatinib, sunitinib
- Unknown mechanism
- Amiodarone, sertraline, chloroquine
- Decreased dose requirement

Decreased need for T4

- Weight loss
- Androgens
- Decreased clearance of T4
- Old age

should be done cautiously or else the resultant peripheral vasodilatation may cause hypotension. Hypotension should be corrected by judicious administration of dextrose saline or if hypotremia is present then normal saline. Most physicians also prefer covering the first few days with intravenous hydrocortisone (50-100mg every 6 to 8 hours) to tackle the impaired adrenal reserve which may manifest when thyroxine therapy is initiated.

Thyroid hormone therapy in patients with myxedema coma: This is a matter of continuing debate especially with regards to use of T3, dose, rapidity of correction and route of administration. While advocates of T3 therapy refer to its shorter half life and faster onset of action, most centres use T4 therapy which has a longer half life, with a likelihood of smoother control. The preferred route of administration is intravenous, with different experts suggesting doses varying from 300-500µg as the initial loading dose, followed by 50-100µg given daily. The high initial bolus probably helps restore the extra-thyroidal pool of T4, and also allows for generating adequate T3 levels by peripheral conversion. If intravenous T3 is selected, its proponents give 10-20µg followed by 10µg every 6 hours for a day or two. Some centres combine parenteral T4 and T3 using the following regimen: 4 micrograms per kg T4 bolus, followed by 100 micrograms daily thereafter; and a concurrent 10µg bolus of T3 along with 10µg every 8-12 hours after that. Once the patient has an improved sensorium, has normal bowel activity and is accepting orally patient can be shifted back to oral thyroxine replacement.

However, in India, intravenous thyroxine is not readily available and most institutions give crushed thyroxine tablets through the nasogastric tube in place of parenteral therapy. The initial dose given is usually 300-500µg followed by 100µg daily thereafter. This route is suboptimal and not only are there concerns of erratic absorption, especially in patients with gastric atony, but also the increased risk of aspiration unless the airway is protected. The interventions mentioned above can only serve as guidelines because each patient manifests with their unique clinical problems which need individualized care (Table 3). However, all the facets mentioned above must be dealt with comprehensively to improve the prognosis.

Subclinical Hypothyroidism

While screening patients for thyroid disease, physicians often find increased thyrotropin-stimulating hormone (TSH) levels in patients whose free thyroxine (T4) levels are not below normal. Subclinical hypothyroidism, characterized by persistently elevated TSH levels and free thyroxine (T4) levels are not below normal, most commonly precedes overt hypothyroidism. In some patients, the condition may resolve on its own or remain unchanged. Rest of the patients proceed to develop overt hypothyroidism (low free T4 and raised TSH levels) within a few years. Patients with larger TSH elevations and detectable anti-thyroid antibody levels are at increased risk of developing overt disease. Patients with subclinical hypothyroidism may have mild hypothyroid symptoms and may have subtle serum lipoprotein and cardiac function abnormalities. Therefore, in patients with definite and persistent elevation of TSH, thyroid replacement therapy should be considered. Progression to overt hypothyroidism occurs at a rate of 5 to 20% per year in patients with both mildly elevated TSH levels and antithyroid antibodies. Clinical manifestations, if present, may be explained by assuming that a T4 level of 6 or 7µg/dl (77 to 90nmol/L), although not outside the normal range of 4.5 to 12.5µg per dl (58 to 160nmol/L), may represent a significant fall from an original level of 9 or 10µg/dl (116 to 129nmol/L) and, thus, is low for this particular patient. The preferred therapy for patients with subclinical hypothyroidism is levothyroxine at a dosage that maintains normal TSH levels.

Treatment of Subclinical Hypothyroidism

Patients with subclinical hypothyroidism, because of the minimal extent of the thyroid hormone deficiency, may be controlled with total daily dosages of levothyroxine as low as 25 to 50µg (Table 4). This initial dosage should be maintained for six to eight weeks before a TSH measurement is repeated to guide adjustment of the levothyroxine dosage. The goal is to maintain the TSH level within normal limits; the dosage of levothyroxine should be increased if the TSH level remains above normal and should be decreased if the TSH level falls below normal. The frequency of TSH assessment can be reduced to every 6 to 12 months after establishing an appropriate maintenance dosage. A common error is the failure to decrease the levothyroxine dosage if the TSH level is suppressed below the normal range, which may occur without the free T4 level rising above normal. Subclinical hyperthyroidism, characterized by suppressed TSH levels without a rise in free T4 levels, is believed to cause undesirable effects on bone density (osteoporosis), cardiac function, and neuropsychologic symptoms together with causing other mild manifestations of hyperthyroidism.5
The treatment of adult hypothyroidism requires replacement with L-thyroxine. The full replacement dose of L-thyroxine in adults is 1.6 to 1.8μg levothyroxine/kg/day. Replacement can be started with the full dose in a healthy young adult. However, caution needs to be exercised in the elderly (age more than 60 years), and in people with co-morbidities like ischemic heart disease or hypocortisolism. In the elderly and those suspected to have ischemic heart disease, therapy should be initiated at the dose of 25μg and increased only at 4 weekly intervals. In patients with co-existent hypocortisolism, glucocorticoid replacement should precede thyroxine replacement. Non-compliance, conditions which interfere with absorption or metabolism of thyroxine or changes in drug clearance necessitate dose changes. Exposure to excess thyroxine has a negative impact on cardiac and skeletal health and should be avoided at all costs. Myxedema coma is a life threatening condition which requires aggressive critical care management in addition to judicious use of parenteral thyroxine therapy.

**References**

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7. Yamada M. Resistance to thyroid hormone. Nippon Rinsho. 2006;64(12):2237-42