Hypothyroidism
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INTRODUCTION
Hypothyroidism was the first endocrine disorder treated by replacement with the deficient hormone, in the form of extracts of animal thyroid glands. Subsequently, the development of purified thyroid hormone preparations and greater understanding of thyroid physiology have made it possible to mimic the function of the normal thyroid gland with thyroid hormone replacement therapy. Thyroid hormone therapy is safe and well tolerated by most patients, and many patients can be treated for prolonged periods with little change in dosage. However, several clinical situations and drugs can alter the absorption, metabolism, and action of exogenous thyroid hormone and therefore may necessitate adjustment of therapy. The range of dose preparations that are available, and the ability of monitor therapy with measurements of serum thyrotrpin (TSH) allow the clinician to provide adequate therapy while minimizing both over- and undertreatment.

HISTORY OF THYROXINE REPLACEMENT THERAPY
Thyroid hormone preparations have been used in the treatment of hypothyroidism since 1891, when George Murray injected a phenolic extract of sheep thyroid into a myxedematous patient and achieved the first breakthrough in the management of what until then had been an incurable disease that frequently resulted in a fatal outcome. Shortly thereafter, Murray observed that the beneficial effects of the injected extract could be duplicated by the ingestion of whole sheep thyroid, a finding that subsequently prompted his discovery of the efficacy of a desiccated glycerin extract of sheep thyroid into a myxedematous patient of hypothyroidism since 1891, when George Murray injected a phenolic extract of sheep thyroid into a myxedematous patient and achieved the first breakthrough in the management of what until then had been an incurable disease that frequently resulted in a fatal outcome. Shortly thereafter, Murray observed that the beneficial effects of the injected extract could be duplicated by the ingestion of whole sheep thyroid, a finding that subsequently favored the use of L-T4 in the treatment of hypothyroidism. L-T4 is now virtually universally used.

Stable serum levels of these hormones facilitate titration of the L-T4 dose to achieve preassigned ranges of thyroid hormones. Two independently initiated studies showing the usefulness of L-T4 in thyroid hormone replacement followed, one published in 1973 and the other in 1974. In both studies the criterion for establishment of the euthyroid status was normalization of TSH in response to TRH administration. Both studies showed that the replacement dose was substantially less than the 200-400 μg/day range recommended in the package insert of L-T4 preparations and in the major textbooks of medicine of the time. One study found that the average replacement dose was 127 μg/day, whereas the other found an average value of 169 μg/day. The fact that the high dosage range for L-T4 administration had been accepted for so many years emphasized the principle that even a doubling in dosage delivery to a hypothyroid patient may not cause clinically obvious symptoms. The demonstration that the daily dose of L-T4 could be conveniently monitored and titrated served to popularize the use of this agent in the management of hypothyroidism. L-T4 is now virtually universally used.

PHARMACOLOGY OF THYROID HORMONE PREPARATIONS
Several preparations of thyroid hormone are available for treatment of patients with hypothyroidism; in India and USA they are levothyroxine (T4), liothyronine (triiodothyronine, T3), liotrix (a 1:4 combination of T3 and T4), and thyroid USP (desiccated animal thyroid containing T3 and T4 in the form of thyroglobulin). The latter and other thyroid extract preparations were used until synthetic preparations of T3, T4, and T3 plus T4 were introduced. Subsequent studies in humans and animals revealed that about 80% of serum T3 is produced in peripheral tissues by deiodination of T4, that administration of T3 is
followed by marked fluctuations in serum T₃ concentrations, and that administration of T₃ alone results in adequate serum and tissue concentrations of T₄ and T₃, and replicates normal thyroid physiology. Now the only recommended and available thyroxine in India is L-T₄ (Thyronorm, Eltroxin).

The most widely used and the preferred preparation for treatment of hypothyroidism is T₄. Overall, about 70-80% of an oral dose is absorbed, mostly in the proximal small bowel; in contrast, almost 100% of an oral dose of T₃ is absorbed. The advantages of T₄ include its long half-life (~7 days), reliable absorption, small (<15%) fluctuation in serum T₄ concentrations between single daily doses, ease of dose titration based on multiple available tablet strengths, and ease of measurement of serum T₄ concentration. Although the proportion of hypothyroid patients receiving T₄ has increased steadily, even today many are probable still being treated with thyroid cancer extract or a combination of T₄ and T₃.

**Brands and Bioavailability**

The T₄ content of tablets is standardised by high pressure liquid chromatography and must be between 90% and 110% of the stated amount. Before 1982, the standard was based on iodine content, and therefore included not only authentic T₄ but also biologically inactive degradation products and, in thyroid extracts, mono- and diiodotyrosines. Several brand-name and generic preparations are available, and their bioavailability is similar. T₄ tablets seem to be stable, but may lose potency if exposed to moisture, light, or air. Although a well-standardised product, reduced T₄ content was reported in tablets from one manufacturer, resulting in high serum TSH concentration among hypothyroid patients receiving supposedly adequate replacement in a defined geographic region. Tablets available now in India range in size from 25-300 µg, which allows very precise replacement in nearly all patients. However bio-equivalence data of Indian preparation find only two thyroxine brands (Thyronorm and Eltroxin) meet the set standards.

There are several drawbacks to administration of T₄ and T₃-containing preparations, in comparison with administration of T₄. T₃ is rapidly absorbed, with peak T₃ concentrations being reached 2-4 hours after oral administration; doses of as little as 25 µg result in supranormal serum T₃ concentrations for 6-8 hours. As compared with T₄, the circulating half-life is much shorter (approximately 1 day). As a result of these characteristics of T₃ absorption and metabolism, serum T₃ concentrations vary in the hours after dosing, as noted above.

**T₄/T₃ Controversy**

"Despite the standard of only supplementing with levothyroxine (T₄) for thyroid replacement, there is some preliminary evidence to show some patients feel better when given both levothyroxine (T₄) and triiodothyronine (T₃). Thyroid extracts are generally not recommended due to variation in potency and contains large amounts of T₃ which can cause palpitations and tremors. Obviously, with only one small human study quoted, there is not enough evidence to support this recommendation. Although T₄ is the recommended form of thyroid hormone replacement in hypothyroidism, the use of combined T₄ and T₃ treatment is again being considered. In thyroidectomized rats, T₄ treatment alone does not normalize T₃ concentrations in all tissues, whereas combined T₄ and T₃ treatment dose. In a study of hypothyroid patients receiving T₄ in whom 12.5 µg T₄ was substituted for 50 µg T₃, the combination resulted in improvement on several scales of cognitive performance and mood compared with T₄ treatment alone, whereas serum TSH concentrations were similar during both treatments. However, the ratio of T₃ to T₄ during combination treatment in this study was considerably lower (mean 1:10) than that in the commercially available preparation of T₄ and T₃, or in thyroid extract. Also there is some evidence to show that T₃ may have some effect on cognitive function on the elderly which prompted publication of a few scant studies. One need to re-think your stance on T₃ treatment for thyroid disease but should be pushing more for T₃ studies. What I mean is pushing for T₃ studies for the right reason, which is because T₃ can help alleviate the misery many patients. Naturally because it is so potent the administration of this hormone has to be very precise. Currently except L-T₄ no other form including T₃ or T₄ is recommended.

**'NONTHYROID ILLNESS SYNDROME' (NTIS)**

During starvation and in illness, thyroid hormones in blood are reduced to levels typical of hypothyroidism. This response has been interpreted over several decades as an adaptive response causing serum total hormone levels to drop while metabolism remains 'normal'. For this reason, it has been described as the 'euthyroid sick syndrome'. However, in severe illness, the changes in thyroid hormone supply are associated with a dramatically increased chance of death. Whether the changes are adaptive or maladaptive remains uncertain. The noncommittal term 'nonthyroid illness syndrome' (NTIS) seems more suitable. In this entity Hypothalamic mRNA for TRH is reduced, and cytokines may be involved. TSH levels are inappropriately low for serum hormone levels, presumably because of reduced secretion. TRH injection causes an elevation in TSH, T₄ and T₃, thereby reversing many aspects of the syndrome and suggesting that low TRH secretion may be a primary problem. Measured serum levels of apparent free T₄ and T₃ may be low or normal and, in some assays, even elevated, but no assay can be certified to be free of artifact. Inhibitors of T₄ and T₃ binding to serum proteins and possibly receptors have been postulated but remain of unproven significance. T₄ and T₃ production rates have been clearly demonstrated to be markedly reduced. Based on scant data, levels of hormone in most tissues are greatly reduced. Replacement hormone therapy has not been shown to be disadvantageous and in some studies appears to be beneficial. Serum hormone was, in the one study available, restored by administration of physiologic doses of hormone.

**THERAPEUTIC APPROACH TO HYPOTHYROIDISM**

**Goals and Monitoring**

The goal of treatment of hypothyroidism is to normalize thyroid status in peripheral tissues, whatever the cause of the hypothyroidism. The usual approach is to give sufficient T₄ to ameliorate all symptoms of hypothyroidism and, in patients with primary hypothyroidism, to reduce serum TSH concentrations to within the normal range; doses effective in these regards
raise serum total and free T₄ concentrations to well within their respective normal ranges or just above them, and serum total and free T₃ concentrations to within the normal range (the difference representing the thyroidal contribution to serum T₄ concentrations in normal subjects). Measuring effects of T₄ on tissues other than the pituitary gland accurately is very difficult, and no other measurement is as sensitive to small changes in dose of T₄ as is that of serum TSH. Thus, measurements of serum TSH are the best way to identify patients who are receiving too much T₄ (low serum TSH concentration) and those who are receiving too little (high serum TSH concentration). In most hypothyroid patients treated with T₄ there is a close correlation between serum free T₄ concentration and measurements of resting energy expenditure and other thyroid hormone actions, notwithstanding the insensitivity of these latter measurements. Rare patients, however, have been reported in whom there was a disparity between serum TSH concentrations and clinical measurements of thyroid hormone action at the tissue level, such as serum cholesterol and ankle reflex relaxation time. The serum TSH value is not an accurate reflection of thyroid status in patients with central hypothyroidism. In these patients some estimate of serum free T₄ should be used as the indicator of thyroid status and to monitor the efficacy of treatment. A similar approach should be used in patients recently treated for thyrotoxicosis, in whom serum TSH concentrations may remain low for several months due to the slow recovery of TSH secretion from prolonged suppression while the patient was thyrotoxic.

**Should the TSH be the sole laboratory criterion of thyroid status?**

Clearly, TSH cannot be used as a sole criterion of thyroidal status in patients with central hypothyroidism (pituitary or hypothalamic), given the fact that the TSH level in such patients can be very low, normal, or even slightly elevated.⁴ The coexistence of normal or marginally elevated TSH and low levels of serum free T₄ may be due to altered glycosylation patterns of TSH resulting in a lowered ratio of the biological potency immunoreactivity.⁵ Thus, for patients with central hypothyroidism, the levels of free T₄ or the free T₄ index should serve as the primary laboratory parameter for determining the L-T₄ replacement dose. As approximately 20% of extrathyroidal T₄ results from direct thyroidal secretion, the level of circulating T₄ should be in the upper half of the normal range. Although the finding of a serum T₃ concentration in the midnormal range can be useful as further confirmation of the euthyroid status of the patient, a low T₃ concentration can also be a reflection of associated nonthyroidal disease. Even in patients with primary thyroidal failure, the serum T₃ concentration provides useful corroboration of the clinical state. A lowering of serum T₃ accompanied by a rise in TSH confirm the need for increasing the L-T₄ dose. This combination of changes can also be due to a further decrease in residual thyroidal secretion of T₃ or to noncompliance by the patient or switching L-T₄ preparations from one brand to another. Rarely, an elevation of a TSH assay is an artifact created by circulating mouse heterophile antibody.⁶ Lastly, a small minority of patients with catabolic nonthyroidal disease⁷ may exhibit TSH values below the lower limits of the normal range (0.4-5.0 mU/L) without any ancillary data, suggesting either clinical hypothyroidism or hyperthyroidism. Similarly, both dopamine infusion and glucocorticoid administration may lower the serum TSH level without overt clinical evidence of thyroid dysfunction. These considerations emphasize the usefulness of the serum T₃ or Free T₄ level or the free T₃ index in assessing the thyroid status of patients suspected of being hypothyroid and in following hypothyroid patients who are being replaced with L-T₄.

**Initiation of Therapy**

The initial dose of T₄ should be based on the age of the patient, the severity and duration of hypothyroidism, and the presence of any other associated disorders. Healthy patients under the age of 60 years with no history of cardiac or respiratory disease can be started on a full replacement dose of T₄, which is about 1.6-1.8 µg/kg body weight/day (usually 75-125 µg/day in women and 125-200 µg/day in men), given once daily. These doses must be given for 4-8 weeks before their tissue effects and serum T₄ and TSH concentrations reach a steady state. In general, bioavailability is not known to be affected by food, but is prudent to advise the patient to take their daily dose of T₄ at the same time in relation to eating every day.

Older patients (>60 years) required 20-30% less T₄ per kg ideal body weight than do younger patients. Because of the very small risk of inducing angina or a cardiac arrhythmia, it is prudent to treat even healthy older patients initially with 50 µg/day, increasing the dose by 25 µg at intervals of at least 6 weeks.

The underlying cause of thyroid disease also can influence the dose requirement. For example, patients with primary hypothyroidism caused by chronic autoimmune thyroiditis or total thyroidectomy require slightly higher doses of T₄ than do patients with Graves’ hyperthyroidism made hypothyroid by radioactive iodine or surgical therapy, because the latter are more likely to have some remaining autonomously functioning thyroid tissue.

Hypothyroid patients who are unable to take oral medication for a brief period of time (several days) do not need parenteral therapy, owing to the long half-life of T₄. For those patients who cannot be given T₄ orally for prolonged periods, or who are unable to absorb T₄, it can be given intravenously. The daily intravenous dose should be 70-80% of the usual oral dose, based on the fraction of an oral dose that is absorbed.

**Thyroxyne Therapy in Patients with Underlying Cardiac Disease**

In hypothyroid patients, T₄ can improve cardiac performance by reducing systemic vascular resistance, reducing end-diastolic volume, increasing the strength of contraction, and increasing cardiac output. Nonetheless, there has been concern that administration of T₄ to hypothyroid patients with ischemic or other cardiac disease would have adverse cardiovascular effects. There is, however, little evidence to support this concern. For example, among a large group of hypothyroid patients treated with thyroid hormone, only 2% developed new-onset angina pectoris. Among those patients with pre-existing angina, 38% improved, 46% had no change, and only 16% worsened.
Despite the low risk, given the serious consequences of worsening ischemic heart disease, patients with cardiac disease or risk factors for it should be given T4 cautiously, for example 25 µg/day. If cardiac disease is present or suspected, evaluation and treatment can proceed as would otherwise occur. For example, patients with angina and hypothyroidism should in most instances have appropriate evaluation and treatment for coronary artery disease at the same time as T4 therapy is initiated.

**Monitoring Thyroxine Therapy**

The intensity with which T4 therapy is monitored depends on the severity of hypothyroidism and the clinical context. Those patients given low doses because of age or another illness should be re-evaluated in 6 weeks, and the dose increased in small increments. For those patients initially given what is estimated to be full replacement dose, the patient should be re-evaluated and serum TSH should be measured in about 8 weeks. The dose of T4 should be increased if the serum TSH concentration is still high, or decreased if it is low. Dose changes of 25 µg are usually sufficient when making an adjustment, depending on the deviation of serum TSH from normal. If the dose is not changed, the patient should be re-evaluated and serum TSH measured again in 4-6 months, because that clearance of T4 can be increased after the euthyroid state is established. If, as a consequence of the change in dose, the serum TSH concentration becomes abnormal at the other extreme, tablets are available that are 12-µg increments between the commonly used doses of 75, 100, 125 and 150 µg. Once the appropriate dose of T4 is determined, annual re-evaluation and measurements of serum TSH are recommended. Most patients can be treated with the same dose until the seventh to eighth decade of life, when the dose may need to be decreased. The requirement for T4 can be altered by several conditions and medications.

The relationship between serum TSH and T4 concentrations is log-linear, so that a small reduction in serum T4 concentration results in a large increase in serum TSH concentrations, as demonstrated in a study of patients receiving a stable dose of T4 who had normal serum TSH concentrations in whom the dose then was increased or decreased in increments of 25 µg/day. These results explain why very small changes in T4 dose can result in substantial changes in serum TSH concentrations.

**Treatment of Central Hypothyroidism**

Patients with central (secondary) hypothyroidism also should be treated with T4, but, as noted earlier, serum TSH measurements are not useful for monitoring therapy. Instead, measurements of serum free T4 (direct or indirect) should be used, although measurements of serum total T4 may be adequate if the patient is known to have normal serum binding of T4. The goal of treatment should be a serum T4 concentration in the middle or upper end of the normal range for the test used. It is important that other aspects of pituitary function be assessed, especially pituitary-adrenal function. Patients with both hypothyroidism and hypocortisolism may have only symptoms of hypothyroidism, but then develop symptoms of hypocortisolism when T4 therapy is begun, because the metabolic clearance of cortisol is reduced in hypothyroidism. For this reason, if there is any question of the adequacy of adrenal reserve, in both T4 and hydrocortisone should be given until hypothalamic-pituitary-adrenal function can be evaluated.

**Response to Thyroxine Treatment**

The response to T4 therapy should be assessed both clinically and biochemically. Normalization of clinical and biochemical manifestations of hypothyroidism, however, occurs at different times and can vary among patients. The earliest change usually is normalization of the serum T4 concentration, which occurs after several weeks of treatment. Normalization of the serum TSH concentration may require up to 8 weeks, depending on the magnitude of the initial elevation. Most patients note improvement of symptoms in several weeks, but complete recovery usually requires several months. A substantial fraction of patients with hypothyroidism complain of weight gain and have an expectation of weight loss when they are treated. Most of the weight that is lost after treatment is begun, however, is fluid, so that the decrease in weight does not usually exceed 10% of body weight, and the weight that is lost usually regained in the following months.

**Conditions Associated with Altered Thyroxine Requirements**

Several conditions and drugs can alter the requirement for T4 (Table 1). Older patients, especially those in their sixties or seventies, may need less T4, perhaps due to a decrease in T4.

### Table 1: Circumstances Associated with Altered T4 Requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Condition/Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>Androgen therapy, Age progression, Pregnancy, Malabsorption, Mucosal disease (e.g. sprue)</td>
</tr>
<tr>
<td>Increased</td>
<td>Amiodarone, Amphotericin, Androgen therapy, Carbamazepine, Calcium carbonate, Calcium polystyrene sulfonate (Kayexalate), Cholestyramine, Ferrous sulfate, High-fiber diet, Lovastatin, Phenytoin, Raloxifene, Rifampin, Selenium deficiency, Sertraline, Valproic acid, Warfarin</td>
</tr>
<tr>
<td>Normalized</td>
<td>Reduced to T3 conversion, Amiodarone, Calcium carbonate, Carbohydrate, Cholestyramine, Ferric sulfate, High-fiber diet, Lovastatin, Phenytoin, Raloxifene, Rifampin, Selenium deficiency, Sertraline, Valproic acid, Warfarin</td>
</tr>
<tr>
<td>Unknown</td>
<td>Certain drugs and dietary supplements</td>
</tr>
</tbody>
</table>

* Single case or very small number of cases
clearance. Hypothyroid patients receiving T₄ replacement who are treated with an androgen also need less T₄ due to a reduction in the T₄ pool as a result of a decrease in serum thyroxine-binding globulin (and loss of ability to reduce T₄ secretion to compensate or the decrease in binding).

More often, an increase in the dose of T₄ is needed. Most hypothyroid women require an increase in T₄ dose during pregnancy. The magnitude of the increase averages 50%, but it is variable and is related to the amount of residual thyroid tissue. It is due at least in part to the increase in serum thyroxine-binding globulin that occurs during that first 15-20 weeks of pregnancy. The prepregnancy dose of T₄ can be resumed after delivery.

Patients who undergo bowel resection, have intestinal disease, or eat a lot of fiber may malabsorb T₄, and hence need a large dose. Similarly, other drugs may cause malabsorption of T₄, including sucralfate, aluminum hydroxide, ferrous sulfate, cholestyramine, and possibly sodium polystyrene sulfonate and calcium carbonate. Other drugs that can lead to need for more T₄ are rifampin, carbamazepine, and phenytoin, which increase T₄ clearance and amiodarone, which slows T₄ clearance, inhibits T₄ to T₃ conversion, and may antagonize the peripheral action of T₃. Other drugs reported to increase the need for T₄ are lovastatin and sertraline. Many of these interactions have been described in only a few patients, and only rarely was the interaction confirmed in the same patient. For the drugs that decrease T₄ absorption, separation of the times at which the T₄ and the drug are taken by several hours eliminates the effect.

**Adverse Effects of Thyroxine Therapy**

Excessive T₄ treatment causes subclinical or overt thyrotoxicosis. Patients with subclinical thyrotoxicosis have few if any symptoms of thyrotoxicosis, but may be at risk for excess bone loss and cardiac arrhythmias or cardiac dysfunction. Excess bone loss may occur in postmenopausal women who receive sufficient T₄ to reduce TSH secretion below normal, and patients who have low serum TSH concentrations may have increased pulse rates and increased cardiac wall thickness and contractility, as well as an increased risk of atrial fibrillation. Hair fall and sometimes even alopecia is a often common occurrence which may respond to treatment of T₄.

**TREATMENT FAILURES**

**Persistently High Serum TSH Concentrations**

In some patients serum TSH concentrations remain high despite a T₄ dose that should be adequate. Poor compliance is the most common reason for this finding and it should be suspected in patients receiving excessive doses of T₄ for their size or in those with widely varying thyroid function studies while taking the same prescribed dose. In patients who take multiple daily doses just before a follow-up visit, serum TSH concentrations may be high despite the presence of normal or even high serum T₄ concentrations.

A persistent elevation in serum TSH despite good compliance may be the result of one of the conditions or drugs that increases the need for T₃ listed in Table 1. In their absence, changing the brand of T₃ can result in improved absorption. Despite the identical content of T₄ in different brands, there is enough variation in the dissolution times among them that absorption of some brands may be decreased in patients with rapid intestinal transit. Finally, a very small number of patients have persistently high serum TSH and T₄ concentrations. These patients should be evaluated for resistance to the action of thyroid hormone, particularly if they have undergone thyroidectomy or received radioactive iodine therapy for a mistaken diagnosis of hyperthyroidism in the past.

**Hypothyroid Symptoms Despite Normal Thyroid Function Study Results**

Hypothyroid patients may complain of persistent symptoms despite adequate T₄ therapy. This is especially true of those previously given excessive doses of T₄. Given the potential complications of excessive doses, it is important to educate the patient to the fact that a normal serum TSH concentration is the best goal of T₄ replacement therapy. Because T₄ has such varied effects, it is not unusual for patients to attribute a broad range of symptom to inadequate therapy, and some will change their dose of T₄ based on their symptoms. Because of the long half-life of T₄ and the unreliability of the subjective assessment of thyroid hormone-related symptoms, this practice is ineffective and even dangerous, and should be discouraged. Many patients are responsive to education about thyroid hormone testing and monitoring of therapy, along with reassurance. If symptoms persist, other causes for them should be investigated.

**HOW TIGHTLY SHOULD HYPOTHYROID PATIENTS BE REGULATED WITH L-T₄?**

The third generation TSH assay is becoming increasingly popular by virtue of its high sensitivity and its ability to set upper assay limits (<0.05 mU/L) for patients with clinical hyperthyroidism. By the same token, this test may present a difficult dilemma when the dose of L-T₄ taken by a hypothyroid patient results in a serum concentration of TSH in the gray zone that lies below the lower limit of normal (0.5 mU/L) but above the upper bounds set for clinical hyperthyroidism (0.05 mU/L). Under such circumstances, the serum free T₄ and free T₃ indexes may still be within the normal population range. The association of such normal levels of free T₄ or free T₃ with depressed concentrations of TSH can be explained if one assumes that the set-point for feedback TSH control is determined for each individual in very narrow bounds of serum free T₄, much narrower than the range in the normal population. For example, if the set-point for T₄ in a given patient maintained on L-T₄ replacement therapy is 100 ng/dL, an increment of 10 ng/dL during the course of treatment may reduce the pituitary TSH feedback system to subnormal levels even though the new steady state value of 110 ng/dL T₄ is well below 160 ng/dL, which is widely accepted as the upper limit of serum T₄ in the normal population. Such a patient probably would exhibit a gray zone TSH (between 0.05-0.5 mU/L). Although biochemically hyperthyroid, the patient would not be expected to manifest any obvious clinical symptoms. A similar argument could be made for an increase in TSH as a result of a small decline in serum T₃ and T₄ but within the normal population range. The practical problem facing the practicing physician is to determine whether such small excursions of TSH concentrations outside the normal range warrant further adjustment of the daily dose. It has been noted that such discrepancies are relatively common not only during the initial stages of L-T₄ replacement but also during
yearly follow-up visits. Concern for such deviations in TSH value is justified only if two conditions are met: 1) that the deviations in TSH value observed are truly indicative of the average TSH maintained over many months and 2) that the steady state changes in the range observed are, in fact, associated with long-term health risks. Unfortunately, neither of these questions can be answered in a definitive fashion at this time. With regard to the first point, Fish et al.14 observed considerable variation in TSH levels when serial determinations were made with a second generation assay in five hypothyroid patients maintained on constant L-T4 replacement therapy. If the levels of TSH are only slightly elevated or depressed by third generation assays, repeat TSH may be helpful before changing the dose. As approximately 6-8 weeks are required for T4 and T3 levels to achieve a new steady state, repeat determinations should be postponed for an additional 2 months after a change in dose. Tight replacement schedules make sense only if the second assumption is also fulfilled: namely that TSH deviations from the normal range result in potentially serious health problems. Two potential target organs that are currently under suspicion are the skeletal system and heart. Several series that have evaluated the effects of L-T4 replacement on bone mineral density are currently available.15,16 Most but not all of such studies conclude that excessive thyroid hormone replacement therapy results in decreased bone mineral density. However, there is disagreement with respect to the areas and age groups most affected. There is also a divergence of opinion as to whether the decrease in bone mineral density induced by L-T4 replacement actually results in an increased fracture rate.17,18 In essence, it appears unlikely that minimal overreplacement should have serious repercussions with respect to either bone mineral density or fracture rate. Recently, claims have been made that patients with thyroid cancer maintained on long term TSH suppression therapy exhibit increased heart rate, increased prevalence of cardiac arrhythmias, enhanced left ventricular systolic function, and increased left ventricular mass.19 Concomitant treatment with cardioselective adrenergic blocking agents antagonized the effects of thyroid hormone.20 However, the TSH assay used by these researchers did not allow them to distinguish between suppression into the gray zone subclinical range and the clinically apparent TSH range. As many of their patients manifested symptoms, it appears likely that such individuals would have had TSH levels below 0.05 mU/L had third generation TSH assays been used. Of interest is the recent report of an increased incidence of ischemic heart disease in patients under the age of 65 yr receiving L-T4 therapy.21 However, no difference in incidence was observed between those who exhibited TSH suppression and those who did not. Similarly, gray zone elevations of TSH in subclinical hypothyroidism may have an effect on lipid patterns and predisposed to atherogenesis. However, these effects do not appear to be marked, and in some patients, restoration of TSH levels after the administration of L-T4 failed to normalize the lipid patterns.22

PRACTISE POINTS

Thus, it appears prudent to make reasonable efforts to normalize the serum TSH level in hypothyroid patients undergoing replacement therapy with L-T4. Keeping the TSH concentration rigidly in the 0.4-4.0 mU/mmol·L range would be expensive, require multiple blood samplings, and most likely not contribute significantly to the health of the patient. The third generation TSH assay is the best and must be used. After an initial equilibration during which L-T4 doses are changed at 2-month intervals, patients are seen, in general, at yearly intervals. However, patients are advised to be rechecked when they become pregnant or require medications known to interfere with the absorption or metabolism of L-T4. Careful distinctions should be made between efforts to replace thyroid hormone in hypothyroid patients and efforts to suppress the production of the last vestige of TSH in the treatment of patients with benign or malignant growths. Ideally, in the case of replacement therapy one would like to achieve a TSH concentration within the normal range. With suppression, one might wish to maximally reduce the level of circulating TSH to arrest the growth/goitrogenic process. In the case of thyroid cancer, one might even be willing to accept potentially adverse consequences of supraphysiological doses of L-T4. In such suppressive doses, analysis of the relationship between TSH and thyroglobulin levels showed that thyroid hormone treatment was effective in reducing the level of serum thyroglobulin only when the level of TSH was initially elevated above the normal range. Doses of L-T4 that lowered the level of TSH below the normal TSH range had no additional effect. It is prudent to maintain the level of TSH in patients with thyroid cancer in the range of 0.1-0.4 mU/L. Clearly, additional studies are necessary to test the assumptions underlying these recommendations. Similarly, the efficacy of suppressive doses of L-T4 in the management of patients with thyroid nodules has been challenged in three prospective randomized studies.24-26 In contrast, a prospective randomized placebo-controlled study has shown that a suppressive dose of L-T4 slows the growth of multinodular goiter. It is not clear, however, whether beneficial effects in this study were due to the lowering of initially supranormal levels of serum TSH. These findings also raise questions concerning whether efforts to reduce TSH levels to below the euthyroid range are warranted in the management of benign processes. Succinct Indian reviews and original work of the author available for further reading.28-33

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