Guidelines for the Use of Thyroid Function Tests

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Indications for Thyroid Function Testing

Screening for Thyroid Dysfunction

Which Thyroid Function Test?

- As a baseline screening test TSH sampling will be done on all samples received for TFTs. Free T4 and T3 will be done if requested for and if warranted by the supplied brief history and on samples with abnormal TSH results.

Special situations:

Goitre and Thyroid Nodules

- In any patient presenting with a suspected goitre, serum TSH should be measured.

Atrial Fibrillation, Hyperlipidaemia, Osteoporosis, Subfertility

- Patients with atrial fibrillation, dyslipidaemia, osteoporosis and subfertility should have an assessment of thyroid function by measurement of serum TSH at presentation.

Women with Type 1 Diabetes

- Women with type 1 diabetes should have their thyroid function, including serum TSH, FT4 and thyroid peroxidase antibody status, established preconception, at booking when pregnant and at 3 months post-partum.

The Normal Healthy Adult Population Including the Elderly

- Screening for thyroid dysfunction in a healthy adult population is not warranted. Case-finding in women at the menopause or if visiting a doctor in primary care with non-specific symptoms may be justified in view of the high prevalence of mild thyroid failure.
- If screening is performed, and a high serum TSH concentration is found, and the FT4 is normal, the measurement should be repeated 3-6 months later, along with measurement of serum FT4, after excluding non-thyroidal illness and drug interference.
- If the serum TSH is greater than 10mU/L and the serum FT4 concentration is low, then the subject has overt hypothyroidism and should be treated with thyroxine.
- If the serum FT4 concentration is normal, but the serum TSH concentration is greater than 10mU/L, then treatment with thyroxine is recommended.
- If the serum TSH concentration is above the reference range but <10mU/L, then serum thyroid peroxidase antibodies should be measured. If the serum antibody concentration is high, then serum TSH should be measured annually or earlier if symptoms develop; thyroxine therapy should be started if the serum TSH concentration rises above 10mU/L. If the serum antibody concentration is not raised, then repeat measurement of serum TSH approximately every three years is all that is required.
- There is no evidence to support the benefit of routine early treatment with thyroxine in non-pregnant patients with a serum TSH above the reference range but <10mU/L.
Physicians may wish to consider the suitability of a therapeutic trial of thyroxine on an individual patient basis.

- If a serum TSH concentration below the reference range but >0.1mU/L is found, then the measurement should be repeated one or two months later together with serum FT4 and FT3, after excluding non-thyroidal illness and drug interferences.
- If the serum TSH is less than 0.1mU/L then the serum FT4 and FT3 must be measured to exclude overt hyperthyroidism.
- If treatment is not undertaken, serum TSH should be measured every 6-12 months, with follow-up measurements of serum FT4 and FT3 if the serum TSH result is low.

Hospital In-Patients

- Routine testing of thyroid function in patients admitted acutely to hospital is not warranted unless specific clinical indications exist.
**Surveillance of Thyroid Function**

**Past History of Post-Partum Thyroiditis**

- All women with a past history of postpartum thyroiditis should be offered an annual check of thyroid function and should also be screened prior to and at 6 to 8 weeks after future pregnancies

**Patients with Diabetes**

- Patients with type-1 diabetes should have a check of thyroid function included in their annual review. Patients with type-2 diabetes should have their thyroid function checked at diagnosis but routine annual thyroid function testing is not recommended

**Down Syndrome and Turner's Syndrome**

- All patients with Down Syndrome and Turner’s Syndrome should have an annual check of thyroid function

**Patients receiving Amiodarone and Lithium**

- All patients on amiodarone therapy should have thyroid function tested before commencing treatment and then should be routinely monitored every 6 months thereafter whilst on treatment and up to 12 months after cessation of therapy
- All patients on lithium therapy should have thyroid function tested before commencing treatment and then should be routinely monitored every 6-12 months whilst on treatment

**Post Neck Irradiation**

- Thyroid function should be tested every 12 months in patients treated by external irradiation to the neck in view of the risk of hypothyroidism

**Following Destructive Treatment for Thyrotoxicosis by either Radioiodine or Surgery**

- Indefinite surveillance is required following radioiodine or thyroidectomy for the development of hypothyroidism or the recurrence of hyperthyroidism.
- Thyroid function should be assessed around four to eight weeks posttreatment, then three monthly up to one year and annually thereafter

Compiled and Adapted by Dr. R. Sirkar - Chemical Pathologist
Monitoring of Thyroid Function

Treatment of Thyrotoxicosis with Anti-Thyroid Drugs

- It is recommended that thyroid function is tested every 1-3 months when initiating antithyroid drug therapy until stable and annually if used as a long term treatment option

Patients on Thyroxine Therapy

- Once thyroxine replacement is initiated, for whatever indication, then long-term follow-up with at least an annual measurement of serum TSH is required to check compliance and dosage and take account of variations in dosage requirement caused by concomitant drug treatment
- In pregnancy there may be a need to increase the dose by at least 50μg daily to maintain a normal serum TSH, which should be measured in each trimester
Hypothyroidism

Primary Hypothyroidism

- The diagnosis of primary hypothyroidism requires the measurement of both TSH and FT4.
- Subjects with a TSH of >10mU/L and FT4 below the reference range have overt primary hypothyroidism and should be treated with thyroid hormone replacement.
- Subjects with subclinical hypothyroidism should have the pattern confirmed within 3-6 months to exclude transient causes of elevated TSH.
- The measurement of thyroid antibodies in subjects with subclinical hypothyroidism helps to define the risk of developing overt hypothyroidism.

Guiding treatment with thyroxine replacement therapy.

- The primary target of thyroxine replacement therapy is to make the patient feel well and to achieve a serum TSH that is within the reference range. The corresponding FT4 will be within or slightly above its reference range.
- The minimum period to achieve stable concentrations after a change in dose of thyroxine is two months and thyroid function tests should not normally be requested before this period has elapsed.

Guiding treatment with tri-iodothyronine.

- The measurement of FT4 is of no value in patients on tri-iodothyronine replacement and the measurement of FT3 is of limited value because of the variability after taking the replacement dose.
- The measurement of TSH is required to optimise tri-iodothyronine replacement therapy.
- There is no consistent evidence to recommend the use of combined therapy with thyroxine and tri-iodothyronine in comparison to thyroxine alone.

Assessing response to thyroxine therapy.

- The optimal dose of thyroxine for long-term therapy is assessed from the results of thyroid function tests together with clinical finding. In determining the optimal dose of thyroxine the biochemical target is a TSH result that is detectable, not elevated, and preferably within the reference range.

Long-term follow-up of patients on thyroxine.

- Patients stabilised on long-term thyroxine therapy should have serum TSH checked annually.
**Subclinical (Mild) Hypothyroidism**

**Diagnosis**
- TSH above the reference range with a FT4 measurement within the reference range.
- Subclinical hypothyroidism should be confirmed by repeat thyroid function testing 3-6 months after the original result.

**Guiding treatment**
- If the serum FT4 concentration is normal but the serum TSH is >10mU/L, then treatment with thyroxine is recommended.
- If the serum FT4 concentration is normal and the TSH is elevated but <10mU/L then thyroxine therapy is not recommended as a routine therapy.
- However, thyroxine may be indicated in non-pregnant patients with goitre; also in patients who are seeking pregnancy

**Assessing response to therapy**
- aim of treatment should be to restore and maintain TSH within the reference range
- TSH should be measured 2-3 months following a change in thyroxine dose

**Long-term follow-up**
- Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody positive should have an annual thyroid function test.
- Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody negative should have repeat thyroid function testing approximately every 3 years.

**Secondary Hypothyroidism**

**Diagnosis**
- necessitates the use of a combination of TSH with FT4.
- Plasma TSH can be low, within or mildly above the reference range in these patients but combined with a low thyroid hormone measurement is suggestive of secondary hypothyroidism
- Secondary hypothyroidism can be distinguished from non-thyroidal illness on the basis of clinical history, measurement of FT3 and tests of other anterior pituitary hormones

**Guiding Treatment**
- The extent of hypopituitarism should be established in all patients with secondary hypothyroidism before commencing thyroxine therapy.
- Some experts suggest that an appropriate target for adequate thyroxine replacement in patients with secondary hypothyroidism may be a FT4 concentration in the upper third of the reference range.

**Assessing Response to Therapy**
- FT4 measurements should be used to help define the adequacy of thyroxine replacement in patients with secondary hypothyroidism.

**Long-term Follow-Up**
An annual check of thyroid hormone concentration should be performed in all patients with secondary hypothyroidism who are stabilised on thyroxine replacement therapy.

Congenital Hypothyroidism

Congenital hypothyroidism (cretinism) is a common preventable cause of mental retardation.

Diagnosis

Confirmation of the diagnosis of congenital hypothyroidism involves measurement of serum TSH and FT4 in both mother and neonate and TSH receptor antibody in the mother.

All hypothyroid neonates should be treated as early as possible. Treatment must be started within the first 18 days of life.

The measurement of both TSH and FT4 are required to optimise thyroxine replacement in infants. Age-related reference ranges should be used.
Hyperthyroidism

Primary Hyperthyroidism

Diagnosis

- The measurement of TSH using an assay with a functional sensitivity of <0.02mU/L is a desirable early stage in the diagnosis of hyperthyroidism.
- In patients suspected of having hyperthyroidism all subnormal TSH results should trigger the measurement of FT4.
- If FT4 is not elevated in the patient with subnormal TSH, FT3 should be measured to identify cases of T3-thyrotoxicosis.
- The co-existence of hyperthyroidism and non-thyroidal illness may result in the finding of a 'normal’ FT3.
- It is important to identify cases of thyroiditis since standard treatment with thionamides/radioiodine is ineffective and contraindicated.
- The measurement of TSH-receptor antibodies and thyroid peroxidase antibodies is not routinely required to determine the cause of hyperthyroidism if this is indicated by clinical features but they may be helpful in certain cases, especially if knowledge of the cause will influence treatment.
- Patients with confirmed hyperthyroidism should be referred for specialist care in order to establish the diagnosis and optimal management plan.
- Particular care is required in the diagnosis of hyperthyroidism in patient taking amiodarone. The measurement of TSH, FT4 and FT3 is required.

Guiding Treatment

- The degree of elevation of serum FT4 and FT3 provides an indication of the severity of hyperthyroidism and should be interpreted in the context of clinical symptoms and signs to direct first-line therapy.

Assessing Response to Therapy

- Serum FT4 and TSH should be measured in all patients receiving thionamides. In most cases the FT4 result will be the marker of choice to guide therapy.
- Thyroid function tests should be performed every 4-6 weeks after commencing thionamides. The frequency of testing should be reduced to every ~3months once a maintenance dose is achieved.

Radioiodine therapy.

- Serum FT4 and TSH should be measured in all patients treated with radioiodine. In most cases the FT4 result will be the marker of choice to guide therapy.
- Thyroid function tests should be performed every 4-6 weeks for at least six months following radioiodine therapy. The frequency of testing may be reduced when the FT4 remains within the reference range, although an annual TFT is still required.
- A fall in FT4 to below the reference range or a rise in TSH to above the reference range should prompt reduction in thionamide dosage or drug withdrawal in subjects prescribed these agents following radioiodine therapy, followed by re-assessment off thionamide therapy.
- A serum TSH result of >20mU/L following radioiodine therapy in a patient not receiving thionamides in the previous 4-6 weeks should trigger thyroxine therapy.
Long-Term Follow Up
  ❖ Life-long thyroid function testing is required for all patients who have received radioiodine therapy or surgery for hyperthyroidism
  ❖ Regular thyroid function testing is required for all patients being treated with long-term thionamides

Subclinical (Mild) Hyperthyroidism
Diagnosis
  ❖ Subclinical hyperthyroidism is defined as a low serum TSH in the presence of normal concentrations of FT4 and FT3
Guiding treatment/follow-up
  ❖ Patients with subclinical hyperthyroidism that cannot be explained by nonthyroidal illness or drug therapy should have repeat thyroid function testing with a frequency initially determined by the clinical findings
  ❖ Persistent subclinical hyperthyroidism should prompt specialist referral
  ❖ Untreated subclinical hyperthyroidism should be followed into the long term by testing thyroid function every 6-12 months

Inappropriate TSH
Diagnosis
  ❖ The finding of an inappropriate TSH in the presence of elevated FT4 and/or FT3 should stimulate the laboratory to consider errors or assay artefacts. Confirmation by repeat, is required
  ❖ The measurement of serum SHBG, alpha subunit and other anterior pituitary hormones (BHCG, FSH/ LH) can help distinguish TSH-oma from thyroid hormone resistance

Reference Ranges - Adults
(for Paediatric ranges please consult the Laboratory)

Thyroid Stimulating Hormone

  0.35 - 5.0 mU/L

T4 - Free
  9.00 - 21.00 pmol/L

T3 - Free
  3.5 - 6.5 pmol/L
## Interpreting Results of Thyroid Function Tests

<table>
<thead>
<tr>
<th>Low TSH</th>
<th>Normal TSH</th>
<th>Raised TSH</th>
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</table>
| **Raised FT4/FT3** | **Low TSH, raised FT4/FT3** | **Normal TSH, raised FT3/FT4** (rare)** TSH-secreting pituitary tumour**  
**Thyroid hormone resistance (receptor defect)**  
**Intermitent T4 therapy/acute overdose**  
**Interfering anti-T4/T3 antibody**  
**Familial dysalbuminaemic hyperthyroxaemia**  
**Acute psychiatric illness** |
| **Normal FT4/FT3** | **Normal TSH, normal FT4/FT3** | **Raised TSH, normal FT4/FT3**  
**Subclinical hypothyroidism**  
**Poor compliance with T4 therapy**  
**Interfering (heterophile) antibody**  
**Recovery from non-thyroidal illness**  
**Hypoadrenalism** |
| **Low FT4/FT3** | **Low/normal TSH, low FT4/FT3** | **Raised TSH, low FT4**  
**Non-thyroidal illness**  
**Pituitary failure**  
**Recent (excessive) treatment for hyperthyroidism** |

**Note:** free thyroid hormone assays are assumed—effects of changes in binding proteins on total thyroid hormone assays are not included.  

**Fig. 2.14** Patterns of thyroid function tests.
Situations in which TSH Usually Provides the Correct Estimate of Thyroid Status.

- In overt primary hyperthyroidism TSH is nearly always below 0.10 mU/L.
- In overt primary hypothyroidism plasma TSH is always increased.
- In mild (subclinical) disorders, TSH will be the most sensitive indicator of failing thyroid function, and plasma FT4 and FT3 are often normal.
- Before the diagnosis of subclinical thyroid disorders can be made, causes of an abnormal TSH other than thyroid disorders must be excluded. These include pregnancy, non-thyroidal illnesses, drug treatment, and assay interference.
- In subjects without thyroid dysfunction TSH will be normal.

Situations in which TSH Results may be Misleading

- Assay interference. All assays are prone to interference from a range of substances in blood including heterophilic antibodies. Heterophilic antibodies can interfere with immunoassays for TSH and produce clinically misleading results.
- Pregnancy. In the first trimester a TSH of <0.10 mU/L may be found in up to 3% of patients.
- Trimester-related reference ranges should be applied for TSH, total and free thyroid hormones.

Situations in which Thyroid Status is Unstable.

- Early months after treatment for hyperthyroidism TSH may be normal or low and thus misleading, when hypothyroidism has been induced during the early weeks or months after treatment of hyperthyroidism, due to delayed recovery of the previously suppressed thyrotroph. At that stage measurement of FT4 is the more sensitive indicator of thyroid failure. If however, the hypothalamic-pituitary-thyroid axis has recovered, measurement of TSH is more meaningful in this respect.
- The recovery of the thyrotrophs cannot be predicted for an individual patient, measurement of both FT4 and TSH is important for appropriate treatment.
- Following an episode of thyroiditis.
- Early weeks of thyroxine therapy.
- Poor compliance. Some patients who are poorly compliant with thyroxine therapy take excessive doses in the days prior to a clinic visit. These individuals can be identified by the seemingly anomalous combination of a raised TSH and FT4. Measurement of TSH alone is likely to lead to a recommendation for increasing the daily dose of thyroxine when diligent adherence to the previous drug regime is all that is required. The use of TSH alone is thus only adequate for patients on replacement therapy once they are stable and compliant.
- Hypopituitarism. Normal TSH is found in about half of patients with central hypothyroidism, FT4 are usually low and in occasional cases of hypopituitarism a raised TSH may be seen.
- TSH secreting adenoma. Very rarely, the cause of the hyperthyroidism is a TSH secreting tumour. The persistent finding of hyperthyroid symptoms and elevated thyroid hormones is consistent with the diagnosis once the common problems of assay interference or non-thyroidal illness have been eliminated.
- End organ resistance. Certain patients with end organ resistance to thyroid hormones may present with abnormal thyroid function tests. Some may have high concentrations of thyroid hormone but normal TSH and others will have raised TSH with normal thyroid hormones.
"Non-thyroidal illnesses" and the "sick euthyroid syndrome" Patients suffering from any of a wide range of chronic or acute non-thyroidal illnesses, may show abnormalities in thyroid function tests even though they are clinically euthyroid. This has been described as the "sick euthyroid syndrome". In the majority of these sick patients TSH will be normal and thus provide the best guide of thyroid status. However in some patients, TSH concentrations may be suppressed in the acute phase and on recovery TSH concentrations may rise transiently into the hypothyroid range. Total T3 and FT3 concentrations usually fall as a result of impaired tissue uptake of T4 and impaired conversion of T4 to T3. However using ultrafiltration or some commercial assays FT3 may be normal or sometimes raised. Illness modifies both the concentration and binding capacity of the plasma thyroid hormone binding proteins which in turn tends to diminish the total thyroid hormone concentrations and raise the FT4 hormone fraction. The contribution of each of the above mechanisms may vary with the severity and stage of the illness and thus the pattern of thyroid function tests may be extremely variable and may mimic the profile seen in primary or secondary thyroid disorders

- In hospitalised patients a TSH <0.10 mU/L is at least twice as likely to be due to non-thyroidal illness as hyperthyroidism.
- In hospitalised patients an increased TSH is as likely to be associated with recovery from illness as hypothyroidism.
- Because of the poor predictive value of thyroid function tests in hospitalized patients, these tests should only be requested if there is a clinical reason for suspecting a thyroid problem.
- Additional investigations such as FT3 may point strongly to non-thyroidal illness as a cause of the abnormal results. A repeat sample may show that the abnormal results have been transient and attributable to an acute illness or a specific treatment regimen.
- Although these procedures may clarify the cause of abnormal thyroid function tests for some patients, clinical assessment by an endocrinologist may be indicated.

Drug treatment.

- Drugs may interfere with TSH secretion or the production, secretion, transport and metabolism of thyroid hormones. Some drugs modify thyroid status whilst others produce abnormal thyroid function test results in otherwise euthyroid subjects. In general, serum TSH is less affected by medication than thyroid hormones, although glucocorticoids and dopamine in high doses inhibit TSH release.
- Certain agents will impair the absorption of thyroxine from the gut and patients on thyroxine therapy should be advised to take their thyroxine at least 4 hours apart from these medications. Patients taking thyroxine are likely to require an increase in replacement dose if drugs such as phenytoin or carbamazepine are prescribed that increase hepatic metabolism of T4. Propranolol may decrease TT3 and increase TSH. Phenytoin, carbamazepine, frusemide and salicylate compete with thyroid hormone binding to serum binding proteins and may increase FT4. In vivo administration of heparin liberates free fatty acids, which displace thyroid hormones from their binding proteins and also increase FT4.
- Similarly the use of some cytokines such as interferon alpha for the treatment of chronic hepatitis C can induce hypothyroidism or hyperthyroidism.
- Certain drugs interfere with thyroid hormone absorption from the GI tract e.g. ferrous sulphate, cholestyramine, cholestapol, and aluminium hydroxide.
Patients taking thyroxine should be advised against taking these drugs until at least 4 hours after taking thyroxine.

- The dose of thyroxine may have to be increased in patients who are taking drugs that increase thyroid hormone metabolism. For example anticonvulsants induce drug metabolising enzymes

Lithium and Amiodarone

- Lithium can cause hypothyroidism and hyperthyroidism in up to 10% of patients. Patients with positive TPOAb are particularly at risk. Patients taking lithium should have their TFT measured at 6-12 month intervals or earlier if goiter develops.
- The anti-arrhythmic drug amiodarone is an iodine-containing drug that has complex effects on thyroid metabolism. These include inhibition of T4 to T3 conversion, inhibition of thyroidal iodine uptake and inhibition of T4 entry into cells. The drug may also induce a destructive thyroiditis. Patients may have an altered thyroid hormone profile without thyroid dysfunction but 14%-18% of patients taking amiodarone may develop clinically significant hypothyroidism or amiodarone induced thyrotoxicosis. Because of the long half-life of amiodarone, clinical problems may occur up to a year after stopping the drug.
- Euthyroid subjects taking amiodarone for more than three months frequently have increased FT4, decreased FT3 but normal TSH. During the first three months of treatment, however, TSH may increase transiently (up to 20 mU/L) particularly in patients receiving higher doses of amiodarone.
- It is important to evaluate patients before they commence therapy with amiodarone. This should include clinical examination and a basal measurement of TSH and TPOAb, together with FT4 and FT3 if TSH is abnormal. After starting treatment these tests should be repeated at 6 months and thereafter every six months including the year after the drug is stopped
<table>
<thead>
<tr>
<th>Decrease in TSH Secretion</th>
<th>Decreased Thyroid Hormone Secretion</th>
<th>Increased thyroid Hormone secretion</th>
<th>Decreased thyroidal synthesis*</th>
<th>Displacement of Hormone from Plasma Proteins</th>
<th>Impaired T4 to T3 Conversion</th>
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<tbody>
<tr>
<td>Dopamine, Dopaminergic agents</td>
<td>Lithium, Iodide, Amiodarone</td>
<td>Iodide, Amiodarone, Lithium (xen)</td>
<td>Mechimazol, Carbimazole, Propylthiouracil, Lithium</td>
<td>Frusemide, Penicillin, Salicylates, Mefenamic acid, Carbamazepine, Non-steroidal AIDs</td>
<td>Beta antagonists, Glucocorticoids, Amiodarone, Propylthiouracil, Iodinated dyes</td>
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<tr>
<th>Increase TBG, TT3, TT4</th>
<th>Decrease TBG, TT3, TT4</th>
<th>Increased Hepatic Metabolism of T4</th>
<th>Impaired Absorption of Thyroxine **</th>
<th>Alter autoimmunity***</th>
<th>Modify Thyroid Hormone Action</th>
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<tr>
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*Drugs listed as causing a decrease in thyroid hormone synthesis or secretion thus leading to altered thyroid status.

** Drugs interfere with thyroid hormone absorption from the GI tract. Patients on thyroidine therapy should be advised to take their thyroxine at least 4 hours apart from these medications.

***Treatment with these cytokines have been associated with cases of transient hypothyroidism and thyrotoxicosis. These usually resolve several months after treatment is stopped. The mechanism is unclear but the changes may be autoimmune.

The other drugs listed are thought to produce abnormal thyroid function tests but patients maintain a euthyroid status. Amiodarone is an exception (see main text).