GUIDELINES FOR THYROID FUNCTION TESTING

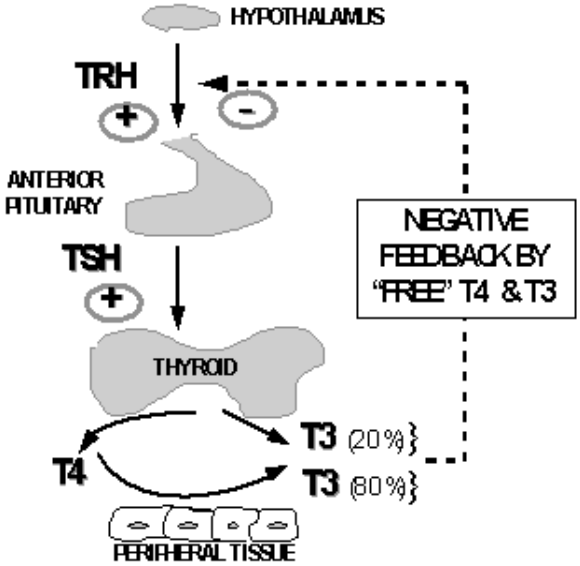
INTRODUCTION

These guidelines outline a thyroid testing strategy that has been developed to accomplish several objectives:-

- Guide appropriate and efficient diagnosis of suspected thyroid disease, especially for the non-endocrinologist.
- Improve turnaround time to diagnosis
- Reduce costs by avoiding unnecessary testing.

TSH and Free T4 will be measured on all requests for thyroid function. Free T3 will also be available on a limited basis.

THYROID HORMONE PHYSIOLOGY



Inhibition of peripheral conversion of T4 to T3 can be caused by:-

- Acute non-thyroidal illness
- Ageing or Fasting
- Drug administration (e.g. propranolol, amiodarone, propylthiouracil)

REQUESTING THYROID FUNCTION TESTS

In order for appropriate tests and any necessary follow up or guidance to be provided it is important that all relevant clinical details are written on the request form. Of particular importance is whether the thyroid investigations are for:

- diagnosis of thyroid disease or
- monitoring of treatment for either hypo or hyperthyroidism
- details of relevant drug therapy (e.g. thyroxine, carbimazole, amiodarone)
- investigation of suspected pituitary disease

To help with provision of clinical details, request forms include several tick boxes for thyroid function tests (please tick one only!):

- ?Thyroid disease
- On thyroxine
- On anti-thyroid Rx

COMMENTS ON REPORT FORMS

A number of interpretative comments appear on thyroid reports and are intended to offer advice on further investigations, appropriate follow-up or treatment. The comments are intended for non-endocrinologists and we would welcome feedback on their usefulness.

REFERENCE RANGES: Adults (without non-thyroidal illness)

TSH	0.3-5 mU/L
Free T4	7.9-16 pmol/L
Free T3	3.8-6.0 pmol/L

DIAGNOSIS OF THYROID DISEASE

Hypothyroidism

TSH is the most sensitive test for diagnosis of primary hypothyroidism and a normal level excludes functional thyroid disease. TSH levels may be normal in secondary hypothyroidism (pituitary disease) and it is important that Free T4 is measured in these cases. Whilst TSH and Free T4 are currently measured as a first line TFT, please ensure that suspected hypopituitarism is included in the clinical details on the request form.

A **Normal Free T4** level with an elevated TSH indicates subclinical hypothyroidism. Thyroid antibodies are indicated in this group of patients and if positive are a strong indicator for replacement therapy Subclinical hypothyroidism with positive TPO antibodies should be monitored on a yearly basis for progression to overt hypothyroidism. Subclinical hypothyroidism with negative TPO antibodies can be monitored 3-yearly. TSH levels above 10mU/L usually indicate hypothyroidism and the need for replacement therapy.

Hyperthyroidism

TSH is the most useful screening test for hyperthyroid disease in most non-critically ill patients and is almost always suppressed (<0.01 mU/L). Free T4 is raised in overt hyperthyroidism.

A **Normal Free T4** level with a low TSH may be found in early hyperthyroid disease (T3 toxicosis). In this situation a Free T3 will be analysed. If this is normal despite a low TSH, subclinical hyperthyroidism is likely.

Non-Thyroidal Illness

Some euthyroid patients with non-thyroidal illness (NTI) develop low TSH levels overlapping the hyperthyroid range - 'sick euthyroid syndrome.' Modest increases in TSH may also be seen during recovery.

Screening of patients on admission to hospital is not recommended unless there is a suspicion of thyroid disease. In patients with acute non-thyroidal illness a TSH of 0.1 to 10.0 mU/L may be due to the effects of the illness and TFTs should be repeated when patient has recovered. TSH levels between 10 and 20 mU/L should be interpreted with caution. If the patient is frankly hypothyroid TSH will still be grossly raised (> 20mU/L) but diagnosis of thyrotoxicosis in the sick patient can be difficult.

TESTS AVAILABLE FOR ASSESSMENT OF THYROID FUNCTION

TSH

Assays for TSH are sensitive enough to distinguish between normal TSH levels and suppressed levels found in

hyperthyroid disease. TSH levels are high (usually >20mU/l) in primary hypothyroidism and are raised in early disease before T4 levels fall below the reference range.

TSH will be measured in all requests for thyroid function

Free T4

Thyroid hormones circulate mostly bound to proteins and thus total hormone levels are influenced by levels of these binding proteins. Therefore we use assays that measure the free active hormone.

Free T4 will be measured all requests for thyroid function

Free T3

Free T3 is of no use in diagnosis of hypothyroidism since normal levels are maintained during early disease.

Although Free T3 rises earlier in hyperthyroidism than Free T4 and is thus a more sensitive test, levels are particularly susceptible to non-thyroidal influences which alter peripheral T4 to T3 conversion.

The primary use of Free T3 will be to help in the differential diagnosis of hyperthyroidism and non-thyroidal illness where TSH levels may also be low, although there is considerable overlap.

Free T3 will be measured in the following circumstances:-

- TSH level is below 0.1mU/L
- Patient is on T3 replacement therapy
- Specifically requested by Consultant / GP.
- Where TSH is within the reference range and FT4 is borderline low – to confirm euthyroid status.

Thyroid Antibodies (peroxidase)

Thyroid antibodies are useful to demonstrate the presence of autoimmune thyroid disease, especially in patients with 'Subclinical Hypothyroidism'. Thyroid antibodies will be recommended where subclinical hypothyroidism is suspected, and can be used to determine frequency of TFT monitoring in such patients.

Thyroid antibody levels do not correlate with degree of thyroid disease and cannot be used to monitor therapy. Negative antibodies do not exclude hypothyroidism.

MONITORING OF THYROXINE REPLACEMENT

Clinical symptoms and TSH are the major parameters used in assessing adequacy of replacement therapy. Following changes in thyroxine dosage, TSH levels take 4-6 weeks to stabilize. Thus, repeat thyroid function tests should only be performed after this period.

Free T4 can be used as an index of recent patient compliance and is necessary to monitor adequacy of treatment in secondary hypothyroidism.

TSH levels in thyroxine replacement therapy for primary hypothyroidism:-

- <0.01 mU/L Indicates over replacement which may be associated with higher risk of osteoporosis and AF especially in older patients.
- 0.01-0.26 mU/L Indicates possible over replacement. Free T4 levels above 30 pmol/L are consistent with over replacement
- 0.27-4.2 mU/L Adequate replacement

- >4.2 mU/L Likely under replacement or non-compliance. High Free T4 levels may be associated with erratic patient compliance or recent dose adjustment (<4 weeks).

SUGGESTED MONITORING REGIME FOR THYROXINE REPLACEMENT

N.B. TFT should only be repeated 4-6 weeks after alteration of thyroxine dose.

- **Newly commenced:** Measure TFT ~6-8 weeks post commencement of thyroxine therapy and adjust dose accordingly to normalise TSH. Repeat TSH ~6 months after normalisation of TSH.
- **On thyroxine:** Repeat TFT annually unless earlier measurement is indicated clinically.

MONITORING ANTI-THYROID TREATMENT

THIOUREA DERIVATIVES (Carbimazole, Propylthiouracil)

Carbimazole may be given either as a reducing dose, titrating treatment against serum Free T4 levels or as a continuing high dose with thyroxine replacement - "block-replace" regime.

N.B. TSH levels are unhelpful in the early stages (first 3 months) of Thiourea treatment since levels may remain low due to prolonged suppression of the pituitary.

Carbimazole - Titrating Treatment

- Initially, check TFTs (TSH and Free T4) every 4-6 weeks until a maintenance dose of Carbimazole is achieved.
- Once maintenance dose is achieved, TFT measurement may be extended to 3 monthly intervals.
- A rise in TSH above normal indicates iatrogenic hypothyroidism and a need for dose reduction.

Carbimazole - Block and Replace Regime

- Initially, check TFTs every 4-6 weeks until euthyroidism is achieved.
- Measure TFT ~6-8 weeks post commencement of thyroxine therapy and adjust dose accordingly to normalise TSH. (N.B. wait 4-6 weeks after alteration of thyroxine dose before repeating TFTs).
- Repeat TFT annually unless earlier measurement is indicated clinically.

RADIOIODINE TREATMENT

- TFTs should be assessed 4-8 weeks after radioiodine treatment. It may take up to 6 months for the full effect of RAI to be apparent.
- Long term follow-up of TFTs should be at intervals of 6-12 months. Longer intervals are recommended only for patients with stable disease.

POST THYROIDECTOMY

- TFTs should be assessed around 4 weeks postoperatively, then at 3 monthly intervals up to 1 year.
- Long term follow-up of TFTs should be at intervals of 12 months.

DRUG INTERACTIONS

Amiodarone

Amiodarone is the most complex and difficult drug that affects thyroid status, sometimes with poor correlation between circulating thyroid hormone levels and clinical severity. Amiodarone may cause hypo or hyperthyroidism:-

- Amiodarone reduces peripheral conversion of T4 to T3 resulting in raised TSH and Free T4 levels.
- Amiodarone contains a considerable iodide load which may on its own cause hyperthyroidism, although this is less common.
- Combination of reduced peripheral conversion of T4 to T3 together with iodide induced stimulation of the thyroid produces biochemical changes that are difficult to interpret.

It is recommended that basal thyroid function tests are checked before commencing amiodarone therapy and assessment of thyroid function during treatment be primarily based on careful clinical evaluation. The long half-life of the drug means that changes in thyroid tests may persist for some time after ceasing therapy.

Lithium

Lithium has multiple effects on the pituitary-thyroid axis, the most important being inhibition of hormone release. Lithium can exacerbate autoimmune thyroid disease with development of goitre and eventual hypothyroidism. Serum TSH, free T4 and free T3 assays generally give a true index of thyroid status during lithium treatment.

Phenytoin

Phenytoin commonly results in apparent lowering of free T4, not accompanied by anticipated increase in TSH. Such findings are hard to distinguish from central hypothyroidism due to pituitary deficiency.

METHODOLIGICAL INTERFERENCES

All assays may be susceptible to a number of analytical artefacts but free hormone assays tend to be less robust than TSH assays. For example, some patients may have antibodies against T4 and/or T3 which interfere with our Free T4 and T3 assays causing artifactually high results. Another possible interference with our in-house assays is biotin supplementation.

We will endeavour to identify discrepancies which may be due to analytical interference (e.g. unsuppressed TSH (>0.01 mU/L) with a raised Free T4 in an untreated patient) and investigate further.

SOME CAUSES OF TSH/FT4 DISCREPANCIES

Patient on Thyroxine

- Recent dose adjustment (TSH high, FT4 normal or high)
- Erratic compliance (TSH high, FT4 normal or high)

Other

- Non Thyroidal Illness (TSH low or may be high during recovery, Free T4 low or normal)
- Thyroid Hormone Resistance (TSH high, Free T4 high, patient euthyroid): very rare
- TSH secreting tumour (TSH high, Free T4 high, patient hyperthyroid): very rare
- Assay interference

REFERENCES

UK Guidelines for the Use of Thyroid Function Tests
http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf/

Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society.
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