

Adapted Summary of

**UK Guidelines for the Use of Thyroid Function
Tests
(July 2006)**

Introduction

The Use of Thyroid Function Tests Guidelines Development Group was formed in 2002 under the auspices of the Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF). The purpose of the guidelines is to encourage a greater understanding of thyroid function testing amongst all stakeholders with a view to the widespread adoption of harmonised good practice in the diagnosis and management of patients with thyroid disorders. This summary is adapted from the July 2006 guidelines.

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Indications for thyroid function testing

Thyroid dysfunction is common. In the UK, the prevalence of spontaneous hypothyroidism is between 1% and 2%, and it is more common in older women and ten times more common in women than in men. Approximately 10% of subjects over 60-years old have serum TSH values above the normal range – so called ‘subclinical hypothyroidism’. The prevalence of thyrotoxicosis in women is between 0.5 and 2%, and it is also ten times more common in women than in men.

The Normal Healthy Adult Population, Including the Elderly: The ageing UK population and the introduction of the General Medical Services contract are providing GPs with more opportunity to consider thyroid dysfunction in the normal community, especially in elderly subjects with few or no symptoms of thyroid disease.

The prevalence of unsuspected overt thyroid disease is low, but a substantial proportion of subjects tested will have evidence of thyroid dysfunction, usually subclinical hypothyroidism. For more information on the recommended follow-up of patients with subclinical hypothyroidism, please refer to the relevant section in the ‘Hypothyroidism’ chapter.

- *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.*

Hospital In-Patients: Isolated alterations in serum TSH concentrations (either slightly low 0.10-0.30 mU/L or high 5-20 mU/L) occur in about 15% of such patients due to altered TSH secretion in response to non-thyroidal illness or drugs.

About 2-3% of hospitalized patients have serum TSH concentrations that are fully suppressed (<0.10mU/L) or significantly elevated (>20mU/L) but less than half will have an underlying thyroid disorder. An accurate diagnosis can be achieved if clinical indications for measuring thyroid function exist.

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

Goitre and Thyroid Nodules: Testing of thyroid function should be performed as part of the routine assessment of all patients who present with a suspected goitre (diffuse, multi-nodular or single nodule) at presentation to detect clinically unapparent hypothyroidism or hyperthyroidism.

- *Serum TSH should be measured in all patients with suspected goitre.*

Atrial fibrillation, Hyperlipidaemia, Osteoporosis, Subfertility: Thyrotoxicosis is a recognised cause of atrial fibrillation and a potentially correctable cause of osteoporosis. Hypothyroidism is a recognised secondary cause of dyslipidaemia. Both thyrotoxicosis and hypothyroidism can cause menstrual abnormalities and subfertility.

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

Patients with Diabetes: There is a high frequency of asymptomatic thyroid dysfunction in unselected patients with type-1 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.*

Women with Type 1 Diabetes: Women with type 1 diabetes are three-times more likely to develop postpartum thyroid dysfunction.

- *Women with type 1 diabetes should have TSH, FT4 and TPO antibody status checked pre-conception, at booking when pregnant and at 3 months post-partum.*

Past History of Post-partum Thyroiditis: Women with a past history of postpartum thyroiditis have a risk of long-term risk of permanent hypothyroidism and recurrence in subsequent pregnancies.

- *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 Receiving Amiodarone and Lithium: Amiodarone contains 75mg iodine per 200mg tablet and is frequently associated with thyroid dysfunction. Amiodarone-induced hyperthyroidism is particularly prevalent (10%) in areas of iodine-deficiency and in patients with underlying thyroid disease. Amiodarone-associated hyperthyroidism should be diagnosed only if high circulating FT4 is associated with high or high/normal FT3 and undetectable TSH since even in euthyroid subjects amiodarone therapy often causes modest elevation in serum FT4 (and reduction in FT3) because of its effect on peripheral deiodination of T4 to T3. A diagnosis of amiodarone-associated hyperthyroidism should prompt specialist referral since management may be complex and involve further investigations. Amiodarone-induced hypothyroidism is more common in iodine-replete communities (up to 20%) and related to the presence of thyroid autoimmunity.

Lithium use is associated with mild and overt hypothyroidism in up to 34% and 15% of patients respectively, and can appear abruptly even after many years of treatment. Lithium-associated thyrotoxicosis is rare and occurs mainly after long-term use.

- *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.*
- *Particular care is required in the diagnosis of hyperthyroidism in patients taking amiodarone. The measurement of TSH, FT4 and FT3 is required.*

- *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: The incidence of hypothyroidism after surgery, external radiation therapy of the neck, or both, in patients with head and neck cancer (including lymphoma) is as high as 50% within the first year after treatment.

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

Down's Syndrome & Turner's Syndrome: The incidence of hypothyroidism in patients with Down's Syndrome or Turner's Syndrome is high.

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

Hypothyroidism

PRIMARY HYPOTHYROIDISM

Diagnosis: Hypothyroidism is associated with a number of classical symptoms and signs. Patients with severe hypothyroidism may exhibit several of these clinical features, however, many patients with milder forms of the disease exhibit few clinical features and some will exhibit none. This is especially true of the elderly. Many symptoms of hypothyroidism are not specific for the disease and therefore hypothyroidism cannot be diagnosed accurately on symptoms alone.

The diagnosis of hypothyroidism requires abnormal TFT results. A TSH greater than 10 mU/L combined with a FT4 below the reference range indicates the presence of overt primary hypothyroidism in ambulant subjects.

- *The diagnosis of primary hypothyroidism requires the measurement of both TSH and FT4.*
- *Subjects with a TSH of >10 mU/L and FT4 below the reference range have overt primary hypothyroidism and should be treated with thyroid hormone replacement.*

Guiding Treatment with Thyroxine: In the majority of patients 50-100 µg thyroxine can be used as the starting dose. Alterations in dose are achieved by using 25-50 µg increments and adequacy of the new dose can be confirmed by repeat measurement of TSH after 2-3 months. The majority of patients will be clinically euthyroid with a 'normal' TSH and having thyroxine replacement in the range 75-150 µg/day (1.6ug/Kg on average).

The recommended approach is to titrate thyroxine therapy against the TSH concentration whilst assessing clinical well-being. The target is a serum TSH within the reference range. Serum FT4 test results can vary immediately following the daily dose of thyroxine, but this is not clinically significant. The ratio of FT4 to FT3 is usually increased in patient taking thyroxine. FT4 concentrations may exceed euthyroid reference range when the TSH is normal whereas FT3 remains within or closer to the reference range.

- *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.*

Once hypothyroidism has been diagnosed and the appropriate dose of thyroxine has been established, the dose remains constant in many patients. Dose requirements may increase if patients are given drugs which decrease thyroxine absorption, such as cholestyramine and iron salts, or increase its clearance, such as phenytoin and carbamazepine.

- *Once thyroxine replacement is initiated 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.*

Guiding Treatment with Tri-iodothyronine: If tri-iodothyronine is used as a replacement hormone increasing doses should be used until serum TSH is within the reference range. 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.

Assessing Response to Therapy: Most patients taking thyroxine will feel well when the serum TSH is maintained within the reference range. Suppression of TSH may result in cardiac problems or bone loss. Therefore, in patients receiving maintenance thyroxine therapy who have TSH values below the reference range it is recommended that a reduction in thyroxine dose is made to bring the TSH within the reference range. Some patients on long term standard replacement doses of thyroxine report an apparent psychological benefit and general feeling of well being when TSH is undetectable. However even in these patients it is still recommended that the dose should be reduced until the TSH is within the reference range. Gradually decreasing the dose by 25µg increments may make this possible.

- *The optimal dose of thyroxine for long-term therapy is assessed from the results of thyroid function tests together with clinical findings.*
- *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: Once stabilised on thyroxine all patients should have their serum TSH checked annually as a change in requirement for thyroid hormone can occur with ageing.

SUBCLINICAL HYPOTHYROIDISM

Diagnosis: Subclinical (mild) hypothyroidism is characterised by a 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, after excluding non-thyroidal illness and drug interference.*

Upon repeat testing:

- *If the serum TSH is greater than 10 mU/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 10 mU/L, then treatment with thyroxine is recommended.*

- *If the serum TSH concentration is above the reference range but <10 mU/L, then serum thyroid peroxidase antibodies (TPO Abs) should be measured.*
- *Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody positive should have an annual thyroid function tests, or earlier if symptoms develop. Thyroxine therapy should be started if the serum TSH concentration rises above 10 mU/L.*
- *Subjects with subclinical hypothyroidism who are thyroid peroxidase antibody negative should have repeat thyroid function testing approximately every 3 years.*
- *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 <10 mU/L. Physicians may wish to consider the suitability of a therapeutic trial of thyroxine on an individual patient basis.*

Guiding Treatment: The decision to treat patients with subclinical hypothyroidism should be guided by repeated TSH measurements. Factors that may prompt thyroxine therapy in a patient with subclinical hypothyroidism include pregnancy, goitre, or a rising TSH level.

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

Assessing response to therapy: The aim of treatment should be to restore and maintain TSH within the reference range. Thyroxine should be given in doses increasing by 25-50µg daily titrated to bring the TSH within the reference range. TSH should be measured 2-3 months following a change in thyroxine dose.

Long-term Follow-up:

The requirement for thyroxine can increase in patients treated for subclinical hypothyroidism as they may develop overt hypothyroidism. TSH should be measured annually and the thyroxine dose altered to maintain TSH within the reference range.

In patients who do not receive thyroxine it is recommended that regular measurement of TSH and FT4 be performed to detect those patients who may develop overt hypothyroidism. Measurement of TPO Abs can be used to determine the appropriate frequency of follow-up, as outlined previously.

SECONDARY HYPOTHYROIDISM

Diagnosis: The biochemical diagnosis of secondary hypothyroidism 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 FT4 measurement is suggestive of secondary hypothyroidism.

Measurement of FT3 may be required to differentiate secondary hypothyroidism from non-thyroidal illness especially in older patients where symptoms are often vague and non-specific.

Patients suspected of having secondary hypothyroidism may require referral to an endocrinologist to accurately make the diagnosis and for additional pituitary function tests (PRL, FSH, LH, ACTH/cortisol). Tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism.

- *Measurement of TSH and FT4 is required to identify 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: Patients with secondary hypothyroidism usually also be deficient in other anterior pituitary hormones and the degree of hypopituitarism must be established before commencing thyroxine replacement. In particular thyroid hormone replacement should not be commenced in patients with cortisol deficiency as this could provoke an Addisonian crisis. Glucocorticoid replacement should be started prior to the initiation of thyroxine therapy.

Thyroxine should be given in increasing 25 µg doses and optimised such that the thyroid hormone concentration is within the upper third of the reference range.

- *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: Measurement of TSH cannot be used in to assess the response to therapy in patients with hypopituitarism and it is essential to monitor treatment by measuring FT4. The optimal FT4 concentration is within the reference range and ideally within the upper third of the reference range.

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.

Hyperthyroidism

PRIMARY HYPERTHYROIDISM

Diagnosis: It is essential that any clinical suspicion of thyrotoxicosis is confirmed or refuted by biochemical testing before further investigation or treatment is contemplated.

In most cases of hyperthyroidism a typical biochemical picture of elevated FT4 and FT3 with associated undetectable serum TSH will be evident. If FT4 is clearly elevated, then a diagnosis of thyrotoxicosis is confirmed. If FT4 is not above the reference range in a patient with low serum TSH, FT3 should be measured since in some cases the biochemistry indicates a diagnosis of "T3-toxicosis" characterised by elevation of serum FT3 in the absence of a rise in FT4. If FT3 is not increased despite an elevation of FT4 and suppression of TSH in a patient thought clinically to have thyrotoxicosis, the lack of rise in FT3 may reflect the presence of "non-thyroidal illness".

A serum TSH concentration within the reference range effectively rules out a diagnosis of hyperthyroidism. Exceptions to this rule are rare TSH-dependent causes of hyperthyroidism, such as TSH-producing tumours of the pituitary and syndromes of thyroid hormone resistance, (see section on Inappropriate TSH).

- *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.*

Once a biochemical diagnosis of hyperthyroidism has been made specialist referral should be sought. Most cases of hyperthyroidism in the UK are due to Graves' disease or toxic nodular goitre. The cause will usually be evident from the clinical picture and further investigations to differentiate between Graves' hyperthyroidism and toxic nodular hyperthyroidism are not essential, unless it will affect the treatment plan.

The presence of TPO Abs is suggestive, but not diagnostic, of Graves' disease. The presence of TSH-receptor antibodies (TSH-R Ab) is a more specific indicator of the diagnosis. Thyroid auto-antibodies are usually negative in toxic nodular hyperthyroidism.

In some cases, other causes of hyperthyroidism should be considered, particularly the diagnosis of thyroiditis. "Sub-acute" thyroiditis is suspected if there is thyroid pain/tenderness, often with a history suggestive of a viral illness. The finding of a raised ESR is helpful in confirming the diagnosis. It is important to identify cases of thyroiditis since standard treatment with thionamides/radioiodine is ineffective and contraindicated. Thyroiditis is generally short-lived and self-limiting (and often followed by a hypothyroid phase).

- *Patients with confirmed hyperthyroidism should be referred for specialist care in order to establish the diagnosis and optimal management plan.*

- *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.*
- *It is important to identify cases of thyroiditis since standard treatment with thionamides/radioiodine is ineffective and contraindicated.*

Guiding Treatment: Patients with a confirmed biochemical diagnosis of hyperthyroidism should generally be commenced on a thionamide (carbimazole or propylthiouracil). These are used on a short-term basis for preparation for definitive treatment and on a medium-term basis in the hope of inducing remission. Occasionally they are used long-term in patients in whom definitive treatment is contraindicated.

Most patients with hyperthyroidism require definitive treatment with ¹³¹Iodine. This reflects the low remission rate with thionamides alone in Graves' disease (<50%) and lack of curative effect of these drugs in toxic nodular hyperthyroidism. In severe clinical or biochemical disease thionamides should be administered (typically for 2-3 months) until the serum FT4 is normal or near normal prior to ¹³¹Iodine therapy. All patients proceeding to surgery should also be rendered euthyroid (normal FT4 and FT3) with thionamides.

- *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:

- Treatment of Thyrotoxicosis with Anti-Thyroid Drugs (thionamides):** Anti-thyroid drugs decrease thyroid hormone secretion and are used in the management of thyrotoxicosis. In patients being treated with thionamides, regular measurement of FT4 and TSH is essential in order to adjust drug doses to allow control of disease and avoidance of iatrogenic hypothyroidism. drug doses should be titrated against measurements of FT4 (or FT3 in cases of T3-toxicosis) as TSH main remain suppressed for week to months.

A fall in FT4 to low normal or to below the normal range should prompt reduction in thionamide dosage. A rise in serum TSH also indicates the development of hypothyroidism and the need for dose reduction. Persistent suppression of serum TSH should not, in itself, prompt an increase in thionamide dose. Persistent elevation in serum FT4 despite apparent adequate prescription of thionamides usually indicates poor compliance. Persistent biochemical hyperthyroidism after weeks to months of therapy makes induction of remission in cases of Graves' disease very unlikely.

- *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.*
- *It is recommended that thyroid function is tested every 1-3 months when initiating anti-thyroid drug therapy until stable.*

- *Thyroid function tests should be performed every 4-6 weeks thereafter.*
- *The frequency of testing should be reduced to every ~3 months once a maintenance dose is achieved.*

b. Treatment of Thyrotoxicosis with Radio-Iodine: Serum FT4 and TSH should be checked every 4-6 weeks for several months after administration of ¹³¹Iodine. Suppression of serum TSH may persist for weeks-months after treatment. In patients not also receiving thionamides, a mild and transient rise in serum TSH may be observed in the first 6 months after ¹³¹Iodine and does not necessarily indicate the need for commencement of thyroxine replacement therapy. A more marked or persistent rise in serum TSH (>20 mU/L for more than one month), especially if associated with symptoms, should prompt thyroxine prescription. Persistent elevation of FT4 six months after radioiodine therapy indicates lack of cure and need for consideration of re-dosing.

- *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: All patients who have received radioiodine therapy for hyperthyroidism or surgery (partial thyroidectomy) require life-long follow-up to identify development of hypothyroidism. TFTs should be performed every 12 months. Regular TFTs should also be undertaken in any patient treated long-term with thionamides (testing every 6-12 months).

SUBCLINICAL HYPERTHYROIDISM

Diagnosis: This is essentially a biochemical diagnosis based on the finding of low serum TSH in association with normal serum concentrations of FT4 and FT3. Clinical symptoms and signs are typically absent or mild/non-specific.

It should be noted that a low serum TSH (especially if reduced but >0.1mU/L) can reflect 'non-thyroidal illness' and various drug therapies. This is a frequent finding in hospitalised patients. In primary care a serum TSH of <0.1mU/L is more likely to indicate mild thyroid hormone excess.

Guiding Treatment/Follow-up: The finding of a low serum TSH should prompt consideration of the cause. Non-thyroidal illness and relevant drug therapies should be excluded first and the diagnosis confirmed by repeat TFTs. Growing evidence suggests subclinical hyperthyroidism in elderly subjects is associated with increased risk of development of atrial fibrillation and increased vascular mortality. Persistent subclinical hyperthyroidism should prompt specialist referral. Treatment with thionamides/¹³¹Iodine may be considered by the specialist.

- *Patients with subclinical hyperthyroidism that cannot be explained by non-thyroidal 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: This is a biochemical diagnosis in which elevation in circulating FT4 and/or FT3 is associated with an “inappropriately” detectable or elevated serum TSH concentration. An assay artefact/laboratory error should be considered first. Common explanations are binding protein abnormalities leading to apparent elevation of FT4 or antibody interference with measurements of FT4, FT3 or TSH, although these problems are assay dependent.

‘True’ causes of inappropriate TSH include a TSH-secreting pituitary tumour (TSH-oma) or a syndrome of thyroid hormone resistance. The finding of an elevated serum sex hormone binding globulin (SHBG) and circulating free alpha subunit may support the diagnosis of TSH-oma, as may the finding of hyper- or hypo-secretion of other pituitary hormones. A syndrome of thyroid hormone resistance can be confirmed by family history and sequencing of the beta thyroid hormone receptor.

- *The finding of an inappropriate TSH in the presence of elevated FT4 and/or FT3 should stimulate the laboratory to consider errors or assay artefact.*
- *Confirmation by repeat, including another assay is good practice.*
- *The measurement of serum SHBG, alpha subunit and other anterior pituitary hormones can help to distinguish TSH-oma from thyroid hormone resistance.*

Guiding Treatment: TSH-secreting pituitary tumours require treatment in a specialist centre. Therapy should be monitored by serial measurement of FT4, FT3 and TSH.

Patients with thyroid hormone resistance often require no therapy or only symptomatic treatment with beta adrenergic blocking agents. Treatment with radioiodine or thionamides is contraindicated.