GUIDELINES & PROTOCOLS
ADVISORY COMMITTEE

Thyroid Disease –Thyroid Function Tests in the Diagnosis and Monitoring of Adults

Effective Date: October 1, 2004

Scope

This guideline applies to the use of thyroid function tests for:
- the assessment of thyroid function in adults (individuals 19 years of age and over);
- monitoring of patients receiving thyroid hormone replacement therapy for hypothyroidism.

RECOMMENDATION 1 — Diagnosis of thyroid disease: asymptomatic adults

Thyroid function testing is not recommended in asymptomatic adults.

Note: In populations with a high prevalence of thyroid disease, testing may be indicated when non-specific signs and symptoms are present.

Patients at higher risk include those with:
- past history of thyroid disease
- goitre
- infertility/anovulation
- lipid disorders
- past history of neck irradiation
- other autoimmune disorders

Populations at higher risk include:
- women after menopause
- women who are within 6 weeks post-partum

RECOMMENDATION 2 — Diagnosis of thyroid disease: TSH

In most clinical situations (see Recommendation 3 for exceptions), TSH should be used as the initial test for investigation of thyroid disease.
- **If TSH is within the reference interval, no further testing is indicated** (repeat test only if there is a change in clinical condition)
- If TSH is abnormal, confirming the diagnosis with free T4 is indicated (laboratories retain specimens for 7 days in case add-on testing is required).

Note: Caution should be used when interpreting thyroid function tests in acutely ill or convalescent patients.

Recommendation 3 Special cases

The following patients require special consideration and may require consultation with a laboratory physician or clinician with expertise in thyroid disease:

- patients receiving suppressive doses of thyroxine for thyroid cancer or goitre responsive to suppressive therapies;
- patients who have had treatment for hyperthyroidism;
- patients with suspected pituitary or hypothalamic disease;
- patients taking medications that may alter thyroid function (e.g. lithium, amiodarone).
- patients with a past history of neck irradiation

Recommendation 4 Subclinical thyroid disease

Treatment for subclinical hypothyroidism is recommended when:

- TSH greater than 10 mU/L;
- TSH is above the upper reference interval limit, but ≤10 mU/L and any of the following present:
  - elevated thyroid peroxidase (TPO) antibodies
  - goitre
  - strong family history of autoimmune thyroid disease
  - past history of thyroid disease

Patients with subclinical hyperthyroidism (suppressed TSH and normal free T4) can be monitored with repeat thyroid function tests at a clinically appropriate interval. If a decision to treat has been made, treat to TSH within reference interval.

Note: Reference intervals may vary between laboratories. Results should be interpreted relative to the reference interval reported by the laboratory.

Recommendation 5 Thyroid disease in pregnancy

- There should be a high index of suspicion for thyroid disease during pregnancy.
- TSH may be suppressed as a normal finding within the first trimester of pregnancy. A normal free T4 generally excludes hyperthyroidism.
- For patients on thyroid replacement therapy, it is important to maintain TSH within the normal range prior to conception and during pregnancy.
- The dosage requirement for thyroxine replacement may increase during pregnancy. In patients on thyroxine replacement, measurement of TSH during each trimester is recommended.

Recommendation 6 Monitoring Thyroxine Replacement Therapy for Primary Hypothyroidism

When monitoring patients receiving thyroxine replacement therapy for primary hypothyroidism:

- TSH is the preferred test;
- TSH testing should be performed no sooner than 6-8 weeks after the start of treatment or a change in dosage;
- Once the appropriate dose is established, TSH testing should be performed annually. If TSH is within the reference interval, no adjustment is required. If TSH is below the reference interval, free T4 testing may be appropriate.
- Dosage adjustment should be considered if the TSH is suppressed. Subjects with a slightly reduced, but measurable TSH may continue replacement therapy at current dose if asymptomatic. Excess replacement does increase the risk of osteoporosis and arrhythmias, especially in elderly subjects.

Recommendation 7 **Other Tests**

Hyperthyroidism: Measurement of total T3 or free T3 in patients with suspected hyperthyroidism is rarely indicated. It should be reserved for situations where hyperthyroidism is suspected (suppressed TSH), but the free T4 is not elevated.

Hypothyroidism: Measurement of total T3 or free T3 is not indicated in hypothyroidism.

Free thyroid hormones: The more accurate free T4 and free T3 measurements have largely replaced measurements of total T4 and total T3 levels. Measurement of both free and total hormones is never indicated. Laboratories are permitted to substitute free hormone assays when total T3 or T4 have been ordered.

Rationale

Approximately $18.6 million was spent on thyroid function testing in British Columbia in 2001/2002. A review of TSH database information indicates that significant proportions of TSH tests are ordered more frequently than would appear clinically useful. The recommendations in this guideline are designed to reduce the costs associated with unnecessary and inappropriate thyroid function testing. To minimize unnecessary billings of these tests, physicians are also encouraged to check available medical records for recent test results and include laboratory information when patients are referred to another physician.

Asymptomatic vs mildly symptomatic patients

It may be difficult to distinguish between truly asymptomatic and mildly symptomatic adults. Considering the high prevalence of thyroid disease, particularly hypothyroidism in women, and the fact that some studies have shown that affected women may benefit from early treatment, the *Canadian Guide to Clinical Preventive Health Care*[1] recommends that clinicians maintain a high index of suspicion and investigate individuals with vague symptoms that could be related to thyroid dysfunction. If initial testing is normal, repeat testing should not be performed unless there is a change in clinical condition.

TSH values change slowly

Because TSH values change slowly,[2] frequent repeat testing is inappropriate. Following a change in a patient's clinical status or a change in replacement thyroxine dose, it is best to allow at least 6-8 weeks before measuring TSH level. This is sufficient for the TSH level to stabilize at a new baseline.

Pituitary secretion of TSH may be suppressed for prolonged periods following hyperthyroidism[2]

At least three months (longer in some patients) should be allowed before TSH assays are used following treatment of Grave's disease or other causes of hyperthyroidism. If a biochemical measurement of thyroid status is required during this time period, an assay of thyroid hormone (free T4 or total T4) is preferred.

Presence of pituitary disease

TSH is only useful as a measure of thyroid disease if the thyroid-pituitary axis is intact. Note, however, that pituitary dysfunction is an uncommon cause of hypothyroidism and hyperthyroidism. Free T4 may be preferred in patients with suspected pituitary or hypothalamic disease.

Unexpected results in thyroid function testing

These recommendations suggest a maximum frequency for TSH orders of once every 6-8 weeks for a patient whose thyroxine replacement therapy is being changed. Less frequent investigations are recommended in other situations.

There are some situations where more frequent biochemical assessments of thyroid function may be useful. Further evaluation may be appropriate, for example, when there is a discrepancy between the results of the initial thyroid function test and the patient's clinical findings. In most cases, repeating the same test is less useful than ordering a different test (e.g. if a TSH result does not appear to correlate with the patient's clinical status, it may be more appropriate to follow with a free T4). It is strongly recommended that an endocrinologist or a laboratory physician be consulted in such situations.

Thyroid Disease in Pregnancy

Research data support a possible connection between untreated maternal hypothyroidism and neuropsychological impairment in the offspring.[3-5] Neuropsychological impairment may occur even when hypothyroidism is mild and no obvious clinical symptoms are present. For women known to be hypothyroid, adequate dosing of thyroid replacement hormone during pregnancy should be maintained. Most women require increased doses of thyroid replacement hormones during pregnancy to maintain TSH within the reference interval.[6]

Post-partum thyroiditis may occur in 5-10% of women. This disease is often mild and transient. The disorder may present as hyperthyroidism followed by hypothyroidism and subsequent recovery of normal thyroid function. Some women may present with hypothyroidism without a hyperthyroid interval. It is important to note that there is an increased incidence of Grave's disease in the post-partum interval and not all hyperthyroidism is post-partum thyroiditis. There is a significant risk for recurrent post-partum thyroiditis after subsequent pregnancies. Post-partum thyroiditis is an automimmune disorder and the presence of anti-TPO antibodies increases the risk of disease. [7]

Subclinical Thyroid Disease

Typically patients with subclinical thyroid diseases are asymptomatic, but have abnormal thyroid test results (usually a TSH outside the reference interval and a free thyroxine within the reference interval).

Subclinical hypothyroidism is most commonly secondary to autoimmune thyroid disease or to under-replacement of thyroid hormones in hypothyroidism. It is usually asymptomatic. In one study,[8] the prevalence of subclinical hypothyroidism was 8%. Forty percent of these patients progressed to overt hypothyroidism over the subsequent 20 years. Treatment for subclinical hypothyroidism has the following potential benefits:

- improves patient well being
- avoids symptomatic hypothyroidism in the patients whose thyroid disease would progress
- treats patients whose children are at risk for neuro-psychological deficits due to hypothyroidism in pregnancy
- improves lipid profiles.

Treatment is recommended for those patients whose TSH is greater than 10 mU/L[9]. Treatment is individualized (observation or treatment) for those patients whose TSH is above the upper reference interval limit, but ≤10 mU/L and is generally given in the presence of positive antibodies, goitre or a strong family history. Other factors favouring treatment with thyroid replacement include:

- young age
- presence of bipolar disorder
- fertility problems
- children, adolescents, pregnant women and women contemplating pregnancy.

Subclinical hyperthyroidism is less common, with a prevalence of 0.6% -1.1%.[8]
In elderly patients (>60 y) with TSH <0.1 mU/L, the relative risk for atrial fibrillation increases threefold.[10,11] Post-menopausal women with endogenous or exogenous subclinical hyperthyroidism may have an increased rate of bone loss; however, studies to date have not demonstrated an

increased fracture rate[11]. Management of subclinical hyperthyroidism should be individualized. Patients with subclinical hyperthyroidism due to multi-nodular goitre or functioning adenoma are unlikely to normalize and are therefore more likely to benefit from treatment.

References

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Sponsors

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- to recommend actions that are sufficient and efficient, neither excessive nor deficient
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Guideline Administration and Audit Implications

Thyroid Function Tests in the Diagnosis and Monitoring of Adults with Thyroid Disease

Required documentation

For audit purposes, responsibility for ensuring sufficient documentation to demonstrate compliance with the recommendations in the protocol is as follows:

Ordering physicians

Physicians should document the reason for ordering the test (e.g. symptomatic patients, suspected noncompliance etc.) in the patient record and provide a written indication on the requisition when ordering thyroid function tests other than TSH.

Laboratory

The Standard Out-Patient Laboratory Requisition encourages compliance with the protocol by stating that thyroid tests other than TSH require a written indication in the designated space.

Laboratories should do only one thyroid function test unless the additional test(s) are ordered and ONE of the following conditions exists

1. the TSH was abnormal.
2. the requisition indicates that the patient is a “special case”, e.g., on thyroid suppressive therapy or thyroid altering medications; has suspected pituitary or hypothalamic disease or treated hyperthyroidism; or a history of neck irradiation.
3. the ordering physician added the test(s) after review of the clinical findings and initial laboratory result(s) or after discussion with a laboratory physician.
   (The laboratory should store the specimen for seven calendar days to enable the physician to request additional testing.
4. the laboratory identifies a medical requirement not specified above (e.g. thyroid cancer treatment)

Laboratories should only perform fT3 in addition to fT4 and TSH if the TSH was abnormal but the free T4 is not elevated and there is suspected hyperthyroidism.

Laboratories should store the patient’s serum for seven days to enable the physician to request additional testing. Suspected hyperthyroidism (or its diagnostic equivalent) must be indicated on the requisition in order for the laboratory to perform total T3 or free T3.

General Notes:

a) The laboratory may know some “special cases” from previous testing.
b) Requests from Endocrinologists or specialists with a recognized practice in Endocrinology may be processed as ordered.
c) Laboratories may substitute free hormone assays when total T4 or T3 are ordered.

Thyroid Function Tests