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Position Statement

Subject: **Thyroid Function Testing for Adult Diagnosis and Monitoring**
Approval Date: July 2017
Review Date: July 2019
Review By: Chemical AC, Board of Directors
Number: 1/2017

Introduction:
This statement is intended to provide guidance for the use of thyroid function testing in the Australian and New Zealand context according to current available evidence.

Scope:
This statement covers testing for thyroid function in the adult population. It does not cover the use of thyroid function testing in neonatal screening or in pregnancy. It does not include testing in the context of thyroid cancer.

Background

Definitions:
Subclinical hypothyroidism: Asymptomatic condition where the individual has free T4 within the reference interval and TSH above the laboratory upper reference limit, in the absence of intercurrent illness.

Subclinical hyperthyroidism: Asymptomatic condition where the individual has free T4 within the reference interval and TSH below the lower limit of the laboratory reference interval, in the absence of intercurrent illness, drug effect or other identified cause.

Overt thyroid disease: when TSH and free T4 and/or free T3 fall outside the limits of the laboratory reference intervals, usually associated with symptomatic disease.

Apathetic hyperthyroidism: Older patients may lack hyperadrenergic symptoms or signs noted in younger patients; tremor, palpitations and heat intolerance may be absent. Patients could present with lethargy, muscle weakness and wasting, unexplained weight loss, cardiac arrhythmias, with absence of goitre or ocular changes.

Technical aspects:
TSH and free thyroid hormones are measured by immunoassay methods. Current thyroid hormone and antibody assays from different manufacturers do not provide completely comparable results at this time.

Reference intervals are derived from the statistical distribution of values in the general healthy population.

Immunoassay techniques are subject to interference. If disparity between clinical assessment and TFTs is identified, the investigating doctor should contact the laboratory and discuss. Additionally a range of medications can affect thyroid function tests, either by their effect on the tests alone, or by their direct effects on thyroid function. The most common are: high dose glucocorticoids, dopamine and dobutamine (measured TSH reduced without thyroid disease), amiodarone (changes in test results and thyroid disease), lithium (can cause hypothyroidism),

iodine (hyper or hypothyroidism). A number of drugs can also change the requirements for thyroxine for patients under replacement. These include cholestyramine, phenobarbitone, carbamazepine, phenytoin, rifampicin and oestrogens.

In the presence of thyroid disease, TSH levels may vary over a 'logarithmic' range (five orders of magnitude) whereas the free thyroid hormones may vary over a 'linear' range (one order of magnitude). This should be borne in mind when interpreting TFT results especially with respect to changes that can occur in measured thyroid hormone levels in response to treatment (1).

Epidemiology:
Three studies provide information about the frequency of thyroid disease in the Australian population:

1. The Blue Mountains Eye study (2): Community cohort, age over 49 years. Prevalence of recognised thyroid disease (history of diagnosed thyroid disease or prescribed thyroxine) was 10%.
   Prevalence of an abnormal TSH was 5.6%.
   Prevalence of unrecognized thyroid disease was 3.6%.

2. The Busselton thyroid study (3): Cross-sectional community health survey of adult population.
   Prevalence of overt hypothyroidism was 0.54%.
   Prevalence of overt hyperthyroidism 0.1%.
   Prevalence of subclinical hypothyroidism was 5.1%.
   Prevalence of subclinical hyperthyroidism was 0.34%.
   Prevalence of positive thyroid autoantibodies was 12.4%.
   Prevalence of elevated TSH: 12.8% in women over 50 years and 3.6% in men over 50 years.

3. Tasmania: Hong et al (4) measured yearly incident abnormal TSH, encompassing periods before and following community iodine repletion which commenced in 2001. The incidence of TSH > 4.5 mU/L was 5.5% in 1999 and 3.8% in 2004. The incidence of TSH < 0.1 mU/L was 1.4% in 1999 and did not change following iodine repletion.

In summary, thyroid disease is highly prevalent, with a proportion of disease unrecognised. Prevalence increases with age and is greater in women (5).

Thyroid Function Testing: Diagnosis and monitoring of thyroid disease

Population screening:
The US Preventive Services Task Force (USPSTF) published a comprehensive evaluation of population screening for thyroid disease in 2015 (6). They found that *"the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant asymptomatic adults."* Evidence of benefit of screening for thyroid disease in reducing cardiovascular disease was considered insufficient. They found adequate evidence to conclude that screening for thyroid disease in asymptomatic adults does not improve quality of life or produce clinically meaningful improvements in BMI, BP, bone mineral density or lipid levels.

A proportion of individuals with subclinical hypothyroidism (up to 37%) will spontaneously revert to a euthyroid state without intervention after several years. The Blue Mountains study identified that 17.9% of those identified with subclinical hypothyroidism progressed to overt hypothyroidism over 5 years. The USPSTF guidelines stated that repeat testing should be followed over a 3-6 month interval following an abnormal test result, to rule out or confirm abnormal findings.

A double-blind randomised controlled trial of treatment for subclinical hypothyroidism in subjects

over the age of 65 years has been recently reported (7). This study found no benefit from thyroid replacement in subclinical hypothyroidism in participants aged > 65 years, with mean follow-up of 17.3 months. No improvement was found in a number of secondary outcome measures, including hand grip strength, BP, waist circumference or BMI. This report diminishes the chance that benefit will result in screening for subclinical hypothyroidism in this older age group, where subclinical hypothyroidism is more prevalent.

Screening in high risk subgroups:
Certain subgroups of the population are at higher risk of developing thyroid disease and active case identification is beneficial in these groups. These subgroups include individuals in areas of iodine deficiency, personal or family history of thyroid disease, ingestion of iodine containing substances including amiodarone, lithium treatment, previous neck irradiation, type 1 diabetes mellitus and other autoimmune diseases, Down syndrome, Turner's syndrome and advancing age. In some of these situations, including amiodarone treatment, lithium treatment, Down and Turner's syndrome, and history of neck irradiations, ongoing monitoring, on a 6-12 monthly basis, is required.

Investigation of symptomatic patients:
Patients presenting with symptoms, or clinical situations where thyroid dysfunction is suspected, should be investigated with thyroid function tests (8).

Symptoms that may indicate thyroid disease include: unexplained weight change, menstrual change, subfertility, goitre, focal thyroid nodule, temperature intolerance, depression and anxiety, constipation, palpitations and new onset atrial fibrillation, heart failure, osteoporosis, muscle weakness and lipid abnormalities.

Patients with nonspecific symptoms such as tiredness or lethargy should also be considered for investigation with thyroid function testing.

For investigation of suspected primary thyroid disease, TSH is generally the most appropriate initial investigation. Free T4 and/or free T3 should never be requested in isolation.

If TSH is abnormal, either above or below limits of the laboratory reference intervals, free T4 should be requested. In suspected thyrotoxicosis with suppressed TSH and free T4 within reference limits, further investigation with free T3 is indicated.

If there is suspicion of pituitary disease (secondary disease), in each case it is essential that TSH is interpreted in the context of a free T4 measurement; both TSH and free T4 should be requested as part of the initial investigation.

Situations where the TSH should be interpreted with caution, and interpreted in the context of free T4 and T3 measurement, include sick euthyroidism associated with non-thyroidal illness, thyroid hormone resistance, and in patients where glucocorticoids or dopamine are being administered.

If subclinical thyroid disease is identified on thyroid function testing, careful clinical assessment for relevant symptoms, thyroid morphology and important comorbidities is required (9).

Repeat thyroid function testing to confirm the finding, is recommended between 2 weeks and 3 months following the initial test (10, 11) for hypothyroid disease.

Subclinical hyperthyroid disease
Subclinical hyperthyroid disease can be divided into TSH <0.1mU/L and > 0.1 mU/L. Patients with TSH < 0.1 mU/L should be referred for specialist endocrinology opinion. Patients with TSH > 0.1mU/L should have the test repeated, including free T4 measurement, within 1 to 2 months. If TSH on repeat testing remains low but > 0.1 mU/L with normal free T4, and a decision is made to monitor rather than treat on clinical grounds, then repeat testing should continue every 6-12 months (11).

Frequency of monitoring patients with subclinical hypothyroid disease:
There is very limited literature that examines the ideal frequency of monitoring in subclinical disease. Karmisholt et al (12) monitored monthly thyroid function tests in a small group of patients and observed significant variation on a monthly basis, which influenced whether the patient was categorised as subclinical or overt thyroid disease.

If a patient is identified with subclinical hypothyroid disease after retesting, and the decision is made, after careful clinical assessment, to monitor rather than treat with thyroid replacement therapy, it is reasonable to repeat thyroid function testing at 6 months. If stable and the intention is to monitor, thyroid function tests should be repeated on a 12 monthly basis (10,11).

Monitoring thyroid replacement therapy in overt hypothyroidism:
The half-life of thyroxine is normally around one week, but may be longer in patients with hypothyroidism. Measurement of thyroid function for dose adjustment should occur after a minimum of six to eight half-lives.

Treatment should generally aim to achieve a TSH within the reference range with alleviation of symptoms and avoiding adverse symptoms of excess replacement, especially in those with cardiac and bone disease. There has been debate as to whether TSH in the lower half of the reference interval (<2.5) should be the treatment goal, based on the nature of the reference range in the normal population. Currently, there is insufficient evidence to support this. A recent publication reported no difference in metabolic parameters (BMI, body composition and energy expenditure) between patients treated with thyroxine replacement, comparing patients with TSH < 2.5 mU/L and patients with TSH > 2.5 mU/L (13).

It is suggested that in the initial monitoring period that both TSH and free T4 are measured (free T3 should only be measured in this setting for patients on T3 therapy). Once thyroid function tests in patients on replacement therapy are stable, patients may be monitored with annual measurement of TSH. If there is a change in situation, such as introduction of drugs which reduce thyroxine absorption or which increase thyroxine binding globulin, a review of thyroid status will be required earlier.

It is important to recognise that there is an increased replacement dosage requirement for hypothyroid patients during pregnancy. [Out of scope for this document.]

As the upper reference limit for free T4 is based upon a healthy untreated population, a mildly increased free T4 level may be seen in patients treated with thyroxine (as all the thyroid hormone introduced into the blood is in this form). In such cases, a decision regarding a change in thyroxine dosage should be based upon the measured TSH rather than the (elevated) free T4 level.

Monitoring treatment of hyperthyroidism:
Frequency of monitoring will depend on the clinical situation and treatment, with monthly testing initially. In some patients taking anti-thyroid medications, a hypothyroid state can develop quite quickly, in these patients more frequent measurements may be required. In treatment with oral anti-thyroid medication, TSH may remain suppressed for several months after free T4 and free T3 return to within the reference range. It is therefore important to use free hormone assessment as well as TSH for adjustment of dosage of anti-thyroid medications.

Related investigations

- Thyroid antibodies: Antithyroid-peroxidase antibody (anti-TPO) is the recommended investigation for assessment of thyroid autoimmunity. This has been shown to be of use in predicting risk of progression to overt hypothyroidism from subclinical disease: 4.3%

per year in antibody positive versus 2.6% per year in antibody negative individuals (13).
- There is no evidence for use of reverse T3 in assessment of sick euthyroid syndrome or other thyroid disease.
- Urine iodine concentration (UIC) is used in population assessment for iodine deficiency. Because of wide day to day variations in UIC it is not useful as a diagnostic tool of iodine nutritional status in an individual (14).

Other considerations

It is important for clinicians to include relevant history on the request form, outlining their patient's thyroid status or clinical symptoms, so that appropriate, rebatable testing can be performed. Specifically, when requesting free thyroid hormone tests in addition to TSH, the Medicare rules require a specific statement related to the reason for the request.

Summary

- Current guidelines do not support general population or opportunistic screening for thyroid disease.
- Active case finding is recommended in patients at high risk of developing thyroid disease or where there is clinical suspicion based on relevant history, symptoms, test results or signs at presentation, including hypercholesterolemia, mild anemia, hyponatremia, increased serum CK, muscle weakness, weight changes, osteoporosis and recent onset arrhythmia.
- TSH is generally the initial investigation for diagnosis of thyroid disease. Certain situations may require free hormone assessment as well as TSH for diagnosis, in particular in the context of known or suspected pituitary disease.
- Patients undergoing therapy with anti-thyroid drugs should have monitoring with TSH, free T4 and free T3 in the initial period of anti-thyroid medication dose adjustment.
- Patients receiving thyroxine replacement therapy for hypothyroidism should have monitoring of TSH, usually 6-8 weeks following dose adjustment, with the aim of normalising the TSH (10).
- Free T3 measurement is indicated in assessment of hyperthyroidism, treatment of hyperthyroidism and in monitoring of patients on T3 therapy, but is not indicated in monitoring of patients receiving levothyroxine therapy.
- There are no situations where measurement of reverse T3 is validated.

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