Thyroid Function Tests

Tar Choon Aw, *FRCP (Edin), FRCPA*, Clementine YF Yap, *MT(ASCP), DLM(ASCP)*

Department of Lab Medicine, Changi General Hospital, Singapore

ABSTRACT

A thyroid panel consisting of thyroid stimulating hormone (TSH) and free thyroxine (fT4) should form the first line of diagnostic tests; tri-iodothyronine (T3) — total or free may be needed occasionally. A TSH assay capable of detecting levels below 0.02mIU/L is required to differentiate the suppressed TSH levels typical in Graves' disease from subnormal levels seen in some geriatric patients, non-thyroidal illness, and patients on medications. Additional tests including thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), and TSH receptor antibody (TRAb) may be ordered to enable differential diagnosis when indicated. Serum thyroglobulin (Tg) may serve as a tumour marker for monitoring patients with differentiated thyroid cancer.

Keywords: fT4, Tg, TgAb, thyroid function, TPOAb, TRAb, TSH

SYNONYMS

Thyroid screen, Thyroid panel, Thyroid profile, Thyroid function tests (TFTs)

TESTS COMMONLY INCLUDED

Thyroid tests commonly used include TSH, fT4 (or fT3), thyroid antibodies (TPO-Ab, Tg-Ab), TRAb, and Tg.

SPECIMEN

Serum is used for testing. The blood sample should be collected in a plain tube and sent to the lab immediately for processing. Thyroid medications (thyroid hormones and anti-thyroid drugs) should be omitted prior to blood taking. To reduce the variability of test results specimens should be obtained at the same time of day and prandial state. Late morning non-fasting serum TSH have been shown to decline by an average of 26% from early morning fasting values[1]. TSH also exhibits diurnal variation — nadir in the late afternoon and peak at midnight; for night shift workers TSH peaks in the morning[2].

INDICATIONS

Thyroid tests are often used to screen thyroid function, assess adequacy of therapy, and monitor treatment of differentiated thyroid cancer. In Singapore, some 4–7% of the population have a thyroid disorder and constitute up to one-third of all endocrine referrals in restructured hospitals[3]. About 90% of thyroid patients in Singapore suffer from hyperthyroidism and the remaining 10% hypothyroidism, with Chinese women at higher risk for hyperthyroidism and Indian ethnic group at higher risk for hypothyroidism[4]. The clinical presentation of thyroid disease is quite diverse thus accurate lab assessment is vital. Besides, patients may require long-term (anti-thyroid drugs) or life-long (thyroid hormones) medications or ablative therapy (radioiodine or surgery). Thyroid testing constitutes the most frequent endocrine tests performed by the clinical laboratory.

Thyroid hormones (T4 and T3) are regulated by TSH while TSH is in turn controlled by the interplay between the hypothalamic thyrotropin releasing hormone (TRH) and feedback inhibition by thyroid hormones[5]. The relationship between TSH and fT4 is inversely log-linear such that a small change in fT4 is accompanied by a large reciprocal change in TSH[6,7]. Consequently, thyroid function is best assessed by measuring TSH when pituitary or hypothalamic disease is absent, steady state conditions prevail,

and patients are not on drugs affecting the thyroid[8]. However, TSH in conjunction with fT4 has been identified as the best screening tool[9]. Each individual has a unique set-point for the fT4/TSH relationship which is genetically determined. In early thyroid dysfunction, pituitary TSH responds to mild fT4 excess or deficiency relative to that set-point. In this subclinical state fT4 is normal while TSH is elevated (subclinical hypothyroidism) or depressed (subclinical hyperthyroidism).

There is no consensus on treating subclinical thyroid disease, but the move towards treatment is growing[10]. Subclinical hyperthyroidism is associated with atrial fibrillation, diastolic dysfunction, more cardiac deaths, and impaired bone health (osteopenia, osteoporosis, and increased fracture rate, especially in post-menopausal women)[11]. Treatment of subclinical hyperthyroidism is beneficial[12] as atrial fibrillation reverts to sinus rhythm, heart rate is reduced, vascular resistance improves, echocardiographic changes revert[13], and bone mineral density is augmented. Progression from subclinical to overt thyrotoxicosis occurs at 8% in year 1, 16% by year 2, 21% at 3 years and 26% at 5 years[14]. The magnitude of subclinical hyperthyroidism requiring treatment at 5 years depends on the underlying aetiology — 9% for Graves' disease, 21% for multinodular goitre and 61% for autonomous nodules. Moreover, patients with TSH <0.1mIU/L are most likely to progress, while those with TSH >0.1mIU/L will not[14–17]. Treatment of subclinical hyperthyroidism also depends on the level of TSH suppression (<0.1 versus >0.1)[16], patient's age, and co-morbid conditions.

While the case for treating subclinical hypothyroidism is less clear, development of myxoedema coma has been reported[18]. In a recent re-analysis of the Wickham survey data, there is an association of subclinical hypothyroidism with coronary events and mortality as well as attenuation of cardiac morbidity and mortality with thyroxine therapy[19]. In a 13-year study of women with thyroid antibodies, 85% with baseline TSH >4.0mIU/L were hypothyroid while 55% of those with TSH between 2.5–4.0 mIU/L developed hypothyroidism in contrast to 70% and 28% respectively in antibody negative subjects[20]. Thyroid hormone replacement was useful in those with positive TPO-Ab[21]. In contrast pregnant subjects with subclinical hypothyroidism merit treatment due to the known adverse outcomes (e.g. spontaneous miscarriage, recurrent miscarriage, and pre-term delivery) in both TPO-Ab negative[22] and positive[23] pregnancies. Moreover, undiagnosed maternal hypothyroidism impacts the neuropsychiatric development of the child[24].

METHODOLOGY

Currently available automated platforms for TFTs can provide rapid and reliable test turnaround times to support same clinic session evaluation of ambulatory outpatients. Clinical labs should keep abreast with advancing technology and replace "comparative" methods with "definitive" methods as soon as they become available[25]. Quality specifications for thyroid function tests are available[26]. Labs should also note the precision and accuracy goals for thyroid function tests, which have been established based on intra-assay and inter-assay biological variation. All immunoassays should be immune to the effects of human anti-mouse (HAMA) and heterophile antibodies.

Thyroid Stimulating Hormone (TSH)

Most of the current TSH assays in use have detection limits of 0.01–0.02 mIU/L or better and can distinguish mild hyperthyroidism from euthyroid subjects. This level of TSH is also known as the functional sensitivity of the assay, defined as that concentration of TSH characterised by an inter-assay imprecision of 20%. Serum TSH in untreated hyperthyroidism is often <0.02mIU/L. However, some sick euthyroid subjects in intensive care units may have TSH values at or near 0.02mIU/L and require TSH assays with lower detection limits (0.004mIU/L) for clarification[27].

The normal range for serum TSH is around 0.4–4.0 mIU/L, but there is some controversy as to the appropriate upper normal limit[28–31]. The National Academy of Clinical Biochemistry[32] argues that the upper TSH limit should be 2.5mIU/L because 95% of rigorously screened euthyroid volunteers have values between 0.4–2.5 mIU/L. The use of a lower upper limit for normal serum TSH will substantially increase the number of patients diagnosed with subclinical hypothyroidism[30]. However, in the United States National Health and Nutrition Examination Survey III (NHANES III) population (n=13,444) the TSH reference range was 0.4–4.5 mIU/L when subjects with a positive family history, drugs, goitre, nodules, or positive TPO-Ab were excluded. Age-based TSH normal ranges have

been advocated, but a close examination of the NHANES III data reveal that the upper cut-point for TSH should be higher (7.5mIU/L) only in subjects over 70 years old[29].

In pregnancy, trimester-specific ranges for TSH should be applied as the TSH cut-points are much lower than for non-pregnant subjects[33]. An upcoming guideline from the American Thyroid Association on diagnosis and management of thyroid disease in pregnancy recommends the following TSH values: 1st trimester 0.1–2.5; 2nd trimester 0.2–3.0; 3rd trimester 0.3–3.0)[34].

Free Hormones

While fT4[35] and fT3[36] assays have largely replaced total T4 and total T3 measurements, they are an estimate of the true free hormone levels. Accurate fT4 concentrations can be determined using liquid chromatography-tandem mass spectrometry but this method is of research interest only[37]. For direct free hormone assays, the use of one-step hormone-labelled analog methods is discouraged. For one-step labelled antibody free T4 methods, the assay should extract only 1–2% of total hormone concentration off the binding proteins. Samples containing high hormone labels should exhibit parallelism when diluted and show <10% deviation from expected values[38]. Locally, most labs use a 2-step labelled antibody fT4 assay. However, the use of fT3 should be limited to the evaluation of T3-toxicosis[25], monitoring treatment of thyroid storm, and in the rapid pre-operative preparation of the acutely thyrotoxic patient. Index methods (fT4I and fT3I) are calculated tests with poor diagnostic sensitivity and have been superseded by free hormone assays.

Thyroid Antibodies

An antibody panel consisting of TPO-Ab and TgAb may be added to enable differential diagnosis of most thyroid disorders[25]. The prevalence of thyroid auto-antibodies is high in the local population. In normal subjects from the executive health screening clinic (n=176) the prevalence of TPO-Ab was method-dependent — RIA (Radio Immuno Assay) 10.2%, chemiluminescence 11.9%, and EIA (Enzyme Immuno Assay) 13.5% — as was Tg-Ab (RIA 13.6% and EIA 8.4%)[39,40].

TRAb

A rapid (27 minute) electro-chemiluminescent TRAb assay is now available[41]. TRAb may be helpful in the prediction of relapse after anti-thyroid therapy, assessment for the risk of neonatal hyperthyroidism, in the evaluation of possible Graves disease without extra-thyroidal features, and in unilateral exophthalmos.

Thyroglobulin (Tg)

Tg has been used for detecting recurrence of thyroid cancer in post-thyroidectomy patients[42]. However, the presence of Tg-Abs in serum will result in under-estimation of the true Tg levels[43].

Thyroid Proteomics

Proteomics has advanced our understanding of thyroid cancer biology. The list of candidate molecular markers for thyroid neoplasia is growing but more work is required[44].

LIMITATIONS

TFT results together with time of specimen collection, clinical evaluation, medical and drug history. Clinicians should look for "internal consistency" by comparing abnormal results against the disease state based on the fact that when the hypothalamic-pituitary function is normal, a log/linear inverse relationship between serum TSH and fT4 is evident. However, raised TSH and fT4 could be encountered in the rare pathologic conditions such as a TSH-secreting pituitary adenoma or states of resistance to thyroid hormone (RTH) while a depressed TSH and normal or low fT4 suggests secondary hypothyroidism.

Large population surveys demonstrate little difference in the prevalence of clinical symptoms between euthyroid controls and subclinical hypothyroid subjects, and hence little added advantage to lower the upper limit of the TSH reference range. Currently, the general consensus is that emphasis should be on clinical stratification and patient-specific factors such as age, gender, ethnic origins, symptoms, presence or absence thyroid auto-antibodies, pregnancy or infertility rather than the TSH upper reference range in subclinical thyroid disease to guide the need for thyroxine therapy on a patient-by-patient basis.

ADDITIONAL INFORMATION

Screening for Thyroid Dysfunction

TSH is more sensitive and specific than fT4 for outpatients if a single screening test is utilised. The use of both TSH and fT4 in all patients for screening purposes is ideal since errors may be made when

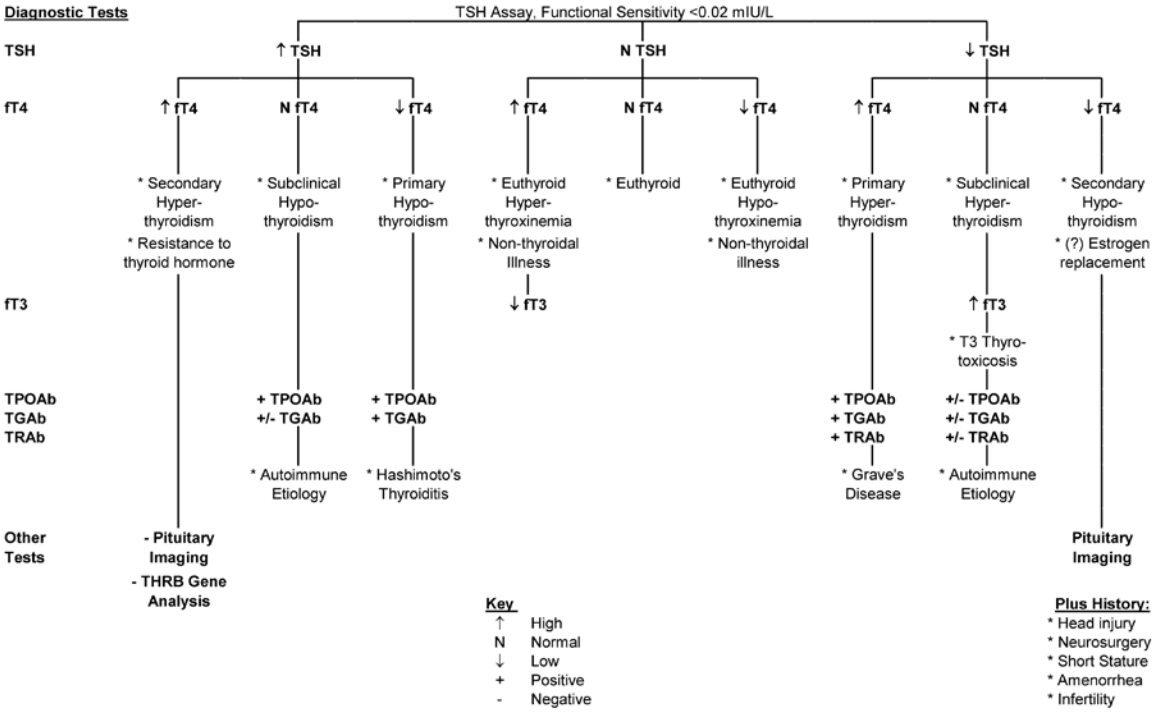

Fig. 1: Flow chart of diagnostic tests to evaluate thyroid function.

only TSH is measured in patients with central hypothyroidism or TSH-mediated hyperthyroidism. To limit unnecessary laboratory testing to detect the few cases of unsuspected pituitary disease the following strategy can be employed (see Fig. 1 for details):

- TSH normal — no further testing performed;
- TSH high — add fT4 to determine the degree of hypothyroidism;
- TSH low — add fT4 and (possibly fT3) to determine the degree of hyperthyroidism

Screening inpatients is not recommended unless thyroid disease is strongly suspected since changes in thyroid hormones, binding proteins, and TSH concentrations occur in severe non-thyroidal illness. Here the use of both TSH and fT4 is necessary to accurately assess thyroid function in them.

The case for universal thyroid screening in pregnancy remains unclear[45] and has not been endorsed by the American Thyroid Association[34]. However, case finding has been shown to miss a large proportion of subjects with thyroid dysfunction and disease[46,47].

Monitoring Thyroxine Therapy

Patients with primary hypothyroidism on thyroxine can be monitored by assessing serum TSH. If TSH is high, the dose needs to be increased; if it is low, the dose needs to be reduced. Excess suppression of serum TSH can increase the risk of both atrial fibrillation and bone disease due to subclinical hyperthyroidism. When commencing thyroxine replacement, fT4 is used to monitor therapy as there is a lag in the pituitary TSH response in adjusting to a new homeostatic state. Moreover, fT4 values should be used to titrate the thyroid hormone dose in patients with secondary hypothyroidism due to pituitary or hypothalamic disease, as TSH release is impaired.

In thyroid cancer patients on thyroid hormone suppression to minimise growth of thyroid cancer cells, the target for TSH suppression is <0.1mU/L for high risk patients while low-risk patients can afford minimal TSH suppression (0.1-0.5 mU/L)[48–50].

Serum TSH is only accurate if steady state conditions are present, which takes 4 to 6 weeks after starting or adjusting the thyroxine dose. Liothyronine (T3) is generally not used for treating hypothyroidism. However, in patients on T3, assessment of therapy then requires measurement of serum T3 and TSH, since the fT4 will remain low.

Monitoring Treatment of Hyperthyroidism

During the early treatment of hyperthyroidism, TSH may remain subnormal for several weeks and rarely for several months. One must therefore rely upon serum fT4 when assessing the efficacy of anti-thyroid drugs, radioiodine, or surgery. Once steady-state conditions are achieved TSH can be used to assess the efficacy of therapy. The risk of hepatotoxicity in patients on propylthiouracil has been highlighted by the US Food and Drug Administration. Thus such patients may require assessment of liver enzymes during treatment[51].

CONCLUSION

Interpreting TFTs is generally straightforward. However, TSH and fT4 results may be at variance with the clinical picture or form an unusual pattern[52]. In most of these cases the anomalous TFTs are clear from a clinical reassessment of the patient. Rarely, aberrant TFTs are due to assay interferences or genetic defects in the hypothalamic–pituitary–thyroid axis.

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