

# San PATHOLOGY UPDATE

## THYROID FUNCTION TESTS REVISITED

by Dr Bevan Hokin

### INTRODUCTION

The symptoms are often vague – fatigue, nervousness, weight gain or loss. The question facing the clinician is: “Could this be a Thyroid disorder?” Epidemiological data suggests that for many, the answer is “yes”, with hypothyroidism being the most common thyroid disorder. The diagnosis of hypothyroidism, hyperthyroidism and the monitoring of thyroid cancer recurrence, depend on pathology test results. Because thyroid testing can be confusing, it is important to understand two common issues:

What tests should be requested, and what reference ranges should apply to patient test results?

### WHAT TEST(S)? AND WHEN?

When testing for thyroid disorders, clinicians have a panel of assays available. (Fig 1)

The most common test and the starting point in any investigation is thyroid stimulating hormone (TSH). Other common tests include free thyroxine (free T4), free tri-iodothyronine (free T3) and Anti Thyroid Peroxidase (Anti-TPO), sometimes referred to as Anti-Thyroid Antibody.

TSH alone – not part of a panel of test is the recommended first step. The primary benefit of TSH testing is that it provides a ‘magnified’ reflection of changed free T4 levels. For example, a two-fold change in free T4 can result in a 100 fold change in TSH level. To achieve such benefits, the testing laboratory must operate a 3rd generation TSH assay with a functional sensitivity of 0.02 mIU/L or less. The method must be able to deliver a better than 20% imprecision at the 0.02 mIU/L level.

If a patient’s TSH is within the reference range, a thyroid condition can almost certainly be ruled out, except when possible confounding factors exist, such

as serious illness, pregnancy and a few medications. Such factors, including routine hospitalisation, can produce results not reflective of the patient’s actual thyroid condition. Consequently in-patients should be re-evaluated after discharge. Remember too that serum TSH levels are pulsatile, varying as much as +/- 0.3 mIU/L within one two-hour cycle.

If the TSH is abnormal, the next step is free T4. There are two possible scenarios:

If free T4 is normal with abnormal TSH: Indicates a mild or sub clinical early thyroid disease.

If both TSH and free T4 are abnormal: Suggests thyroid disease

Some clinicians request both free T3 and free T4. This is usually unnecessary. If you are suspecting hypothyroidism or hyperthyroidism, free T4 and TSH give sufficient information to make a diagnosis. However it is useful to remember that free T3 is the most biologically active hormone, while TSH levels most strongly reflect the free T4 concentrations.

Free T3 does have a role in screening for T3 thyrotoxicosis. Where a patient has symptoms of hyperthyroidism, with TSH low, but free T4 normal, a check of free T3 is warranted.

If autoimmune disease is suspected, an anti-TPO test is recommended. Diseases such as atrophic autoimmune thyroiditis and Hashimoto’s disease are common examples. In these cases, there is a progressive destruction of thyroid tissue. Circulating thyroid antibodies are present, often in high concentration. Early Hashimoto’s disease may be associated with a mild hyperthyroid picture.

As anti -TPO is the most sensitive biochemical marker of autoimmune thyroid disease, it is usually the only test needed.

Thyroglobulin auto antibodies (Anti-TG) are also often present in patients with autoimmune thyroid disease, but are not recommended for monitoring treatment. When thyroglobulin assays are used to monitor differentiated thyroid carcinoma, sensitive anti-TG testing becomes important, as the presence of anti-TG auto antibodies can interfere with the thyroglobulin assay.

### REFERENCE RANGES FOR TSH TESTING

Reference ranges are critical to the interpretation of thyroid test results. Differences between individuals make it difficult to define what is ‘normal’ for any one person. Variation between laboratories and methods is also a confounding factor, although standardisation of methods has markedly improved over recent years.

The traditional reference range cited by many laboratories is 0.5 – 5.0 mIU/L. Over recent years, evidence has emerged that people who are at the upper end of this range had an increased risk of developing hypothyroidism compared with those at the lower end of the range. Consequently this range has undergone substantial research scrutiny. The American Association of Clinical Chemistry (AACC) reported in 2002 that the upper limit of this reference range was almost certainly too high. When the 0.5 – 5.0 mIU/L range was established, researchers inadvertently included subjects who had mild or sub-clinical thyroid disease, and this pushed the upper limit higher than appropriate.

Based on their reassessment, the AACC predicted that an upper limit of 2.5 mIU/L was likely to be used in the future, because subsequent research reported that 95% of rigorously screened healthy



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volunteers had serum TSH values between 0.4 and 2.5 mIU/L. The AACC Guidelines state: "Ambulatory patients with a serum TSH above 2.5 mIU/L, when confirmed by a repeat TSH measurement made after three weeks, may be in the early stages of thyroid failure, especially if anti thyroid antibodies are detected."

Over more recent years many studies have supported an upper limit for TSH of 3.0 mIU/L and others propose 4.0 mIU/L. The American College of endocrinologists recommend a range of 0.3 – 3.0 mIU/L. The TSH range quoted on the RCPA Website is 0.4 – 5.0 mIU/L.

Sydney Adventist Hospital Pathology has adopted as its TSH reference range 0.4 – 4.0 mIU/L. The method used has a

functional sensitivity of 0.014; analytical sensitivity of 0.005 and between run imprecision of 14.4% at the 0.035 mIU/L level and 6% at the 3.6 mIU/L level.

#### REFERENCE RANGES FOR T3 AND T4

The reference ranges for free T3 and free T4 are well established and less contentious. A commonly accepted range for free T3 is 3.1 – 6.8 pmol/L, and for free T4 12 – 22 pmol/L.

Individual Pathology Laboratories determine what is right for their method and patient demographic. Importantly, however, there is no absolute single point where treatment is 'always' or 'never' indicated. The TSH result, assessed in conjunction with the quoted

reference range and other factors including patient history, family history and increased serum lipids must all be considered.

#### CONCLUSIONS

Early diagnosis of thyroid problems is important as even mild disease may play a role in elevated cholesterol and lipids, osteoporosis, depression and other serious conditions. Clinical laboratory staff and clinicians can work together in understanding what tests to order and in identifying what to consider in interpreting results.

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**FIGURE 1. CIRCULATING MARKERS OF THYROID STATUS**

<b>THYROID TEST OPTIONS</b>
Measuring the level of thyroid stimulating hormone (TSH)
Measuring serum levels of T3 and/or T4
Measuring serum levels of free T3 and/or free T4
Assessing levels of antibodies to thyroid proteins: anti-TPO, anti-Thyroglobulin, TSH-receptor

**FIG 2 CLINICAL UTILITY OF COMMON THYROID TESTS**

<b>DISEASE/CONDITION</b>	<b>TSH</b>	<b>FT4</b>	<b>T4</b>	<b>FT3</b>	<b>T3</b>	<b>ANTI-TPO AB</b>	<b>ANTI-TG AB</b>
Euthyroid	N	N	N	N	N		
Subclinical Hypothyroidism	H	N	N	N	N	*	*
Hypothyroid	H	N	L	N/L	N/L	*	*
Subclinical Hyperthyroidism	L	L	N	N	N	*	
Hyperthyroid	L	H	H	H	H	*	*
Pregnancy (high TBG)	N	N	H	N	H	*	
Low TBG	N	N	L	N	L		
T3 Thyrotoxicosis	L	N/L	N/L	H	H		
Acute Thyroiditis	Transient hypothyroidism or hyperthyroidism						
Hospitalized patients	Results may be ambiguous and should be interpreted with caution						

N = normal; L = low; H = high; \* = test may be helpful. See above