Review Article

MAKING SENSE OF THYROID FUNCTION TESTS

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ABSTRACT

BACKGROUND: Thyroid disorders are second only to diabetes mellitus among endocrine problems encountered in practice. Many patients with thyroid disorders tend to present with nonspecific symptoms to clinicians in different specialties, who are often quick to request for a thyroid function test. Although interpretation of the results of most thyroid function tests (TFTs) is straightforward, in a small number of situations the results seem to point in different directions, thereby producing clinical confusion. Knowledge of the different patterns of TFTs and their causes will help clinicians to properly manage their patients and avoid unnecessary, and often expensive further investigations.

OBJECTIVE: To highlight the causes of the different patterns of abnormal thyroid function tests seen in clinical practice and to provide a practical approach to the evaluation of patients with such results.

METHOD: We searched PubMed, Google scholar and Medline for articles written in English on the interpretation and pattern of thyroid function tests.

RESULT: Interpretation of the results of most TFTs is straightforward especially when combined measurements (TSH with T4 or T3 or both) are ordered. Careful clinical reassessment of thyroid status and consideration of possible confounding factors such as pregnancy, intercurrent (non-thyroidal) illness or drug therapy will readily identify the cause of such apparently discordant TFTs.

CONCLUSION: A sound knowledge of the conditions that can be associated with different patterns of TFTs will go a long way in guiding the choice of additional investigations and allowing a correct diagnosis, thus avoiding inappropriate treatment.

KEYWORDS: Thyroid function tests (TFTs), patterns of abnormal TFTs, non-thyroidal illness

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INTRODUCTION

The clinical recognition of thyroid disease, especially in its most florid form is relatively easy. However, in some cases, the presence of thyroid disease is not immediately obvious and a diagnosis is made only when thyroid function tests (TFTs) are requested on the basis of nonspecific symptoms/signs such as lethargy, weight loss or palpitations. Fortunately, the interpretation of the results of most TFTs is straightforward especially when combined measurements (TSH with T4 or T3 or both) are ordered. Nevertheless, a small albeit important number of situations in which the results of TSH, T4 and T3 seem to point in different directions remain, thereby producing clinical confusion. In most of these cases, careful clinical reassessment of thyroid status, together with consideration of possible confounding factors such as pregnancy, intercurrent (non-thyroidal) illness or drug therapy will readily identify the cause of such apparently anomalous/discordant TFTs.[1] On rare occasions, thyroid hormone assay interference or genetic/acquired disorders of the hypothalamic-pituitary-thyroid (HPT) axis may need to be screened for to arrive at a diagnosis.[1] This review highlights the causes of the different patterns of abnormal thyroid function seen in clinical practice, including the so-called 'funny' TFTs and the practical approach to their evaluation.

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ASSESSING THYROID FUNCTION: WHICH TEST IS THE BEST?

In any given individual, thyroid hormone (both thyroxine, T4 and triiodothyronine, T3) levels remain relatively constant, reflecting the set-point of the HPT axis in that individual.[2] Changes in thyroid status are almost always associated with concordant changes in thyroid hormones and thyrotropin (TSH)

concentrations (e.g. raised T3 and T4 with suppressed TSH in thyrotoxicosis; low T3 and T4 with elevated TSH in hypothyroidism). However, because the population reference ranges for thyroid hormones(TH) are relatively wide, changes in TH levels sufficient to render a patient hypo-or hyperthyroid may not necessarily be associated with numerically abnormal T4 or T3 levels (the so-called subclinical hypo-or hyperthyroidism). Consequently, TSH measurement has been recommended as the frontline screening test for thyroid dysfunction, since relatively modest changes in TH concentration are associated with marked excursions in TSH.[1] However, when TSH assay is used alone, the result can be misleading in the following situations: central hypothyroidism (due to hypothalamic or pituitary disease) in which the TSH can be low, normal or even slightly elevated; recent treatment for thyrotoxicosis (TSH remains suppressed for up to a year after TH levels have returned to the reference range); non-thyroidal illness; TSH-secreting pituitary tumour or in individuals with resistance to thyroid hormones. For these reasons, most laboratories now routinely offer combination screening with both T4, T3 and TSH. It is important to note that free TH (FT4/FT3) measurements are preferred to total TH (TT4/TT3) because of the potential for the latter to be affected by changes in circulating binding protein levels.

INTERPRETING TFTs: WHAT TO CONSIDER

In any patient with suspected thyroid disease in whom TFTs are requested, the patient's clinical status should be reassessed to ascertain whether they are euthyroid, hypothyroid or hyperthyroid. This will provide an important clue to the test (TSH, T4 and/or T3) that is likely to be discordant which will in turn guide further management. In addition to the aforementioned, the following should be considered while interpreting TFTs.

Non-thyroidal illness

Non-thyroidal illness (NTI) formerly called 'sick euthyroid syndrome', describes a condition characterized by abnormal TFTs encountered in patients with acute or chronic systemic disease. NTI may affect 60-70% of critically ill patients and occurs in both organic and psychiatric disease.[3] Whether it is a beneficial response (e.g. to reduce metabolic rate) or a maladaptive response (with potential response to TH replacement therapy) has been much debated, but compelling evidence for the use of T3 or T4 in the majority of patients with NTI is lacking.[4] A variety of abnormal patterns of TFTs can be seen in NTI. A decrease in T3 is the most common finding in these patients, occurring in even the mildest forms of NTI.[3] Levels of FT4 and FT3 are usually low or low normal, with low normal or partially suppressed TSH. Where total TH concentrations are measured, reductions in TT4 and in particular TT3 are common even in mild NTI, and are usually more marked than the corresponding decreases in free hormone concentrations (likely reflecting reduced serum TH binding capacity in acute and chronically ill patients, secondary to a fall in TH binding protein concentrations and/or impaired T4/T3 binding).[3] The magnitude of T4 decrease has been reported to correlate with a less favourable outcome.[5]

Effect of Medications

Medication history is an essential part of the evaluation of any patient with thyroid disease since commonly prescribed medications can affect thyroid function leading to anomalous and/or discordant TFTs. In patients taking levothyroxine, the finding of elevated TSH in conjunction with elevated free T4 and/or T3 may indicate poor compliance, with the ingestion of a large dose of levothyroxine just prior to the test. This pattern of TFTs may also be caused by malabsorption of levothyroxine.[6] Poor absorption can be due to small bowel disease, or iatrogenically by cholestyramine or iron therapy.[7] Amiodarone, by inhibiting conversion of T4 to T3 can cause similar pattern of TFTs. A less well recognized cause is heparin administration. Both fractionated and unfractionated heparin can produce artefactual increase in measured levels of free thyroid hormones. Heparin activates endothelial lipoprotein lipase which produces an increase in free fatty acids that in some individuals, leads to displacement of T4 and T3 from their carrier protein binding sites thus raising free TH levels.[8,9] For this reason, when thyroid disease is suspected, samples for TFTs should be collected before administration of heparin.

Pregnancy

Pregnancy has a significant impact on HPT physiology and may be associated with marked changes in serum TH and Thyrotropin concentrations.[10] The levels of thyroxine binding globulin (TBG) increase during pregnancy due to stimulation of its synthesis in the liver by oestrogen. Consequently, the concentration of serum total TH increases up to 150% of the values in non-pregnant women. Transient increases in serum free T4 concentration with a corresponding suppression of TSH is often observed in the first trimester of pregnancy due to the stimulatory effects of human chorionic gonadotropin (hCG) on the TSH receptor. Therefore as much as possible, trimester-specific reference ranges for TH and TSH should be used in the evaluation and management of thyroid disorders in pregnancy.

PATTERNS OF THYROID FUNCTION TESTS

Low TSH and raised FT4 and/or FT3

This pattern of TFTs indicates primary hyperthyroidism the causes of which include Graves' disease, Toxic Multinodular Goitre and Toxic solitary adenoma. In all of these cases, the TSH should be undetectable (i.e. <0.1mu/L). The causes of this pattern of TFTs are shown in Table 1 below. The three most common causes of primary hyperthyroidism can usually be separated based on clinical criteria. The presence of Orbitopathy and a diffuse goitre that is nontender makes the diagnosis of Graves' disease likely. This is further confirmed by a diffuse uptake on radioiodine thyroid scanning and positive antithyroid antibodies (especially anti-TSH-Rab (stim) although they are negative in about 10% of cases. Transient thyroiditis (subacute, silent, or postpartum) should be suspected when the history of hyperthyroid symptoms is relatively short (<1 month), goitre is tender or symptoms occur within 9 months of delivery. Thyroiditis can be confirmed by a low uptake on radioiodine or technetium thyroid scanning. Elevated erythrocyte sedimentation rate (ESR) suggests post-viral (de Quervain's) thyroiditis. In silent thyroiditis, the goitre is usually painless and ESR is normal. Ingestion of L-thyroxine, either therapeutic or factitious, causes thyroxicosis with low radioiodine uptake on thyroid scanning. Amiodarone causes thyrotoxicosis in up to 10% of patients treated and can be difficult to treat.[11] Hyperemesis gravidarum can be associated with mild thyrotoxicosis due to overstimulation of TSH receptor by very high human chorionic gonadotropin concentrations in the first trimester of pregnancy. Familial gestational hyperthyroidism is characterized by thyrotoxicosis which recurs in subsequent pregnancies and spontaneously resolves postpartum. In this rare condition, a K183R mutation in the TSH receptor increases its ability to be activated by human chorionic gonadotropin.[12] Other rarer causes of thyrotoxicosis are shown in Table 1.

Raised TSH and low FT4 and/or FT3

This pattern of TFTs always indicates primary hypothyroidism. Iodine deficiency with associated endemic goitre (urinary iodine excretion of <45µg daily) is the commonest cause of primary hypothyroidism worldwide and should be strongly suspected in all patients resident in iodine deficient areas. In iodine sufficient areas including the UK, primary hypothyroidism is most usually due to either autoimmune thyroiditis (Hashimoto's disease or atrophic thyroiditis) or follows radioiodine therapy or thyroidectomy.[13] Antithyroid peroxidase (anti-TPO) antibodies are found in 95% of patients with autoimmune hypothyroidism and these should be searched for in such patients.[14] Riedel's thyroiditis is a rare cause of primary hypothyroidism in which the thyroid gland is replaced by fibrosis that often involves the surrounding tissues. Autoantibodies are usually negative and the condition may be associated with mediastinal and retroperitoneal fibrosis.[15] Other causes of primary hypothyroidism are shown in Table 2.

The patterns of TFTs discussed so far are consistent with the normal negative feedback mechanism of the hypothalamic-pituitary thyroid axis whereby when THs are high, TSH levels fall and vice versa. These TFTs are therefore said to yield convergent results. The remaining part of this review will focus on the interpretation of divergent TFTs.

Low levels of TSH and normal levels of FT4 and FT3

This pattern of TFTs suggests subclinical hyperthyroidism, a term also referred to as mild hyperthyroidism in some quarters. Most Endocrinologists are of the opinion that the term 'subclinical hyperthyroidism' should be reserved for those patients in whom TSH is fully suppressed, because this is the group for whom there is the greatest evidence of adverse sequelae (in the form of atrial fibrillation and osteoporosis) if TSH remains suppressed in the longterm (especially postmenopausal women and patients older than 65 years of age).[16] Non-thyroidal illness is another common cause of transiently low (albeit not fully suppressed) TSH, with resolution following recovery.[17] In hospitalized patients, treatment with high dose glucocorticoids or dopamine can directly suppress pituitary release of TSH leading to a similar pattern of TFTs. Other causes are shown in Table 3.

Low or normal levels of TSH and low levels of FT4 and/or FT3

This combination of TFTs is the typical pattern seen in patients who are systemically unwell, indicating the presence of the so-called non-thyroidal illness (NTI). The TFTs usually revert to normal with recovery.[17] In the absence of any obvious NTI, central hypothyroidism must be considered in the differential diagnosis of this pattern of TFTs. In such cases, a full assessment of anterior pituitary hormones is necessary especially to rule out concomitant secondary hypoadrenalism. This is because administration of T4 in a patient with undiagnosed hypocortisolism can prove fatal. Imaging studies should also be requested to confirm the presence of a pituitary macroadenoma which if unrecognized can compress the optic chiasm and lead to irreversible visual loss. Other rare causes of the above pattern of TFTs are shown in Table 4.

Increased levels of TSH and normal levels of FT4 and/or FT3

This pattern of TFTs signifies the so-called 'subclinical hypothyroidism'. The condition is reported to affect 5% - 10% of women and is commonly associated with positive anti-TPO antibodies.[16] Positivity for anti-TPO antibodies predict a higher risk of subsequent progression to overt hypothyroidism. The TSH level should be monitored and if it is persistently elevated (>10mU/L), L-thyroxine (LT4) therapy should be considered. Other indications for LT4 therapy include: younger patients (especially when symptomatic); women who wish to become or who are pregnant; and the presence of marked hypercholesterolaemia.[16] If the level of TSH is increased to a value that is usually associated with frankly low level of FT4 or FT3 (>20mU/L) or the TSH does not show appropriate suppression with the introduction or titration of LT4 therapy, the possibility of interference with TH assays should be considered. Other causes of increased levels of TSH with normal levels of FT3 and FT4 are shown in Table 5.

Normal or increased levels of TSH with increased levels of FT4 and/or FT3

This pattern of TFTs is most commonly due to assay interference e.g. by anti-T4 antibodies or anti-T3 antibodies or both in the patient's serum, may yield artificially increased levels of the hormones; effects of drugs such as Amiodarone or heparin or thyroxine replacement therapy, including occasional patients who ingest large doses of thyroxine just prior to the blood test.[18] Non-thyroidal illness especially acute psychiatric illness may also be associated with similar pattern of TFTs. If all these possibilities have been excluded, two rare but important conditions must be considered: a TSH secreting pituitary adenoma (TSHoma) and resistance to TH (RTH). Features that favour a diagnosis of TSHoma include an increased α-subunit: TSH molar ratio, the presence of a pituitary adenoma on magnetic resonance imaging or computed tomography, an attenuated TSH response to exogenous TRH administration and an increased level of sex-hormone binding globulin (SHBG) (hepatic production of SHBG is strongly dependent on thyroid hormones).[19] Resistance to thyroid hormone is a genetic disorder in which loss-of function mutations in the thyroid receptor β (TRβ) isoform are associated with variable tissue refractoriness to thyroid hormone action, which leads to an altered set-point of the HPT axis. A family history of similarly affected individuals strongly favours the diagnosis of RTH.[20] Table 6 summarizes the causes of this pattern of TFTs.

CONCLUSION

Since relatively modest changes in TH concentration are associated with marked excursions in TSH, it is reasonable to suggest the use of TSH alone as the initial screening test for thyroid dysfunction provided the limitations of the test are taking into consideration. The results of thyroid function tests must always be interpreted in the light of the clinical status of the patient. When the results appear divergent or discordant, confounding factors that may influence thyroid status such as intercurrent illness, medications or assay interference should be excluded before embarking on further biochemical, radiological or genetic testing. A sound knowledge of the conditions that can be associated with each pattern of TFTs listed will go a long way in guiding the choice of additional investigations and allowing a correct diagnosis, thus avoiding inappropriate treatment.

Table 1: Conditions in which levels of TSH are low with increased levels of FT4 and/or Ft3

• Graves' disease
• Toxic Multinodular goitre
• Toxic solitary adenoma
• Transient thyroiditis
  ○ Postpartum
  ○ Silent
  ○ Postviral(e.g. De Quervain's)
• Ingestion of thyroxine
• Drugs (e.g. Amiodarone)
• Iodine induced
	• Pregnancy related
	  ○ Hyperemesis gravidarum
	  ○ Hydatiform mole
	  ○ Familial gestational thyrotoxicosis
	• Ectopic thyroid tissue or struma ovarii
	• Metastatic follicular thyroid carcinoma

Table 2: Conditions in which levels of TSH are high with low levels of FT4 and/or Ft3

• Autoimmune thyroiditis
  ○ Hashimoto's thyroiditis
  ○ Atrophic thyroiditis
• Previous treatment for thyrotoxicosis
  ○ Thyroidectomy
  ○ Treatment with radioiodine
• Hypothyroid phase of thyroiditis
• Drug-induced (e.g. antithyroid agents, Amiodarone or lithium)
• Deficiency or excess of iodine
• Neck irradiation
	• Riedel's thyroiditis
	• Infiltration
	  ○ Tumour
	  ○ Amyloid
	• Congenital
	  ○ Thyroid agenesis or hypoplasia
	  ○ Defects in hormone synthesis
	  ○ Resistance to TSH

Table 3: Conditions in which levels of TSH are low with normal levels of FT4 and Ft3

• Subclinical hyperthyroidism • Recent treatment for hyperthyroidism • Drugs(glucocorticoids or dopamine)	• Non-thyroidal illness • Assay interference

Table 4: Conditions in which levels of TSH are low or normal with low levels of FT4 and Ft3

• Non-thyroidal illness • Central hyperthyroidism (for example due to anterior pituitary disease)	• Isolated TSH deficiency

Table 5: Conditions in which levels of TSH are high with normal levels of FT4 and/or Ft3

• Subclinical hypothyroidism
  ○ Autoimmune
  ○ Post-thyroid ablation treatment
• Poor compliance with thyroxine replacement therapy
• Malabsorption of thyroxine
• Assay interference
• Drugs e.g. Amiodarone
• Non-thyroidal illness recovery phase
	• TSH resistance (for example , inactivating germline TSH receptor mutation)

Table 6: Conditions in which levels of TSH are high or normal with increased levels of FT4 and/or Ft3

• Interference with assays (for example ant-T4 or T3 antibodies) • Thyroxine replacement treatment (including poor compliance) • Drugs (for example Amiodarone or heparin) • Non-thyroidal illness ○ acute psychiatric illness	• TSH-secreting pituitary tumour (TSHoma) • Resistance to thyroid hormone (RTH)

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