INTERPRETATION OF THYROID FUNCTION TESTS

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Introduction:
Thyroid dysfunction can result in a wide range of symptoms and thyroid function tests (TFT) are therefore one of the most common endocrine tests ordered in general practice. The interpretation of TFT results however, can often be challenging. Not every abnormal value requires therapeutic intervention but at the same time one must not miss important values that are apparently normal but may require treatment. An understanding of when to order TFTs, how to interpret the results and when to treat is therefore crucial for the optimal treatment of thyroid dysfunction.

The clinical status of the patient is the most important factor that needs to be considered before deciding on treatment. To illustrate this, two sets of thyroid function test results are presented, each with two different clinical scenarios. The answers to the questions are explained at the end of the article.

Case 1
A 32 year old lady with no previous history of thyroid dysfunction comes to the outpatient department because of an abnormal TFT done elsewhere. The TFT results are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (normal range in bracket)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µ IU/ml)</td>
<td>6.2 [0.3 - 4.5]</td>
</tr>
<tr>
<td>T4 (µg/dl)</td>
<td>5.6 [4.5 - 12.5]</td>
</tr>
<tr>
<td>Free T4 (ng/dl)</td>
<td>0.9 [0.8 - 2.0]</td>
</tr>
</tbody>
</table>

Clinical Scenario 1
- Recently treated for infertility.
- Pregnant now, 2 months of gestation, conceived by IVF.
- Past history of 2 pregnancy losses.
- Precious pregnancy

Clinical Scenario 2
- Being evaluated for Obesity.
- BMI-36 Kg/m²
- Has sedentary lifestyle and very limited physical activity.
- No history to suggest secondary causes of obesity.

Question:
What would be your line of treatment in each of these clinical scenarios, for the 32 year old lady with the abnormal TSH level?

Case 2
A 57 year old man with no previous history of thyroid dysfunction has the following TFT results.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (normal range in bracket)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µ IU/ml)</td>
<td>2.1 [0.3 - 4.5]</td>
</tr>
<tr>
<td>T4 (µg/dl)</td>
<td>1.6 [4.5 - 12.5]</td>
</tr>
<tr>
<td>Free T4 (ng/dl)</td>
<td>0.2 [0.8 - 2.0]</td>
</tr>
</tbody>
</table>

The TSH level is within normal limits but T4 and free T4 levels are below normal.

Now consider two clinical scenarios for the same man with the same TFT results (See below).
Clinical Scenario

- Past history of a pituitary surgery 2 years earlier.
- Came for a regular follow up.
- No symptoms of hypothyroidism.

Clinical Scenario 2

- Obese patient who came to casualty diagnosed to have acute appendicitis with sepsis, was operated as an emergency.
- Post operatively on inotropes, the doctor had sent thyroid function tests to rule out hypothyroidism as a cause of obesity.

Question:

What would be your line of treatment in each of these scenarios, for the 57 year old man with the abnormal T4 level?

THYROID PHYSIOLOGY AND PATHOPHYSIOLOGY – A brief review

An understanding of the physiology and pathophysiology of the thyroid and thyroid disorders is important in knowing when to order TFT and how to interpret the results.

Normal physiology - The pituitary produces Thyrotropin releasing hormone (TRH) which acts on the pituitary gland, stimulating it to release Thyroid stimulating Hormone (TSH) which in turn stimulates the thyroid gland to secrete thyroxine (T4) and triiodothyronine (T3). TSH and T4/T3 have a negative feedback on the hypothalamus and pituitary gland respectively.

Primary hypo- and hyperthyroidism:

As the name suggests, the dysfunction in these disorders, is at the level of the thyroid. In primary
hypothyroidism, a deficiency in the secretion of thyroid hormones (T3/T4) results in raised serum TSH levels. In primary hyperthyroidism, the increased secretion of thyroid hormones causes a negative feedback resulting in decreased serum TSH levels.

**Secondary hypo- and hyperthyroidism:**
In these disorders, the abnormality is at the level of the hypothalamus or pituitary gland. Surgery of sellar and suprasellar masses (pituitary and hypothalamus) are an important surgical causes for secondary hypothyroidism.

It is important to remember that in secondary hypothyroidism, even though the T4 level is low, the TSH level may be within the normal range. Such a patient will still require treatment with thyroid hormone replacements. The “normal” TSH value is in fact is an inappropriately low value. In these patients we monitor T4 levels to adjust the thyroxine dose.

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**Thyroid function tests - “Clinical Pearls”**

<table>
<thead>
<tr>
<th>TSH (Thyroid stimulating hormone)</th>
<th>Serum T4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>➢ TSH should be the first test to be done in any patient with suspected thyroid dysfunction.</strong></td>
<td><strong>➢ T4 may be done in a patient with hyperthyroidism, to assess the severity of hyperthyroxinemia.</strong></td>
</tr>
</tbody>
</table>

**Why is serum TSH level useful?**

1. Small changes in thyroid function cause significant increase in TSH secretion. TSH may be elevated even in subtle thyroid dysfunction.
2. The tests done to assess TSH levels are reliable. The most advanced (third-generation) chemiluminescent TSH assays can now detect both elevation and significant lowering of TSH levels.
3. In many situations, a normal TSH level can be sufficient indication to halt further testing of thyroid function.

**Serum T3**

**➢ T3 is not advisable in routine clinical practice.**

**Reasons**

1. Because of its short half life and near normal levels maintained by several homeostatic mechanisms, the level is usually normal.
2. T3 should be measured in a patient with suppressed TSH and normal T4 but who shows clinical features of hyperthyroidism. This is to rule out T3 toxicosis, which is seen in 5% of patients with Graves disease.
3. T3:T4 ratio >20 ng/mg suggestive of Graves disease.
In pregnancy, there is increased level of T4 and a corresponding decrease in TSH level. The physiological processes behind this are:

1. HCG secreted by the placenta has an alpha subunit that is similar to that of TSH. Thus it is able to bind to TSH receptors in the thyroid resulting in increased T4 secretion. This leads to a negative feedback on the pituitary resulting in reduced TSH secretion.
2. Oestrogen secreted by the placenta acts on the liver resulting in increased SHBG (Sex hormone-binding globulin) secretion. This in turn acts on the thyroid to increase T4 secretion. A similar effect is seen in women who use oral contraceptive pills containing oestrogen.
3. The increased glomerular filtration rate (GFR) in the kidney in pregnancy results in increased T4 excretion and therefore increased demand on the thyroid to secrete T4.

Table 2: Trimester-wise cut-off for TSH (µ IU/ml)

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Cut-off (µ IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, first trimester</td>
<td>2.0-2.5</td>
</tr>
<tr>
<td>Pregnancy, second trimester</td>
<td>3.0</td>
</tr>
<tr>
<td>Pregnancy, third trimester</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Recommendations in pregnancy:¹
- T4 should be one and a half times the upper limit of normal
- Thyroid functions to be assessed every 6 weeks during pregnancy

Fig 2: Increased T4 and reduced TSH in pregnancy

Abbreviations: T4 – Thyroxine, T3 – Tri-iodothyronine, TSH – Thyroid stimulating hormone, SHBG (Sex hormone-binding globulin)

Sick euthyroid syndrome / Non Thyroidal Illness syndrome (NTIS)

Sick euthyroid syndrome is a clinical situation where there are abnormal thyroid function tests in a patient who is seriously ill (“non-thyroid illness”). T4/T3 levels are elevated, TSH may be normal or low.

In conditions associated with high metabolic demand like critical illnesses, the body tries to conserve energy by reducing the metabolism and energy expenditure in tissues so that energy is available to the vital organs of the body. One of the mechanisms involved is a reduction in the production of thyroid hormone. There is therefore a reduction in T3 and T4 levels and increase in reverse T3 (rT3 – an inactive form of T3). According to latest guidelines, replacement therapy with levothyroxine is not recommended in such patients.²

Table 2: Conditions associated with sick euthyroid syndrome
- Gastrointestinal diseases
- Pulmonary diseases
- Cardiovascular diseases
- Renal diseases
- Infiltrative and metabolic disorders
- Inflammatory conditions
- Myocardial infarction
- Starvation
- Sepsis
- Burns, Trauma, Surgery
- Malignancy
- Bone marrow transplantation
Subclinical hypothyroidism:
This is a condition where TSH is raised by thyroid hormone levels are normal.

Subclinical hyperthyroidism:
This is a condition where TSH is suppressed but T4 levels are normal. The patient may be euthyroid clinically.

When should subclinical hyperthyroidism be treated?³

<table>
<thead>
<tr>
<th>Factor</th>
<th>TSH (&lt;0.1 µU/L)</th>
<th>TSH (0.1-0.5 µU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65 with co morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Menopausal</td>
<td>Consider treating</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Hyperthyroid symptoms</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65, asymptomatic</td>
<td>Consider treating</td>
<td>No</td>
</tr>
</tbody>
</table>

*Where 0.5 µU/L is the lower limit of the normal range
Source: Hyperthyroidism Management Guidelines, EndocrPract. 2011;17(No. 3)

Answers to case scenarios

CASE 1 – 32 year old lady with abnormal TSH and normal thyroid hormone levels.

Scenario 1 –
This patient has subclinical hypothyroidism. In pregnancy, the cut-off for TSH is 2.5 µ IU/ml in the first trimester. Since her TSH level is high and she is pregnant, she will definitely require treatment with thyroid replacements in order to normalize her thyroid function status and meet pregnancy targets. Pregnancy is a condition where treatment of thyroid abnormalities is imperative.

Scenario 2
This lady has subclinical hypothyroidism and blames her obesity on the high TSH value. She does not fit into any criteria for treatment of subclinical hypothyroidism and will not benefit from treatment for thyroid dysfunction. She will require counseling about diet and exercise so that she is motivated to lose weight.

Learning point: In both the above scenarios, the diagnosis, age and thyroid function test results were the same but one required treatment while the other did not because of different clinical scenarios. It is important to decide on treatment based on the clinical scenario rather than numbers on a test result.
CASE 2- A 57 year old man whose TSH level is within normal limits but T4 and free T4 levels are below normal.

Scenario 1
This patient has secondary hypothyroidism (history of pituitary surgery) and will require treatment. In this patient, it is important to monitor T4/Free T4 levels and ensure normalization of its levels rather than TSH.

Scenario 2:
This patient is obese and is recovering from a sepsis secondary to appendicitis. He probably has sick euthyroid syndrome and treatment of the thyroid hormone abnormality is not recommended in such a situation. Thyroid function assays may be repeated once he recovers from the sepsis. Thyroid hormone assays are not recommended in patients who are very sick unless one suspects severe hypothyroidism or a thyrotoxic storm.

CONCLUSIONS:

- The first test to be done in any patient with suspected thyroid dysfunction is TSH.
- T4 levels are recommended in patients with hyperthyroidism and T3 levels are rarely needed.
- Free thyroid hormone assessment is recommended in conditions altering thyroid binding globulin levels. (Eg. Oral contraceptive pills/Nephrotic syndrome).
- In pregnancy over treatment might be better than under treatment. First trimester TSH must be <2.5, Check every 6 weeks.
- The clinical scenario is the most important factor in deciding whether to initiate treatment or not. In case of doubt, when TFT results are not in line with the clinical status, treatment must be based on the clinical status after reconfirming with the lab for any possible analytical error.

References:
1. ATA/AACE Guidelines for Hypothyroidism in Adults, Endocr Pract. 2012;18(No. 6)
3. Hyperthyroidism Management Guidelines, EndocrPract. 2011;17(No. 3)

Medical news: Counterfeit drugs more dangerous than terrorism

More people have died due to consuming counterfeit medicines than those who have died of terrorism in the last 40 years, CBI director Anil Sinha said last month. A few years ago, Interpol estimated that while more than 65,000 people were killed in over 40 years in transnational terrorist incidents, the estimates of deaths caused by fake medicines range from tens of thousands to hundreds of thousands annually.

Source: Pharmacy Bulletin, July edition, CMC Vellore