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REVIEW

The interpretation and management of thyroid disorders

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Abstract

This short review is intended to simplify the interpretation of thyroid function tests (TFTs) in general practice. The relationship between thyroid hormones and the use of TFTs, as well as thyroid antibodies, is discussed. An overview of the management of common thyroid disorders is included. Less common conditions, e.g. thyroid-stimulating hormone-secreting pituitary tumour and thyroid hormone resistance, are not discussed in this review.

Keywords: hyperthyroidism, hypothyroidism, subclinical, thyroid antibodies, TSH

Introduction

To properly interpret thyroid function tests (TFTs), one must understand the normal relationship between free tetraiodothyronine (thyroxine) (T_4) and thyroid-stimulating hormone (TSH).

When the hypothalamus-pituitary-thyroid axis functions normally and the thyroid status is normal, the relationship of FT_4 and TSH is an inverse log-linear one. Each individual has his own free thyroid hormone set-point and any changes in the free FT_4 (FT_4) and/or free triiodothyronine (T_3), even if still within the population reference range, will induce very pronounced TSH changes. This happens because of the negative feedback of the thyroid hormones on the pituitary gland. With the sensitive TSH assays in use today, TSH is more sensitive in detecting thyroid dysfunction than FT_4 while the thyroid status is stable.[1,2]

The thyroid status is unstable during the commencement phase of treatment for hyperthyroidism or hypothyroidism, or with treatment adjustment. In this unstable phase, the TSH may take weeks or months to normalise.[3] During this phase, the thyroid hormones and clinical presentation will be a more accurate indicator of thyroid status than TSH. When the patient is stable on treatment, the TSH should be used to monitor treatment.[2,3]

Other common causes of an abnormal TSH without thyroid dysfunction include nonthyroidal illness and medication, e.g. lithium, amiodarone, glucocorticoids or certain antiepileptic drugs. Rare disorders that may be missed with a "TSH only" approach include central hypothyroidism, TSH-secreting pituitary adenoma and thyroid hormone resistance.[1,3]

TSH levels vary considerably during the day (normal diurnal variation) and a slightly low TSH may still be normal.[3] Heterophile antibodies that are present in the patient's serum may interfere with the laboratory method and will affect FT_4, free T_3 (FT_3) and/or TSH. The clinical presentation of the patient should always be considered.[4] The pathologist should be contacted for possible further investigation if the biochemistry and clinical presentation is discrepant. Table I summarises some thyroid disorders.

Screening

Screening for thyroid dysfunction is recommended from the age of 35 years, and every five years thereafter.[1,3] Screening should especially be carried in the elderly, in women, people with Down's syndrome, during pregnancy, and when other autoimmune diseases are present.[1,5]

Thyroid antibodies

Antithyroid peroxidase antibodies (TPOAb) are produced against thyroid peroxidase (TPO) enzymes in the colloid of the thyroid. TPO catalyses the oxidation of iodide (I^-) to iodine (I) and iodination of thyroglobulin (Tg).[6] TPOAb may be useful in the diagnosis and prognosis of hypothyroidism and indicates the presence of an autoimmune process. Positive TPOAb in subclinical hypothyroidism indicates a possible need for treatment because of a risk of developing overt hypothyroidism. TPOAb should be measured with newly diagnosed hypo- or hyperthyroidism, goitre or subclinical hypothyroidism, to evaluate the risk of developing postpartum thyroiditis in at-risk women, e.g. those with type 1 diabetes and a history or symptoms of thyroid dysfunction, and with lithium or amiodarone therapy to evaluate the risk of developing autoimmune thyroid disease.[3,7]

TPOAb should not be measured if the thyroid function tests are normal and no goitre is present, or if it was previously performed, since it is not useful for follow-up. The TPOAb may be positive in

Table I: Summary of some thyroid disorders

	FT_4	FT_3	TSH	TPOAb	Comments
Hypothyroidism	Low	Low	High	Usually positive	
Subclinical hypothyroidism	Normal	Normal	High	Usually positive	
Central hypothyroidism	Low	Low	High, normal or low		TSH may be increased, but is biologically inactive
Hyperthyroidism	High or high-normal	High	Low	Usually positive	TSHRAb-sensitive and specific for Graves' disease
Subclinical hyperthyroidism	Normal	Normal	Low		TSHRAb-sensitive and specific for Graves' disease
Nonthyroidal illness	Normal (high or low)	Low (normal or high)	Low, normal or high	May help distinguish if thyroid dysfunction is present	Repeat 2-3 months after illness resolves
Noncompliance with L-T_4 treatment (common)	High	Normal	High		
Thyroid hormone resistance or TSH-producing pituitary adenoma (rare)	High-normal or high	High-normal or high	High-normal or high		Symptoms of hyperthyroidism if there is adenoma and mild hyper- or hypothyroidism with resistance (depending on the type)
Thyrotoxicosis factitia	High	Normal or high	Low		Zero radioactive iodine uptake, low Tg

FT_3: free triiodothyronine, FT_4: free thyroxine, L-T_4: levothyroxine, Tg: thyroglobulin, TPOAb: antithyroid peroxidase antibodies, TSH: thyroid-stimulating hormone, TSHRAb: antithyroid-stimulating hormone receptor antibodies

Table II: Antithyroid antibodies[3,7]

Antibodies	Indications	Notes
TPOAb	• Newly diagnosed hypo- or hyperthyroidism • Goitre • Subclinical hypothyroidism • Evaluate risk of developing postpartum thyroiditis • Evaluate risk of developing autoimmune thyroid disease with lithium or amiodarone therapy	Do not do TPOAb if: • TFTs are normal and no goitre is present • If previously performed
TSHRAb	• May assist in the diagnosis of Graves' disease • Evaluate the risk for neonatal hyperthyroidism in pregnant women with previous Graves' disease • Distinguish postpartum thyroiditis from Graves' disease in postpartum hyperthyroidism	• Monitor treatment for Graves' disease to predict remission • Indication of risk of developing thyroid eye disease
TgAb	• Evaluate antibody interference with the Tg test	• Not specific enough for the diagnosis of autoimmune thyroid disease

TFT: thyroid function tests, Tg: thyroglobulin, TgAb: thyroglobulin antibodies, TPOAb: antithyroid peroxidase antibodies, TSHRAb: antithyroid-stimulating hormone receptor antibodies

10% of the normal population, in other autoimmune diseases and with thyroid carcinoma.[7]

Anti-TSH receptor antibodies (TSHRAb) are not necessary for the diagnosis of Graves' disease, but may assist in the diagnosis if overt clinical symptoms are not present, or if the cause of the hyperthyroidism is not apparent.[8] TSHRAb are also used to evaluate the risk of neonatal hyperthyroidism in pregnant women with previous Graves' disease and to distinguish postpartum thyroiditis from Graves' disease in postpartum hyperthyroidism.[7]

Antithyroglobulin antibodies are not specific enough to diagnose autoimmune thyroid disease. Diagnosis should only be carried out in the case of thyroid cancer to evaluate antibody interference with the Tg test.[3] The indications for the use of antithyroid antibodies are summarised in Table II.

Autoimmune thyroid disease is associated with pernicious anemia, coeliac disease, systemic lupus erythematosus, rheumatoid arthritis, urticaria, systemic vasculitis, repeated miscarriages, Addison's disease, polycystic ovary syndrome and mood disorders.[9,10]

Tg is used as a tumour marker in thyroid cancer. It can also help to distinguish hyperthyroidism from *thyrotoxicosis factitia* (external thyroid hormone ingestion, low Tg).[3]

The effect of medication

Medication may interfere with thyroid function tests (Table III). Glucocorticoids and dopamine inhibit TSH secretion and may cause normal FT_4 and low TSH. Glucocorticoids also have an effect on the conversion of FT_4 to FT_3 by inhibiting type 1 5′-deiodinase, resulting in a decreased FT_3. Type 1 5′-deiodinase is present mainly in the liver and kidneys, with the major function of providing T_3 to the circulation.[6] Lithium and iodine inhibit thyroid hormone synthesis and release, thus causing low FT_4/FT_3 and increased TSH.

Amiodarone contains 37% iodine by weight. Increased thyroid peroxidase (TPO) may indicate the risk of patients on amiodarone

Table III: Medication that influences thyroid function tests[1-3]

Medication	FT_4	FT_3	TSH
Glucocorticoids, dopamine	Normal	Normal	Low
Lithium and iodine	Low	Low	High
Amiodarone	Normal to high	Low	High or low
Phenobarbital, phenytoin, carbamazepine and rifampicin	Low	Low	Normal

FT_3: free triiodothyronine, FT_4: free thyroxine, TSH: thyroid-stimulating hormone

developing thyroid dysfunction. TSH and FT_4 may increase, and FT_3 decrease, during the first six months after initiation of amiodarone treatment. Usually, the TSH normalises with long-term treatment. The thyroid status should be monitored every six months with TSH. Patients on amiodarone may develop hyper- or hypothyroidism. A low TSH, as well as an increased T_3, suggest hyperthyroidism. There are two types of amiodarone-induced hyperthyroidism. Type 1 is iodine induced which may be a nodular goitre or Graves' disease and is treated with antithyroid drugs. Type 2 is an amiodaron-induced destructive thyroiditis which is self-limiting, but may be treated with glucocorticoids. It may be difficult to distinguish between the two types, in which case treatment should be directed at both forms.[3–]

Phenobarbital, phenytoin, carbamazepine and rifampicin induce liver microsomal enzymes that metabolise FT_4 and FT_3, causing a slight decrease in these hormones, but the TSH stays normal.[1]

Hypothyroidism

Primary hypothyroidism affects 1.8-4.6% of the general population.[2,11] Thyroid disorders are more common in women than men, and increase with age.[2,11]

The most common cause of primary hypothyroidism is Hashimoto's thyroiditis (chronic lymphocytic thyroiditis), followed by radioactive iodine therapy or surgery. Other causes include external irradiation of the neck, iodine deficiency, and very rarely, infections and infiltrations of the thyroid. Iodine excess may cause hypothyroidism by inhibition of the organification of the iodide into the Tg molecule. An example of this is hypothyroidism which may occur during the first 18 months of amiodarone treatment.[1,10]

Hashimoto's thyroiditis is an autoimmune disease of the thyroid and is characterised by massive lymphocytic infiltration. Some patients have an initial transient hyperthyroid stage owing to the initial inflammatory changes. This may eventually cause overt hypothyroidism. The distinguishing feature of Hashimoto's thyroiditis is the presence of TPOAb, formerly known as thyroid microsomal antibodies.[1] Overall, women are more affected by Hashimoto's thyroiditis than men, and the incidence increases with age. Although most patients will need lifelong T_4 replacement, spontaneous recovery occurs in approximately 5% of cases.[1]

Screening for hypothyroidism should be performed with TSH, and if abnormal, FT_4 and TPOAb could be added.[3]

With primary hypothyroidism, the increase in TSH appears first, with the FT_4 still within normal reference range in mild hypothyroidism (subclinical hypothyroidism). When the disease worsens, the FT_4 decreases and lastly, the FT_3 decreases in severe hypothyroidism.[1]

Low FT_4/FT_3 and inappropriately normal or low TSH are indicative of central hypothyroidism (pituitary or hypothalamic disease) and may warrant investigation of the rest of the hypothalamic-pituitary axis.[1,10]Another uncommon form of hypothyroidism, in which the target tissues are unresponsive to thyroid hormone, is called thyroid hormone resistance.[1]

Subclinical hypothyroidism

Subclinical hypothyroidism is present in 4-10% of the general population, and in up to 18% of elderly individuals.[1,12] The TSH is increased with subclinical hypothyroidism, but the free thyroid hormones are still within the normal population reference range. This happens when the FT_4/FT_3 is already low in the patient, causing the increase in TSH. The most common causes are Hashimoto's thyroiditis, previous radioactive iodine treatment or surgery.[1] Other causes of an elevated TSH, but where the diagnosis of subclinical hypothyroidism should not be made, are antibody interference in immunoassays, nonthyroidal illness (recovery phase), impaired renal function, Addison's disease and obesity.[1,3]

To confirm the diagnosis, especially if the initial TSH was only slightly elevated, the TSH should be repeated in 3-6 months.[1] Preferably, a fasting lipogram, FT_4 and TPOAb, should be carried out in this second sample. This may assist in determining the risk of the development of overt hypothyroidism.[1] The risk of developing hypothyroidism is increased in women, the elderly, and those with high initial TSH and positive TPOAb. The titre of the TPOAb is not important when deciding whether or not to treat.[1]

Treatment for subclinical hypothyroidism remains controversial, but is generally indicated when the TSH is more than 10 mIU/l with or without TPOAb present, when symptoms of hypothyroidism are present, if the total cholesterol is increased, other cardiovascular risk factors are present, when TPOAb are positive and during pregnancy.[1,3] If treatment is not indicated, the TSH should be followed-up annually. The TSH may normalise spontaneously in approximately 5.5% of patients per year.[1,9] TPOAb are not indicated for follow-up, since it stays positive, even after treatment and normalisation of thyroid functions.[1]

Central hypothyroidism

Central hypothyroidism is rare and may affect 0.005% of the general population.[1]The pathology may involve the pituitary with decreased TSH secretion, or the hypothalamus with decreased thyrotropin-releasing hormone (TRH) secretion. Causes include tumours, e.g. pituitary adenoma, trauma, surgery, irradiation, infections and infiltrations. Another cause is medication, e.g. therapy with dopamine or glucocorticoids and levothyroxine (L-T_4) withdrawal, where the thyrotroph cells of the pituitary are suppressed.[1] Because of the resulting low TSH, the thyroid gland will not receive the message to produce the thyroid hormone.[1]

Biochemically, the patient will present with a low FT_4/FT_3 and an inappropriately normal or slightly elevated, but less than 10 mIU/l, TSH.[3] The paradoxically elevated TSH seen in central hypothyroidism is caused by biologically inactive isoforms of TSH that are detected by the immunoassay in the laboratory. These isoforms are produced when the pituitary is damaged, or when there is insufficient TRH.[3]

Thyroid hormone replacement therapy

The replacement treatment of choice is $L\text{-}T_4$ (Eltroxin™). The half-life of T_4 is seven days. This allows a convenient once-daily dose.[1,10] The replacement dose in adult hypothyroid patients averages 1.6 µg/kg/day.[2,3]

In healthy young adults, especially if the disease is of acute onset, e.g. post-surgery, the full replacement dose can be given from the start. However, in the elderly (> 60 years), in patients with cardiovascular risk or with longstanding severe hypothyroidism, the treatment should be initiated at a low dose, e.g. 25 µg/day, and titrated very slowly, e.g. 25-50 µg increments every eight weeks.[1,10] Most importantly, when initiating therapy, the duration of hypothyroidism, age, severity of hypothyroidism and presence of heart disease should be considered.[1] Evaluation of clinical signs of cardiac symptoms and total cholesterol levels in these patients is even more important than the follow-up TSH, since TSH may take months to normalise.[1,13]

$L\text{-}T_4$ should be taken at the same time every day, preferably half an hour before breakfast.[1] Absorption seems to be more complete if taken in the fasting state.[1] Drinking espresso at the same time as taking $L\text{-}T_4$ reduces its absorption.[1] Colestyramine, sucralphate, antacids containing aluminium hydroxide or iron decrease $L\text{-}T_4$ absorption. $L\text{-}T_4$ should be taken at least four hours apart from these medications.[3] Any other medication that the patient may be taking that could influence thyroid hormone levels, and which may necessitate $L\text{-}T_4$ dose adjustments, should be taken into consideration.[1,3]

The therapeutic target for TSH is between 0.5-2 mIU/l.[3] If the patient is elderly or has cardiovascular disease, the TSH target is 0.5-3.0 mIU/L.[3,13] The target level for FT_4, and FT_3 if used in replacement therapy, is in the upper third of the reference range.[3] FT_4 generally normalises first. TSH takes weeks or months to normalise, depending on the degree of suppression caused by the hypothyroidism. Both FT_4 and TSH may normalise before all the symptoms of hypothyroidism disappear.[1]

Typically, the dose is adjusted by 25 µg increments every 6-8 weeks, until the target TSH is reached.[1,3] During this unstable phase of treatment, FT_4 and clinical evaluation is of more importance than TSH levels. When the TSH has stabilised, the patient may be followed-up annually with TSH only.[1,3]

Oestrogen increases the T_4-binding protein, thyroxine-binding-globulin (TBG), and the concentration of this protein affects total serum T_4 concentration. TBG levels are increased in pregnancy or with oestrogen use (oral contraceptives and hormone replacement), and decreased with testosterone or corticosteroid treatment, sudden cessation of oestrogen use, liver cirrhosis or nephrotic syndrome. The FT_4 stays stable despite the TBG, and total serum T_4 changes in normal subjects. However, when a hypothyroid patient on treatment starts oestrogen therapy, the TSH and FT_4 should be measured after 8-12 weeks, since an adjustment to the $L\text{-}T_4$ dose may be necessary. Likewise, the $L\text{-}T_4$ dose may need to be adjusted during pregnancy.[1,14]

The most common cause of treatment failure is intermittent use or noncompliance with treatment. These patients should be followed-up with FT_4 and TSH, and usually the result is an increased FT_4 and TSH when the $L\text{-}T_4$ is taken just prior to blood sampling. An elevated TSH with normal or low FT_4 indicates under-replacement. Otherwise, a suppressed TSH may indicate over-replacement or deliberate overdosing.[1,3,10]

If treated for central hypothyroidism, follow-up should only be carried out with FT_4, with the target level in the upper third of the reference range. In these patients, the daily dose should be withheld until after blood sampling, since the FT_4 may be elevated above baseline for up to nine hours after the last dose.[3]

The vast majority of patients are satisfied with T_4-only treatment, but some are not (having excluded other autoimmune diseases).[1] These patients may benefit from treatment with extra T_3.[1] There is no indication for the use of T_3-only preparations to treat hypothyroidism. The half-life of T_3 is approximately one day and preparations should be taken more than once a day. This causes wide FT_3 peak-to-trough variation, with peaks 2-3 hours after dosage.[1] Normally, as is also the case in hypothyroid patients, the T_3 in the tissues is derived from T_4 by enzymatic conversion, resulting in stable FT_3 concentrations during the day.[1] With T_3-only therapy, there is no regulation of the T_3 supply to the tissues according to the body's needs since the T_3 is ingested directly. Combination T_4/T_3 preparations are usually taken once a day and do not take the short half-life of T_3 into consideration. The FT_3 peaks after dosing may also cause symptoms like tachycardia, insomnia and anxiety. If T_4/T_3 combination therapy is desired, separate T_4 and T_3 preparations as indicated should rather be given, to determine if the patient's symptoms will improve.[1,15]

Hyperthyroidism

Hyperthyroidism affects 1.3% of the general population, is more common in women than men, and increases with age.[2,11]The causes of hyperthyroidism include Graves' disease, multinodular goitre, toxic solitary adenoma, thyroiditis, $L\text{-}T_4$ ingestion (over replacement with $L\text{-}T_4$ or *thyrotoxicosis factitia*), iodine-induced hyperthyroidism, e.g. amiodarone treatment, and human chorionic gonadotropin-induced thyrotoxicosis.[8,10]

The TSH test is the best screening test with which to detect overt or mild (subclinical) hyperthyroidism. The TSH decrease precedes the FT_4 and FT_3 increase with hyperthyroidism.[3,10,16] If the patient is in the unstable thyroid state, e.g. recently treated hyperthyroidism or over-replacement with thyroid hormone, the FT_4 and clinical picture are more reliable than TSH.[3]

The diagnosis of Graves' disease is predominantly clinical, but TSHRAb may be used if goitre, overt clinical features or Graves' ophthalmopathy are not present, as well as to predict neonatal hyperthyroidism in pregnant patients who previously had Graves' disease, or if the cause of the hyperthyroidism is not clear. A radioactive iodine uptake test may also be valuable in this

setting, showing increased uptake with Graves' disease.[8] Serial TSHRAb measurements may be helpful in monitoring a patient on antithyroid drug therapy. A decrease predicts probable remission.[3,8]

Tg is always elevated with hyperthyroidism, except with *thyrotoxicosis factitia,* where a very low Tg is expected.[8] The FT_3 may sometimes increase above the normal reference range before the FT_4 rises as a stage in the development of hyperthyroidism. This is sometimes called T_3-thyrotocicosis. FT_3 may also increase more than the FT_4 when T_3-containing medication or supplements are used, with TSH secreting pituitary tumours (rare) or thyroid hormone resistance syndromes (rare).[1,3 8]

Subclinical hyperthyroidism

Subclinical hyperthyroidism is present when the TSH is low (even suppressed) and the FT_4 and FT_3 are still within the normal reference range, and presents in 2% of the population.[3] Other causes for low TSH, e.g. glucocorticoid, dopamine or amiodarone treatment, should be excluded. Nonthyroidal illness may also cause a low TSH. TSH should be repeated after eight weeks to confirm the diagnosis. The causes of subclinical hyperthyroidism may be exogenous, e.g. L-T_4, or endogenous, e.g. early Graves' disease, thyroid adenoma or multinodular goitre. These patients have an increased risk of developing osteoporosis, cardiovascular complications and progression to overt hyperthyroidism.[10] If the patient is using L-T_4, the dose should be adjusted. If the cause is endogenous and the patient does not have any symptoms, he or she should be followed up-every six months. If the patient is symptomatic, he or she should be treated with a beta blocker, low-dose carbimazole or radioactive iodine.[1,17]

Treatment of hyperthyroidism

Antithyroid drugs

Carbimazole (Neo Mercazole™) is metabolised to its active metabolite, methimazole, which inhibits thyroid hormone synthesis. It is used as primary treatment or to lower thyroid hormone levels before radioactive iodine treatment or surgery. Long-term treatment may cause remission of Graves' disease. Antithyroid drug therapy may last from six months to two years.[4]

Liver disease is a very rare complication of treatment and monitoring with liver function tests is unnecessary. Agranulocytosis is a serious, but rare, reaction to treatment. It is advisable to conduct a baseline white cell count with a differential count for comparison with a later test if clinically indicated.[4]

There must be follow-up every 1-2 months until the patient is euthyroid and the dose can be changed. After that, the patient must be monitored every 3-4 months clinically and with FT_4. FT_3 may be indicated if the signs and symptoms of hyperthyroidism persist.[4]

After cessation of treatment, the patient may be followed-up at longer intervals.[4]

Radioactive iodine therapy

Radioactive iodine therapy is commonly used and is safe. Some patients may need pretreatment with antithyroid drugs to avoid radioactive iodine-induced thyroiditis and exacerbation of the hyperthyroidism. Antithyroid drug treatment may also be necessary after radioactive iodine therapy.[4,8]

Initially, patients should be followed-up clinically and with FT_4, and then later with TSH, so that the development of hypothyroidism in the patient can be evaluated.[4]

Surgical intervention

Patients with large goitres, pregnant patients who are intolerant to antithyroid drugs, and those who do not want radioactive iodine treatment, are candidates for surgical intervention. Complications include hypoparathyroidism and vocal cord paralysis.[10] Hyperthyroidism may recur if insufficient thyroid tissue is removed. Hypothyroidism usually occurs after total thyroidectomy. The patient should be evaluated clinically and with TSH and FT_4 two months after surgery, and then annually with TSH.[4,8]

Nonthyroidal illness (euthyroid sick syndrome)

Patients may have abnormal thyroid function tests without thyroid dysfunction during a serious, acute or chronic nonthyroidal illness. Preferably, the TFT should be repeated 2-3 months after recovery if possible, since the interpretation during illness is complicated.[3]

The FT_3 is usually low, FT_4 normal (but may decrease with increased severity of the illness), and the TSH may be low to high (0.02-20 mIU/l) in critically ill, hospitalised patients. TSH may be elevated transiently during the recovery phase of the nonthyroidal illness and should be followed-up in 4-6 weeks.[3]

Also, the medication that the patient may be on may influence the TFTs. TPO may help to distinguish autoimmune thyroid versus nonthyroidal illness.[2]

Examples of TFTs interpretation during nonthyroidal illness are as follows:

- An ill patient with a low FT_4 and TSH > 20 mIU/l probably indicates hypothyroidism.[3]
- An ill patient with a high FT_3 and TSH < 0.1 mIU/l probably indicates hyperthyroidism.[3]
- If the patient is not very ill, the FT_4 is low and the TSH is within normal range (inappropriately low for the low FT_4), secondary hypothyroidism should be excluded.[3]

Conclusion

Understanding the relationship between the different thyroid hormones is essential when interpreting TFTs. TPOAb measurement may aid in the diagnosis of the cause of the thyroid disorder, the prediction of risk of developing overt disease and in the decision of whether or not to treat in the case of subclinical hypothyroidism. TSHRAb may assist in the diagnosis of Graves' disease and in monitoring the antithyroid treatment. Proper clinical evaluation of the patient, taking into account all

medication taken, should precede biochemical evaluation. If clinical and biochemical findings are discrepant, a pathologist should be consulted.

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