Thyroid dysfunction

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Presented by the Journal Discussion Group of the Faculty of General Practice of the College of Medicine of South Africa.

Rapid advancements have been made in the understanding and therapy of thyroid disorders. With this, a profusion in the number and type of thyroid function tests has occurred.

This talk outlines the available thyroid function tests, their roles in the diagnosis of thyroid disorders and some recent thoughts on the management of common thyroid pathology.

Thyroid physiology: basic facts

The negative feedback for the production of Thyroid stimulating hormone (TSH) is regulated primarily by the circulating T_3 and T_4 directly on the pituitary gland. Further control is exercised by Thyrotropin releasing hormone (TRH), which is also necessary for the synthesis of TSH.

Iodine in the plasma is trapped by the thyroid gland and converted to I_2 which is conjugated with tyrosine to form mono-iodo-thyronine (MIT) and di-iodo-thyronine (DIT). Together they form T_3 while the DIT + DIT forms T_4.

T_3 and T_4 are incorporated into thyroglobulin for storage and are then released into the plasma by the action of proteolytic enzymes. In the plasma they are more than 99,9% bound to thyroid binding globulin though a small amount is bound to albumin. T_4 is the major hormone secreted and only a minimal amount of T_3 is formed by the thyroid gland.

T_4 and T_3 must be in the free form to be released from the plasma although there is a steady state balance between free and bound thyroid hormone.

In the tissues T_4 acts primarily by conversion to T_3 which is the more active hormone. Some of the T_4 is however converted to inactive reverse T_3 (RT_3). T_4 can be considered a prohormone with T_3 being the active form of the hormone.

The action of the thyroid is mainly to stimulate oxidative processes though there are numerous other actions in various cells depending on the nature of these cells. T_3 is three to ten times as potent as T_4 while RT_3 is inactive.

Thyroid function tests

Serum T_4 measures the total serum T_4 both bound and free by radioimmunoassay. T_3 Resin Uptake is an indirect measurement of Thyroid binding globulin, which may be altered by non-thyroidal illness and drugs.

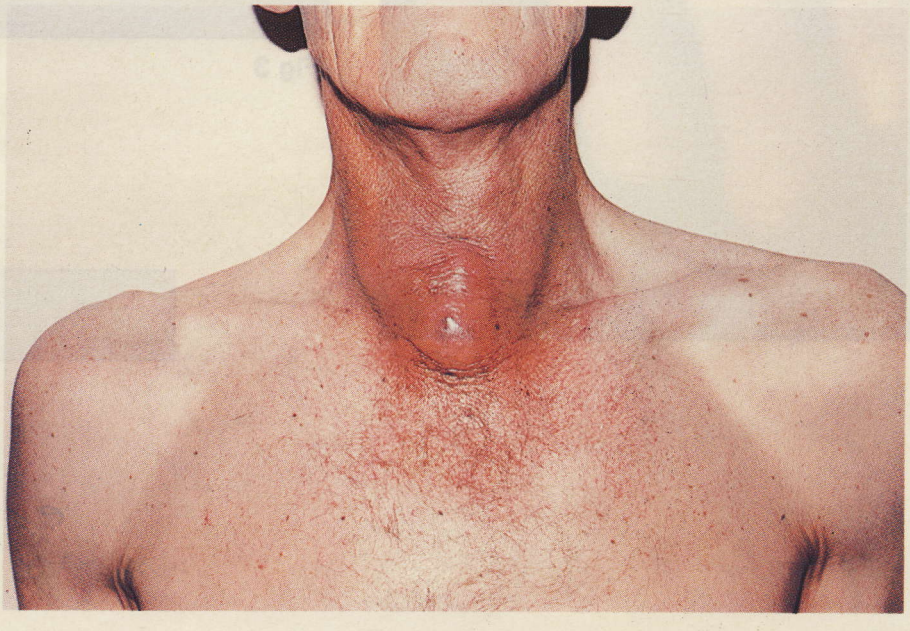
Free thyroxine index (FTI, T_7) reflects an estimation of free T_4 using T_4 and T_3 resin uptake.

Free T_4 supplies a measurement of the available active T_4 present and is therefore a more accurate assessment of thyroid function.

Serum T_3 measures the total amount of T_3 and is a useful confirmatory test for hyperthyroidism. In some cases of hyperthyroidism the T_3 alone may be elevated ("T_3 toxicosis"). In some situations there may be a decrease in conversion of T_4 to T_3

TSH - only useful in the diagnosis of hypothyroidism, and may be normal or low in hypothyroidism.

Reverse T_3 can be measured, but usually only in research laboratories. The I^{131} uptake remains a useful confirmatory test for hyperthyroidism.



TSH response to TRH - is useful for diagnosing secondary and tertiary hypothyroidism, and rarely for mild primary hypothyriodism. Also can be used to confirm the presence of hyperthyroidism, particularly in dubious cases.

Thyroid antimitochondrial antibodies suggest autoimmune thyroiditis. Low titres may be found in Graves' disease and high titres occur with Hashimoto's thyroiditis. Antithyroglobulin antibodies occur following any damage to the thyroid gland including trauma infection and autoimmune disease.

Hyperthyroidism

Hyperthyroidism is caused by an excess of T_3 and T_4 and may be due to Graves disease; toxic multinodular goitre; toxic "hot" nodule; exogenous T_4.

Graves' disease is a genetic disorder due to an increase in the HL-A8 histo-compatibility antigen. It is an autoimmune disease, primarily cell mediated with secondary IgG antibodies producing thyroid stimulating immunoglobulins. It is related to Hashimoto's thyroiditis and can be considered a differing degree of the same disease.

Treatment of Graves' disease remains controversial and must be individualised. Medical therapy using methimazole ± Propanolol, may be suitable for young patients with small goitres and mild thyroidoxicosis. Medical treatment is also the treatment of choice in pregnancy.

Alternatively radioactive iodine may be the treatment of choice overall and especially for older patients. There is a high incidence of post treatment hypothyroidism but the overall incidence of all complications of this therapy is not significantly different from thyroidectomy.

Thyroidectomy is a third form of therapy, but is rarely the treatment of choice. It is indicated in failed medical therapy, where there is a fear of malignancy, where there are large goitres, where obstructive symptoms occur, or by patients choice.

Thyrotoxicosis in pregnancy should be treated medically using two-thirds of the usual dose of methimazole thus keeping thyroid function at the upper limit of normal. Control residual symptoms with propanolol, but reassesses this every six weeks. Drug-induced maternal hypothyroidism must be avoided.

Thyroiditis

Acute Thyroiditis is rare. More often seen is a subacute presentation (De Quervain's thyroiditis). This is viral in origin and the features are: sore throat, painful ears, fever, raised ESR and in 80% of cases a swollen tender thyroid.

This is followed by a period of mild hyperthyroidism lasting four to six weeks, a period of euthyroidism, and then transient hyperthyroidism for the next three to four months.

Most cases resolve but the disease may recur.

The diagnosis may be difficult but should be confirmed by the presence of antithyro-globulin antibodies and the absence of thyroid antimicrosomal antibodies.

Treatment is by non-steroidal anti-inflammatory agents, temporary T_4 replacement, and, only in severe cases, by steroids.

Hashimoto's thyroiditis is the most common cause of hypothyroidism. It is a cell-mediated immune disease and there is a shared familial incidence with Graves' disease. It may present as hypothyroidism, mild hyperthyroidism (in the early phase), a euthyroid goitre, a multinodular goitre, a "hot" nodule, or a cold nodule or nodules, and thus may mimic any form of thyroid disease. The diagnosis is made by the presence of strongly positive thyroid antimicrosomal antibodies though they may be absent in up to 10% of cases.

Other forms of thyroiditis include the chronic fibrosing type (Reidal's) which is rare. It can mimic anaplastic thyroid cancer clinically.

Finally post I^{131} thyroiditis, traumatic thyroiditis, sarcoid and amyloid of the thyroid are occasionally seen.

Graves' disease in pregnancy

Medical therapy preferred
Keep thyroid function at upper limits of normal
Control residual symptoms with prophanolol
Reassess six weeks post-partum

Beware transient thyrotoxicosis in infant

Thyroiditis

1. Acute infectious thyroiditis
2. Subacute granulamatous (De Quervain's Thyroiditis)
3. Chronic lymphocytic (Hasimoto's) Thyroiditis
4. Chronic fibrosing (Riedel's) Thyroiditis
5. Miscellaneous
   a) Radiation thyroiditis
   b) Traumatic thyroiditis
   c) Associated with other disorders (Sarcoidosis, amyloidosis, syphilis, etc)

Hypothyroidism

Hypothyroidism presents in three forms. The first is primary and, as stated above, the commonest cause in Hashimoto's disease. Other causes are Post I^{131}, Postoperative and Idiopathic.

It is diagnosed by finding an elevated TSH, a low T_4, a low T_3RU, and a low free T_4. It is usually permanent and is sometimes associated

Findings in thyroid function disorders

	T_3	T_4	FT_4	FT_4I	T_3RU	RT_3	TSH	TSH response to TRH
Hyperthyroidism	↑	↑	↑	↑	↑	↑	↓ or N	↓
T_3 thyrotoxicosis	↑	N	N	N	N	N	↓ or N	↓
Thyroidal hypothyroidism	↓ or N	↓	↓	↓	↓	↓	↑	↑
Pituitary hypothyroidism	↓ or N	↓	↓	↓	↓	↓	↓ or N	↓
Hypothalamic hypothyroidism	↓ or N	↓	↓	↓	↓	↓	↓ or N	N and delayed
Low T_3 syndrome	↓	N or ↓	N or ↑	N or ↓	N or ↑	↑	N or ↑	N

↑ = increased ↓ = decreased N = Normal

with an enlarged pituitary fossa or low pituitary function tests. Hypothyroidism may be transient in three circumstances - immediately after I^{131} for ± six weeks, in subacute thyroiditis and after withdrawal of T_4 therapy.

Secondary hypothyroidism occurs as a manifestation of hypopituitarism and is diagnosed by finding a low TSH, low T_4 and T_3RU, and a low free T_4. There is also a flat TSH response to TRH.

The tertiary form is usually due to congenital hypothalamic disease. The same parameters as in the secondary form are also low but there is an excessive TSH response to TRH.

The Euthyroid sick syndrome

In severe illness there appears to be a substance produced which binds to TBG and this results in a low total serum T_4 level, with a normal or increased T_3RU. The free thyroxin index is usually low-normal but may be subnormal. The TSH is normal because of a normal free T_4.

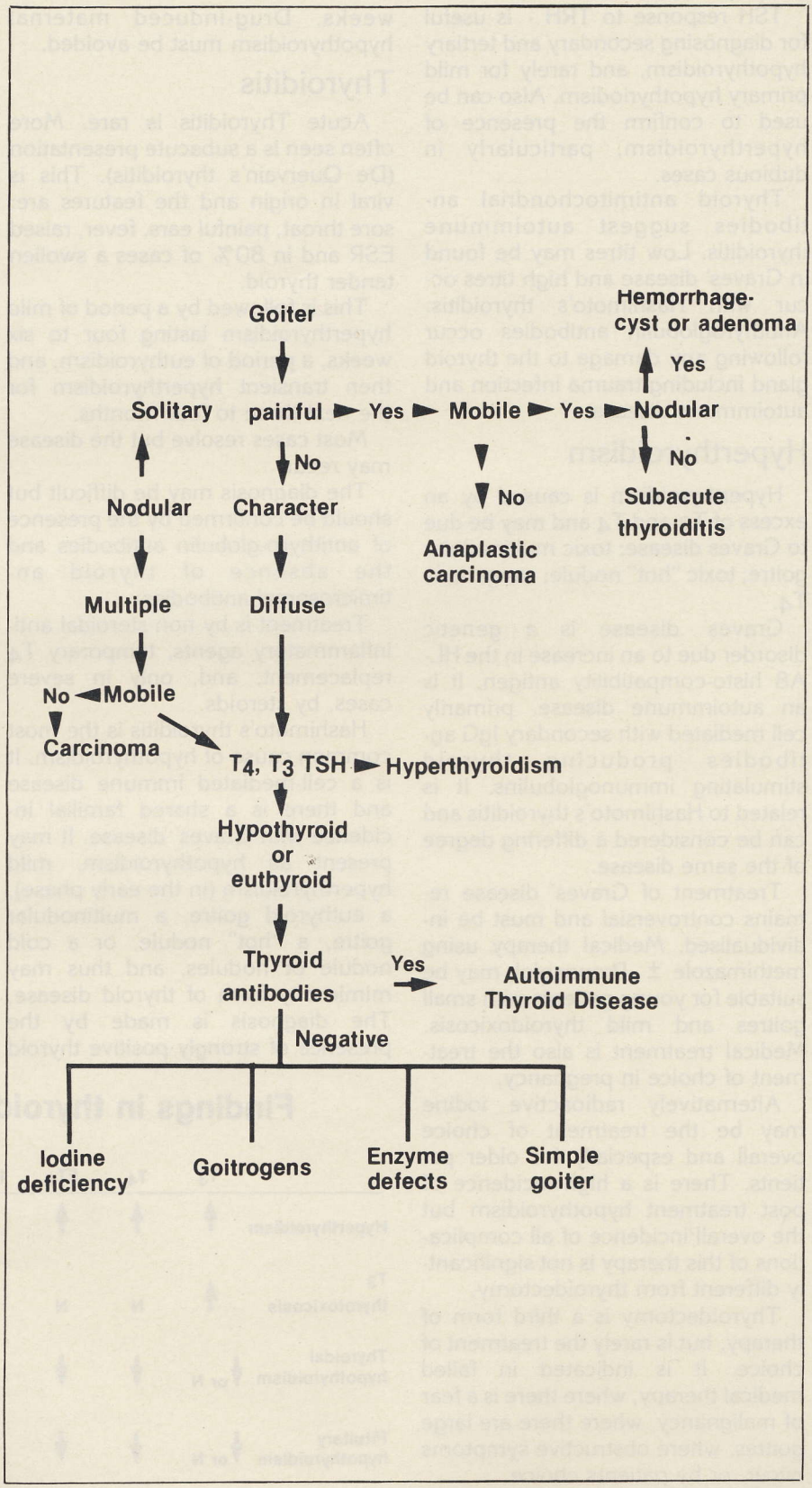
Chronic illness also results in increased RT_3 formation from T_4; with a concurrent decrease in free T_3. Thus in the euthyroid sick syndrome, the total serum T_4 decreases, the T_3RU is normal or increases, the T_7 may be low, the TSH and free T_4 are normal, the free T_3 is decreased, and the RT_3 increased.

It is not a thyroid disorder and does not require treatment.

Conclusion

The selective usage of appropriate thyroid function tests and an understanding of their interpretation should make the diagnosis of thyroid dysfunction a relatively simple task in the majority of patients.

Thyroid antibody studies are mandatory for a full thyroid work-up, irrespective of the patients presentation, since autoimmune thyroiditis can mimic any form of thyroid pathology. □



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