REVIEW

The Appropriate Use of Diagnostic Services (iii) Thyroid Disease and the Laboratory

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INTRODUCTION

Diseases of the thyroid are common, approximately 2% of women will have an episode of hyperthyroidism, 1.5% will become hypothyroid, and the overall prevalence of goitre may be up to 9% of the female population; the figures for men are lower but nevertheless in aggregate are substantial.[1] Hyper and hypo–thyroidism most commonly develop in middle age but both may present in the elderly when clinical diagnosis is notoriously difficult.

The diagnosis and management of thyroid disorders now rest considerably, but not solely, on laboratory tests of thyroid function. During the past 15 years laboratory methods for the investigation of thyroid disease have evolved rapidly. This article considers the methods available at present, and strategies for their effective and economical use.

BACKGROUND CLINICAL PHYSIOLOGY

The principal output of the thyroid gland is thyroxine (T_4) which can be regarded as a prohormone that requires conversion to the metabolically active triiodothyronine (T_3). This conversion of T_4 to T_3 may be reduced in severe illness, especially in the old, and may be retarded by drugs. The normal thyroid gland secretes only a small proportion of the daily requirement of T_3 but produces relatively more in hypothyroidism and hyperthyroidism. Patients with hypo-thyroidism treated with thyroxine have normal levels of T_3 all of which is derived from T_4 by deiodination.

Both T_4 and T_3 are largely bound by three plasma proteins, the 'free T_4' fraction (i.e. the proportion circulating in the non-protein-bound form) being less than 0.05% of 'total T_4' concentration and 'free T_3' being about 0.5% of 'total T_3'. It is believed that the biologically active form is the unbound fraction. The most important of the binding proteins is thyroxine binding globulin (TBG) and the concentrations of 'total T_4' and 'total T_3' in plasma largely depend on the concentration of TBG; this may vary in disease and is markedly increased by oestrogens. Moreover, some drugs are also bound by TBG from which they displace T_4 and T_3. Measurements of 'total' thyroid hormone concentration have always therefore to be considered in conjunction with the likely binding of hormone by TBG.

Thyrotrophin (TSH) is secreted by the pituitary gland and maintains the normal output of T_4 and T_3 from the thyroid. The secretion of TSH increases in response to a lack of thyroid hormone and conversely its release is inhibited by an excess; the basal TSH level therefore reflects indirectly the output of the thyroid gland.

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METHODOLOGY

'Total T_4' and 'total T_3' are customarily measured by radio-immunoassay (RIA). Many laboratories have developed their own reagents and methods, others use commercial reagents or kits. Almost all the methods are partially or fully automated. In many laboratories 'total' thyroid hormone concentration measurements are complemented by a parallel estimation of protein binding, either by direct immunoassay of TBG concentration or more commonly by indirect assessment of unoccupied binding sites ('T_3 uptake'). The two measurements are often used in conjunction to calculate an indication of available thyroid hormone (the so-called 'free indices'). Local considerations will dictate whether these estimates of binding are performed on every sample, hence generating two assays for a single thyroid function test request, or on samples selected by 'banding' of the results of 'total' hormone assays, a procedure which slows the reporting of the final results.

Direct measurements of 'free T_4' or 'free T_3' by dialysis are not practicable in a routine laboratory. Nevertheless the complexities of interactions between binding protein and thyroid hormone and the desire to replace two measurements by one have led to the development of new techniques which circumvent the effect of TBG and give results which closely approximate to the 'free' hormone concentration. These new methods for both 'free T_4' and 'free T_3' are RIAs which depend upon the use of radioactive tracer analogues of T_4 and T_3 which are not bound by TBG.

Radioimmunoassays for TSH have been in clinical use for over a decade. Few of these assays have sufficient sensitivity to distinguish between normal TSH levels and the suppressed levels in hyperthyroidism. Recently more sensitive immunoradiometric (IRMA) assays have been produced which are capable of this distinction.

It is necessary before using any assay in a clinical situation to define the laboratory range for the population by age (e.g. neonatal) and condition (e.g. stage of pregnancy). It should be remembered, however, that thyroid function is precisely regulated in health and that results for any individual are fairly constant and do not stray widely within the confines of the group normal range.

USE OF THYROID FUNCTION TESTS

Thyroid function tests are used to diagnose disorders of thyroid hormone output, to define the cause of thyroid gland enlargement, and to monitor treatment of thyroid disease. In certain specified circumstances such tests may be employed to screen for occult disease. They are also used in defining rare endocrine disorders secondary to pituitary disease. To order thyroid function tests as an unthinking routine ('box-ticking') is a waste of laboratory resources; the physician should be able to justify every request if challenged. The nature of thyroid disorders should be firmly established at the outset; it is wasteful and time-consuming to reconstruct the diagnosis once treatment has been started.

Hyperthyroidism is best diagnosed by measurement of the serum concentration of T_3, for in a small proportion of cases the T_4 is not raised. Unequivocal hyperthyroidism should be confirmed biochemically but initiation of treatment need not wait on the results. The TSH response to an injection of thyrotrophin releasing hormone (TRH) is abolished in hyperthyroidism and the TRH test may be used to identify minor degrees of over–production of thyroid hormone. A 'flat' TRH test may also be found, however, after clinically satisfactory treatment of hyperthyroidism or in autonomously functioning multinodular goitres; such a result is not of itself a mandatory indication for anti-thyroid treatment. It is not yet clear whether a single IRMA measurement of TSH will supplant the TRH test in clinical practice.[2]

Drug treatment of hyperthyroidism may be monitored by measurement of thyroid hormone levels; these fall rapidly after the start of treatment, during which time tests every few weeks may be helpful in tailoring the dosage. A patient on long-term treatment requires biochemical checks only two or three times a year. Thyroid failure develops within a year in about a quarter of hyperthyroid patients treated with non-ablative doses of radioactive iodine. During this time tests should be done sufficiently frequently to avoid the development of symptomatic hypothyroidism, but after a year those patients who

remain euthyroid require checks of their thyroid function not more than once a year.

Hypothyroidism is most readily diagnosed by a low T_4 concentration, for T_3 concentration may be sustained at normal levels by preferential synthesis and secretion by the thyroid. In primary disease of the thyroid gland the TSH is considerably elevated whereas in hypopituitarism, which only rarely presents as hypothyroidism, the TSH is inappropriately low. Hypothyroidism requires life-long therapy and should be documented by a minimum of two tests, treatment being deferred until the results are known.

In hypothyroidism the dose of thyroxine should be increased until the patient is clinically euthyroid *before* repeating thyroid function tests. Any necessary adjustments to dosage may then be made. Treatment with thyroxine does not require precise regulation. In the past larger doses of thyroxine than are now customary were used without ill effects; it is now known that although free T_4 may be high in such patients the free T_3 is little if at all elevated.[3] Either T_4 or T_3 measurements may be used to assess the adequacy of replacement. The only reason for performing a test in a patient stabilized on thyroxine is to check compliance; it is quite sufficient to do this annually, and at the same time haematological tests can be done to pick up developing pernicious anaemia.

Goitre requires that thyroid function be assessed biochemically but other investigations may be more helpful in leading to a diagnosis (e.g. thyroid auto-antibody screen, thyroid ultrasound or scintography, or fine needle aspiration cytology).

Screening for thyroid disease in the *neonatal* period is now routine to detect hypothyroidism, T_4 or more usually TSH from capillary samples being assayed in regional centres. Screening of the *geriatric* population in the community yields few undiagnosed cases, but the prevalence of thyroid dysfunction (undiagnosed or lapsed from treatment) amongst elderly patients admitted to hospital is high enough to warrant routine testing of thyroid function. In unexplained *atrial fibrillation* hyperthyroidism should be considered, but patients with otherwise explicable atrial fibrillation do not need thyroid function tests.

'Low T_3 syndrome' is characterised by low, often very low, total and free T_3 concentrations in the presence of a usually normal T_4 concentration and a normal TSH. This condition is common in elderly patients on first admission to hospital but may occur at any age in the very ill. It is due to failure to convert T_4 to T_3 and is probably an appropriate adaptive response; it does not require treatment *per se*. The use of T_3 or free T_3 measurements alone to determine thyroid function in in-patients may be very misleading; low levels must be checked against TSH or T_4 in order to define the clinical situation.

The antiarrhythmic drug *amiodarone* causes particular problems as it inhibits the conversion of T_4 to T_3 and its iodine content may directly affect thyroid function to cause either hypo- or hyper-thyroidism. Patients with normal thyroid function on treatment with this drug may have very high T_4 levels but T_3 and TSH are normal. Thyroid function tests (T_3 and TSH measurements) should be performed regularly (every two or three months) during treatment, and, because of the very long half-life of the drug, for several months afterwards.

All types of assays for T_4 and T_3 are affected by the presence of abnormal binding proteins or of auto-antibodies which combine with thyroid hormones.[4] Although these circumstances are rare they have in the past led to patients being treated inappropriately for both hyper- and hypothyroidism. The results of thyroid function tests should always be set against the state of the patient and any incongruity should lead to a thorough reappraisal. No patient should ever be treated on the basis of biochemical results alone.

INVESTIGATIVE STRATEGY

It will be clear from the foregoing discussion that there is no one biochemical test which can define thyroid function in all clinical circumstances. Moreover a test or combination of tests which may accurately characterise one condition may be less reliable in delineating another. Whereas laboratories serving a specialist endocrine unit may need on occasion the full range of thyroid function tests routine laboratories will rely on two or three.

The choice of thyroid function tests is wide and the practice in each laboratory differs. The analytical strategy for the investigation of thyroid disease should be decided by discussion between the clinicians and the laboratory staff. The strategy should provide the maximum clinical information for the minimum cost. For example, it may be decided that T_4 (or free T_4) is to be measured in all samples but that TSH is to be measured only when the results obtained fall outside a certain range.

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