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**DIAGNOSIS AND MONITORING
OF DISEASES
OF THE THYROID**

by

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ABBREVIATIONS

CV	coefficient of variation
EDTA	ethylenediamine tetraacetate (sodium or potassium salt)
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
hCG	human choriogonadotropic hormone
IRP	international reference preparation
LH	luteotropic hormone, luteotropin
mU	milliunits (international)
MRC	Medical Research Council
NTI	Non-thyroid illness
Tg	thyroglobulin
TgAb	thyroglobulin antibody
TPO	thyroid peroxidase
TPOAb	thyroid peroxidase/microsomal antibody
TRH	TSH releasing hormone
TRAb	TSH receptor antibody
TSH	thyroid stimulating hormone
T3	triiodothyronine
T4	thyroxine
WHO	World Health Organization

1. GLOSSARY

Biochemical and clinical terms

Autoantibodies: Antibodies against the patient's own body tissues.

Basedow's disease: see Grave's disease

Cretinism: Congenital hypothyroidism (decreased activity of the thyroid gland at birth) resulting in growth retardation, developmental delay and other abnormal features. Cretinism can be due to deficiency of iodine in the mother's diet during pregnancy. The condition is detected today by screening of the newborn's thyroid function.

Graves' disease: The most common cause of hyperthyroidism, Graves' disease is due to a generalized (diffuse) increased activity (toxic) of the whole enlarged thyroid gland (goitre); it is also commonly known as diffuse toxic goitre. There are three components to Graves' disease: hyperthyroidism, protrusion of the eyes (ophthalmopathy), and skin lesions (dermopathy). Ophthalmopathy can cause sensitivity to light and a feeling of "sand in the eyes." Dermopathy is a rare, painless, reddish lumpy skin rash that occurs on the front of the leg. Graves' disease can run in families. Factors that can trigger Graves' disease include stress, smoking, radiation to the neck, medications, and infectious organisms such as viruses. In addition to the symptoms of the triad, useful laboratory testing includes measurement of serum TSH, FT4, FT3 and TSH receptor antibody (TRAb). In certain cases a scan of the thyroid uptake of radioactive iodine can be helpful.

Primary hyper-/hypothyroidism,: elevated/decreased function of the thyroid gland are not caused by an increased or decreased stimulation by a governing hormone (TSH or TRH). The concentrations of thyroid hormones (T4,T3) in blood are usually increased.

Secondary hyper-/hypothyroidism: hyper- or hypofunction of the thyroid gland caused by increased or decreased stimulation by TSH.

Tertiary hypothyroidism: decreased activity of the thyroid gland caused by decreased stimulatory function of the hypothalamus, whereas the TSH secretion from the pituitary gland is normal.

Subclinical hypothyroidism: clinical condition with normal to slightly decreased thyroid hormone concentrations, but elevated compensatory TSH concentrations in blood.

Thyroid hormones: thyroid hormones are thyroxine (T4) and triiodothyronine (T3).

Thyroiditis, Hashimoto's: autoimmune thyroiditis. A progressive disease of the thyroid gland with antibodies in the blood stream directed against the thyroid. The Hashimoto thyroiditis may be familial.

Thyroiditis, postpartum: inflammation of the thyroid gland after pregnancy.

Thyroliberin: see TRH

Thyrotropin releasing hormone (TRH): hormone produced by the hypothalamus that stimulates the release of TSH from the anterior lobe of the pituitary gland

Thyroid stimulating hormone (TSH): hormone produced by the pituitary gland in response to signals from the hypothalamus. TSH promotes the growth of the thyroid gland and stimulates the production of thyroid hormones. When there is an excessive amount of thyroid hormones (e.g. primary hyperthyroidism), the pituitary gland stops producing TSH. This mechanism is the basis for the use of TSH in the diagnosis of primary hyperthyroidism.

Thyrotropin: see TSH

Thyroid peroxidase (TPO): membrane bound haemoprotein with peroxidase properties. The protein can be purified from the thyroid microsomal fraction.

TPO/microsomal antibody (TPOAb): IgG antibody against TPO, typically occurring in auto-immune thyroiditis (Hashimoto).

Thyroglobulin (Tg): protein produced by and found in the thyroid gland. Some thyroglobulin can be found in the blood serving as a possible tumour marker.

Thyroglobulin antibody (TgAb): antibody against thyroglobulin, which predominantly occurs in auto-immune thyroiditis.

Thyroxine (T4): major hormone of the thyroid gland, containing four iodine atoms per molecule. Thyroxine is the precursor of triiodothyronine (T3)

Thyroxine binding globulin: Transport protein for thyroxine (T4), produced by the liver.

Toxic adenoma: condition in which the thyroid gland contains active nodules that produce thyroid hormones without being stimulated by TSH, thereby causing primary hyperthyroidism.

TSH-receptor antibody (TRAb): antibody binding to the TSH receptor that, by a stimulating effect, can induce the development of Grave's (Basedow) disease.

Triiodothyronine (T3): hormone produced by deiodination of thyroxine (T4) in peripheral tissues. T3 contains three iodine atoms. It is the most active thyroid hormone, and affects almost every process in the body, including body temperature, growth, and heart rate. Also known as liothyronine.

Terms related to laboratory performance

Accuracy (of measurement) (analytical accuracy): closeness of the agreement between the result of a measurement and a true value of the measurand (analyte) (VIM, 3.5:1993).

NOTE 1: Accuracy is a qualitative concept.

NOTE 2: The term precision should not be used for "accuracy".

Calibration material (reference material, standard or calibrator): material used for calibrating a measurement procedure or a measurement instrument, or in making corrections to the values obtained.

External quality assessment (laboratory proficiency testing, proficiency testing): determination of laboratory testing performance by means of inter-laboratory comparisons (ISO/IEC Guide 43, part 1, 3.6:1996).

NOTE: The term “external quality assessment” (EQA) is sometimes preferred if proficiency testing is thought to convey an unintended impression of an official regulatory function.

Imprecision (imprecision of measurement): dispersion of independent results of measurements obtained under specified conditions (ISO 3534-1, 3.14:1993).

NOTE 1: Imprecision of measurements, when applied to sets of results, depends solely on the dispersion of random error of measurement and does not relate to a true value of the measurable quantity.

NOTE 2: Imprecision is the inverse of precision of measurements.

International reference preparation (material): reference material for calibration recommended by the World Health Organization.

Limit of detection (detection limit, detectability): lowest result of a measurement by a given measurement procedure that can be accepted with a stated level of confidence as being different from the value of the quantity obtained on blank material (IUPAC 1978).

Precision (precision of measurement): closeness of agreement between independent test results obtained under stipulated conditions (ISO 3534-1, 3.14:1993).

NOTE 1: Precision depends only on the distribution of random errors and does not relate to the true value or the specified value.

NOTE 2: The measure of precision usually is expressed in terms of imprecision and compute as a standard deviation of the test results. Less precision is reflected by a larger standard deviation.

NOTE 3: “Independent test results” means results obtained in a manner not influenced by any previous result on the same or similar test object.

Prevalence: the proportion of individuals in a population having a disease at a given time.

Quality assurance: all those planned and systematic actions necessary to provide adequate confidence that a product, process or service will satisfy requirements for quality (ISO 8402, 23.5:1994).

Quality assessment: systematic examination of the extent to which an entity is capable of fulfilling specified requirements (ISO 8402, 4.6: 1994).

Quality control: operational techniques and activities that are used to fulfil specified requirements for quality (ISO, 8402, 3.4:1994).

NOTE: Quality control involves operational techniques and activities both at monitoring a process and at eliminating causes of unsatisfactory performance at all stages of the quality loop in order to achieve economic effectiveness.

Reference interval: set of biological reference values usually referring to the central 95 percentile of values collected from a defined population.

Reflex testing: additional measurements based on the outcome of previous measurements and initiated by the laboratory.

Reproducibility, reproducibility of results of measurement: closeness of the agreement between the results of measurements of the same measurand carried out under changed conditions of measurement (VIM, 3.7:1993).

NOTE 1: A valid statement of reproducibility requires specification of the conditions changed.

NOTE 2: The changed conditions may include: principle of measurement - method of measurement - observer - measuring instrument - reference standard - location conditions of use - time.

Standard (measurement standard): material measure, measuring instrument, reference material or measuring system intended to define, realise, conserve or reproduce a unit or one or more values of a quantity to serve as a reference (VIM 6.1, 1994):

Example:

- a. 1 Kg mass standard
- b. Standard hydrogen electrode
- c. Reference solution of cortisol in human serum having a certified concentration

NOTE 1: A set of similar material measures or measuring instruments that through their combined use constitutes a standard, is called collective standard.

NOTE 2: A set of standards of chosen values that individually or in combination provides a series of values of quantities of the same kind is called a group standard.

Traceability: property of the result of a measurement or the value of a standard whereby it can be related to the stated references, usually national or international standards through an unbroken chain of comparisons all having stated uncertainties. (VIM 6.10, 1994)

Uncertainty (of measurement): parameter, associated with the result of a measurement, that characterises the dispersion of the values that could be reasonably attributed to the measurand (VIM, 3.9:1993).

NOTE 1: The parameter may be, for example, a standard deviation (or a given multiple of it), or the half-width of an interval having a stated level of confidence.

NOTE 2: Uncertainty of measurement comprises, in general, many components. Some of these components may be evaluated from the statistical distribution of the results of series of measurements and can be characterised by experimental standard deviations. Other components, are estimated from assumed probability distributions based on experience or other information.

NOTE 3: It is understood that the result of the measurement is the best estimate of the value of the measurand, and that all components of uncertainty, including those arising from systematic effects, such as components associated with corrections and reference standards, contribute to the dispersion.

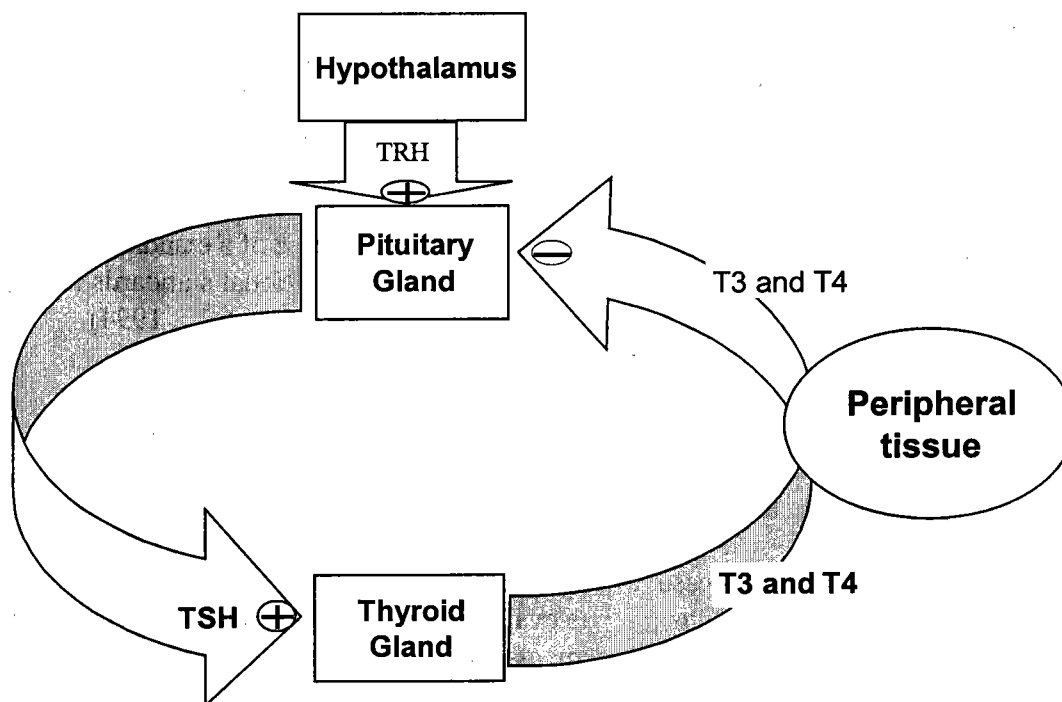
2. INTRODUCTION

2.1 Diseases of the thyroid gland

Diseases of the thyroid gland are among the most abundant endocrine disorders worldwide, second only to diabetes. Hyperfunction - hyperthyroidism - as well as hypofunction - hypothyroidism - occur in about 2 % and 1 %, respectively. The prevalence in men is about one tenth of that in women. Hyper- and hypothyroidism may be due to diseases of the thyroid gland, secondary to malfunction of the pituitary gland, or, tertiary, to malfunction in the hypothalamus. Goitre or active thyroid nodules may occur endemic in some areas due to dietary iodine deficiency, with a prevalence of up to 15 %. The thyroid gland may also be the site of various types of tumours and be damaged by endogenous antibodies (autoantibodies).

Severe maternal hypothyroidism due to iodine deficiency or thyroid blocking agents may lead to cretinism in newborns if untreated. It is of vital importance that this condition is recognised. In many countries screening of newborns by measuring thyroid stimulating hormone (TSH) has therefore become mandatory. Sampling should be performed during the first to second or 5th to 7th day after birth. Secondary congenital hypothyroidism is very rare and will not be recognised in the screening of newborns with TSH measurements.

Figure 1 Feedback loop of thyroid hormones



There is a delicate regulation of the thyroid function through a feed back loop. The pituitary gland produces thyrotropin (thyroid stimulating hormone, TSH), which stimulates the thyroid gland to produce and excrete thyroxine (T4). More than 99 % of the T4 is bound to proteins in plasma (thyroxine binding globulin, pre-albumin (transthyrenin) and albumin) and transported in the bound form. Less than 1 % of T4 is transported in the free form (FT4). The concentration of bound and free T4 make up the total T4. The thyroxine is de-iodinated to triiodothyronine (T3)

in the periphery. Free T₃, together with the free fraction of T₄ are the active hormones. The feedback loop is closed by the action of T₃ and T₄ on the pituitary gland. Thus, hyperfunction of the thyroid gland suppresses the production of TSH, whereas thyroid hypofunction stimulates the pituitary, to produce more TSH (Figure 1).

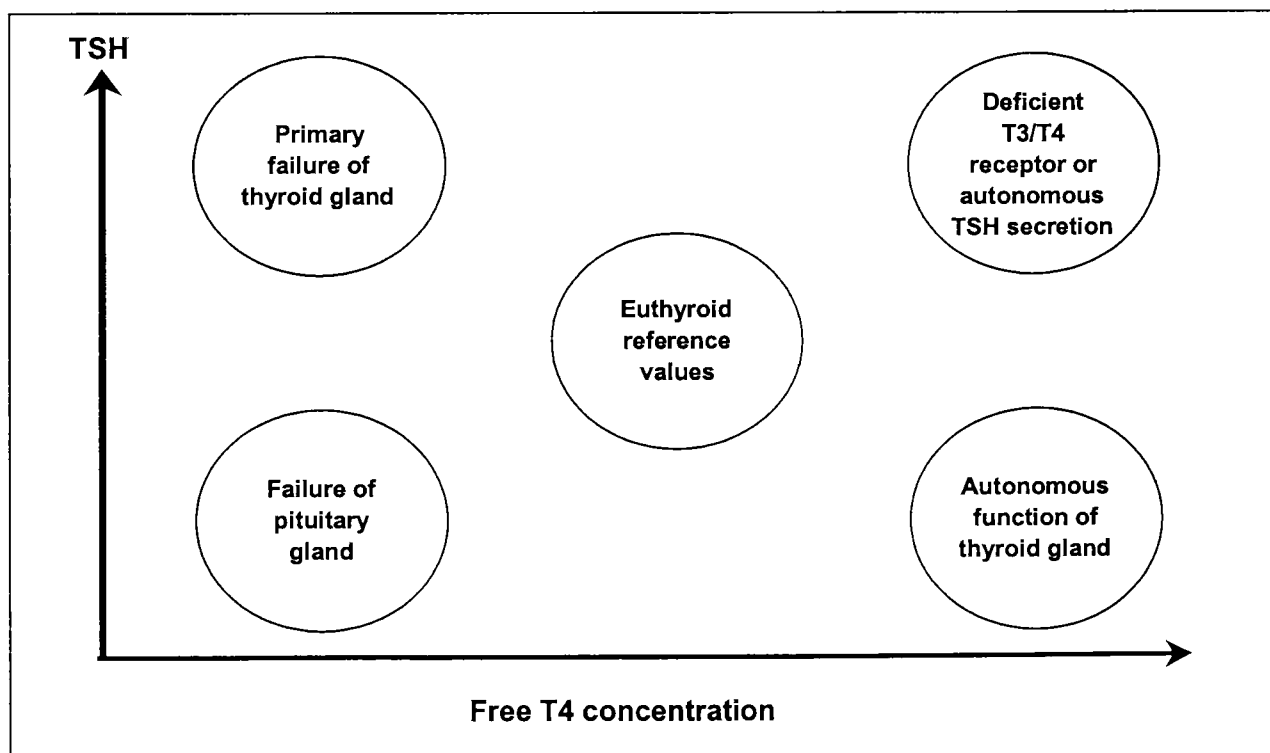
Thyroid diseases are serious and even life threatening but usually curable, manageable and treatable. Signs and symptoms of overt hyper- and hypothyroidism are well-known and usually recognised. In contrast, subclinical conditions have subtle clinical manifestations and may mimic other diseases. Non-thyroidal illnesses (NTI, see below), e.g. renal failure, liver disease, fulminant infections and metabolic diseases may cause adaptive responses of the thyroid. Furthermore, thyroid diseases may be only partly responsible for a complex presentation of symptoms. It is therefore important to develop rational laboratory strategies to differentiate the various conditions to guide the physician towards a correct diagnosis and treatment.

2.2 Laboratory diagnosis

Efficient diagnostic strategies can be based on the initial measurement of serum TSH concentrations, provided that a measurement procedure with sufficiently low detection limit is available. Differential diagnosis of thyroid disease requires additional measurement of FT₄, FT₃ and autoantibodies.

The thyroid hormones (thyroxine, T₄ and triiodothyronine, T₃) participate in the energy regulation. Biochemical tests and function tests e.g. basal metabolic rate were developed to diagnose thyroid disease. These investigations have lost their role in modern medicine and are substituted by direct measurement of the hormones. Typical interpretations of the measurement

Figure 2. Relations between thyroid hormones and clinical conditions



results are illustrated in Figure 2. Occasionally, the biochemical situation may be more complex. Thus a combination of decreased TSH and FT4 concentration may be due to non-thyroid illness (NTI). The pituitary gland is stimulated by thyroliberin (TRH, Thyrotropin releasing hormone) from the hypothalamus. However, measurement of this hormone does not play any role in the diagnosis of thyroid diseases.

2.3 Non-thyroid illness (NTI)

Non-thyroid illness is characterized by low serum T3 concentration and occurs in many conditions, including acute and systemic diseases. In NTI FT4 is increased, whereas TSH and FT3 are low. On recovery increased TSH may prevail for months, whereas FT4 is often low and FT3 is normal. Therefore it is not justifiable to attempt biochemical diagnosis of thyroid diseases during the acute phase of a disease. NTI symptoms may result from inhibited or decreased deiodination of T4 leading to low T3 concentrations.

3. PRINCIPLES OF MEASUREMENTS

3.1 General aspects on the performance of immunoassays

The measurement of low hormone concentrations in a complex serum matrix is an analytical challenge. Methods based on immune reactions between antigens and specific antibodies have been applied to solve the problem. Two principles of measurement are applied, the competitive and non-competitive assays. Competitive assays are preferably used for smaller antigens, whereas the non-competitive assays are used for antigens of larger molecular weight.

In competitive assays the sample is mixed with small amounts of a labelled antigen (tracer). After subsequent addition of a specific antibody the antigen-antibody complex formed is immobilized and nonreacted tracer removed. The signal observed during subsequent measurement correlates with the concentration of the analyte.

Several principles are used to identify the tracer. A radioactive isotope (^{14}C , ^3H or ^{125}I) may be inserted into the molecular structure, or conjugated to the antigen. The labelled antigen is then used as the tracer. Other principles use enzymes, fluorescent or luminescent substituents as non-radioactive tracers. Non-radioactive assays are nowadays preferred. The major advantage is safety in handling and disposal of reagents, longer shelf-life of reagents and a greater versatility in the design of the measurement procedure. In many countries radioactive isotope techniques require formal approval for the procurement of reagents and licensing of their use by the national authorities.

Non-competitive assays use two antibodies, one of which is bound to a solid phase and the second antibody carries a marker, which can be an enzyme, dye, etc. Non-competitive assays can be applied to measure large series of samples and instruments are available for automated measurement. The measuring unit is a photometer, luminometer or other suitable unit.

For the measurement of FT4 and FT3 there exist different types of immunoassays, analogue and two-step. In the two-step immunoassay FT4 and FT3 are separated from the hormone binding proteins (mainly albumin and pre-albumin) in the serum, before the antibody is reacted with the antigenic hormone. In the analogue method hormone binding proteins in serum are not separated and therefore undue interferences may occur. This explains why the quality of performance of the two step immunoassay may be superior to that of the analogue single step method.

3.2 In vitro measurements

Measurement of thyroid stimulating hormone (TSH)

TSH concentration is increased in primary hypothyroidism and decreased in primary hyperthyroidism. The same assay can be used to identify both conditions provided that the measuring interval covers pathologically increased and decreased concentrations of TSH. The 3rd and 4th generations of TSH assays can be used for the measurement of TSH concentrations of 0.01 mU/L or less and above 20 mU/L. The methods can be calibrated against an international reference material for TSH (IRP 80/558)¹

¹ Provided by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, South Mimms, Potters Bar, Herts. U.K. Tel.0044 1707 654753, Fax 00441707646730
e-mail: enquiries@nibsc.ac.uk

<i>Generation</i>	<i>Detection limit mU/L</i>
1 st	1 - 2
2 nd	0.1 - 0.02
3 rd	0.01 - 0.02
4 th	0.001 - 0.002

The problem of artefactitious elevation of TSH concentrations, observed by earlier methods in patients' sera contaminated with heterophilic antibodies, has been largely overcome by modern assays.

Measurement of total T4

The total T4 concentration is influenced by the concentration of thyroxine binding proteins. Although good methods for total thyroxine (T4) measurement are available, the results do not provide clinically relevant information.

Measurement of free thyroxin (FT4)

The biologically active form of thyroxin is its **free form**. Commonly, non-isotopic immunoassays are applied using enzymes or chemiluminescent markers. There is no international reference material available for FT4 and therefore results will be procedure dependent.

Measurement of total (T3) and free triiodothyronine (FT3)

T3 is the biologically most active thyroid hormone. Like total T4, total T3 concentrations are highly dependent on the binding proteins, and results of total T3 measurement may therefore be misleading. For FT3 measurements several non-isotopic assays are available. There is no international reference material available for FT3.

Measurement of serum thyroglobulin (Tg)

The thyroid intracellular protein, thyroglobulin (Tg), is released into serum in minute amounts. The Tg serum concentration is elevated in patients suffering from carcinoma, and Tg is also used as a marker for monitoring the development of metastases. The release of Tg is stimulated by TSH, and the evaluation of measurement results should be made whilst considering any suppression treatment. The results may be confounded by crossreactivity of the reagents and the presence of Tg antibodies. The detection limit is important for the specification of Tg measurement procedures, since low concentrations of Tg are of diagnostic value. An international reference material is not available.

Other methods

FT4 index and related indirect methods, such as T4 uptake, T3 uptake (thyroid hormone binding ratio), and thyroxine binding capacity, are no longer recommended.

Autoantibodies against thyroglobulin and TSH receptors (TRAb)

The quality of measurement of autoantibodies against thyroglobulin is inferior to that of TRAb in terms of their diagnostic sensitivity and specificity. Presently, there is no international agreement on the calibration of the existing measurement procedures. Therefore unpredictable variations between results may be evident when using different reagents and calibrators.

TPO/microsomal antibodies

The antigen of microsomal antibodies has been identified as thyroid peroxidase (TPO); hence the antibodies are called TPO antibodies. At present there is no international agreement on the calibration of the existing TPO antibody assays. Therefore one might experience variations between results using different reagents and calibrators.

Tg antibodies

There is presently no internationally agreed reference material available for the immunometric measurement of Tg antibodies.

3.3 In vivo measurements

3.3.1 Function tests

Thyrotropin releasing hormone (TRH) stimulation test.

TRH is administered intravenously (200 µg or 7 µg/kg for children), intranasally (2 mg) or orally (40 mg). The basal concentration of TSH and a peak concentration should be measured after 30 minutes intravenously or intranasally and 180 minutes for oral application.

3.3.2 Diagnostic imaging procedures

Diagnostic imaging is used for the diagnosis of:

- suspected or proven diffuse thyroid enlargement,
- thyroid nodules,
- Grave's (Basedow) disease.

Ultrasound examination, possibly combined with Doppler technique is the method of choice for the anatomical localisation and determination of the size of the thyroid gland, and/or for the exploration of structural changes indicating pathological conditions. Occasionally, fine needle aspiration biopsy of the thyroid gland is made under control by ultrasound.

Isotope examinations with ^{99}Tc pertechnetate or ^{123}I iodide, using a gamma camera provide good information on the function of the thyroid gland, or of specific areas ("nodules"). However, the precise anatomical location or size of a nodule cannot be determined.

In patients with diffuse thyroid enlargement imaging with computed tomography (CT) should be additionally considered to evaluate the thoracic inlet for possible tracheal deviation and compression.

4. QUALITY MANAGEMENT OF TESTS

External quality assessment schemes have been established for the majority of analytes discussed above. Laboratories should regularly participate in the surveys to assure comparability of results.

Reproducibility of measurements is imperative for all activities in the diagnosis and monitoring of endocrine disorders. Therefore, laboratories should establish an efficient quality system. This should include a continuous recording and evaluation of results of measurements of control samples using Shewhart type procedures and taking the Westgard rules for quality control into account.

4.1 Preanalytical aspects

In general serum is used for the measurements; however, heparinized, citrated or EDTA plasma may also be used according to the recommendations of the manufacturer of reagents. There may be a difference between results obtained from serum or plasma. With the exception of the antibodies all the described analytes are stable for several weeks at 4 to 8 °C. Samples for the determination of antibodies should be frozen if measurements are not made at the same day.

Turbid samples must be centrifuged prior to measurement.

Patients undergoing therapy for thyroid disease should discontinue treatment one month before sampling to establish a true baseline.

TSH is secreted into blood in a circadian rhythm with high levels during early morning (2 to 4 h) and low levels during late afternoon (17 to 18 h).

During early pregnancy FT4 and FT3 concentrations increase and TSH concentration decreases.

No significant changes in FT3 occur from the 2nd day, and for FT4 from the 30th day of life.

After delivery of birth women may suffer from post partum thyroid dysfunction that may be caused by auto-immune thyroiditis or, auto-immune hypothyroidism (Graves disease).

Drugs, including amiodarone, salicylates, carbamazepine and fenclofenac interfere with FT4 and FT3 measurement. Lithium therapy has a side effect on the thyroid function.

4.2 Specifications of measurement procedures

Acceptable coefficients of variations for measurements are shown in table 2. The values in table 2 are for general guidance only, since reference intervals are assay dependent.

Special criteria are important for certain analytes and should be provided by the manufacturer of the reagents used, e.g. for measurement of TSH:

- detection limit <0.05 mU/L, inter-assay variation < 20 %
- cross reactivity of <0.01 % with glycoproteins like hCG, FSH and LH
- parallelism between the dilution curves of patient's serum samples and the calibration curve (± 10 % deviation)
- precise measurement of the standard material that is added to the patient's serum ± 10 %
- measurement results of the WHO or MRC reference materials with ± 5 % of the expected value.

Table 2 Quality specifications and tentative reference intervals		
Analyte	Quality specification, imprecision (CV %)	Reference interval
TSH, adults, mU/L	< 10	0.4 - 5.0 ²
TSH, newborn, mU/L	< 10	<20
FT4 pmol/L*	< 10	10 - 23
FT3 pmol/L*	< 10	5.4 - 12.3
TPO antibody, kU/L*	< 15	< 100
TRAb, U/L	< 15	Method dependent
Tg antibody, U/L	< 15	Method dependent
Thyroglobulin (Tg) µg/L	< 10	<60 <1 in patients after total thyroidectomy

* Based on several kits

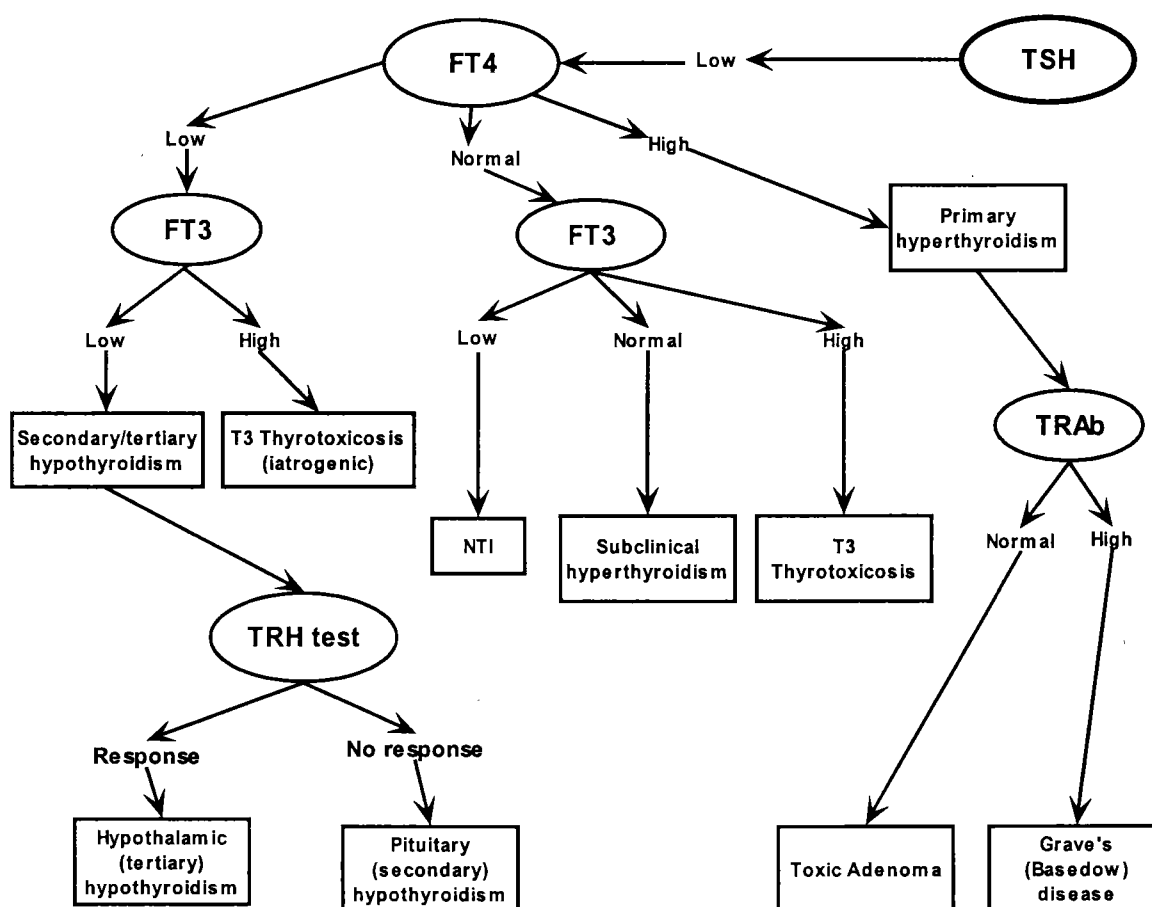
² The lower limit of the reference interval for TSH is not well defined. Some individuals may have low TSH levels without showing clinical symptoms of hyperthyroidism.

5. INDICATIONS FOR BIOCHEMICAL INVESTIGATIONS

TSH

The improved measurement of TSH has made the TSH assay the first line test in the assessment of thyroid function. TSH is also widely used for the screening for hypothyroidism in the newborn.

Figure 3 Diagnostic Strategies with decreased S-TSH. Ovals indicate measurements, boxes suggested diagnosis



In combination with measurements of the free thyroid hormones TSH is used for the

- diagnosis of primary and secondary hypothyroidism
- diagnosis of clinical hyperthyroidism, mild/subclinical conditions and non-thyroid diseases
- fine tuning of T4 and T3 replacement therapy in hypothyroidism and after thyroid ablation;

FT3 and FT4

As illustrated in the flowcharts (Figures 3 and 4) measurements of FT3 and FT4 are made in combination with TSH to establish diagnosis (e.g. hypo-, hyperthyroidism and secondary hypothyroidism).

In addition, FT3 is measured

- to exclude T3 thyrotoxicosis in case of decreased TSH and normal or decreased FT4 (Figure 3);
- to monitor the progress of substitution after thyroid ablation.

Antibodies

There are only a few clinical situations when antibodies should be measured. TPO antibodies should be assessed, (and Tg antibodies, if TPO antibodies are normal), if thyroiditis is suspected. Other indications are post partum thyroiditis, where increased concentrations of TPO antibodies are common whereas an increase of Tg antibodies is unusual, and sub-acute thyroiditis (De Quervain's) where only the concentration of Tg antibodies may be raised.

Measurement of TRAb is useful in assessing the aetiology of primary hyperthyroidism.

Thyroglobulin (Tg)

Thyroglobulin is measured for the monitoring of patients with differentiated papillary or follicular thyroid carcinoma, after ablative therapy and for the early detection of the recurrence of malignant disease. Tg measurement is also useful to distinguish factitious thyrotoxicosis from other forms of hyperthyroidism.

TRH stimulation test

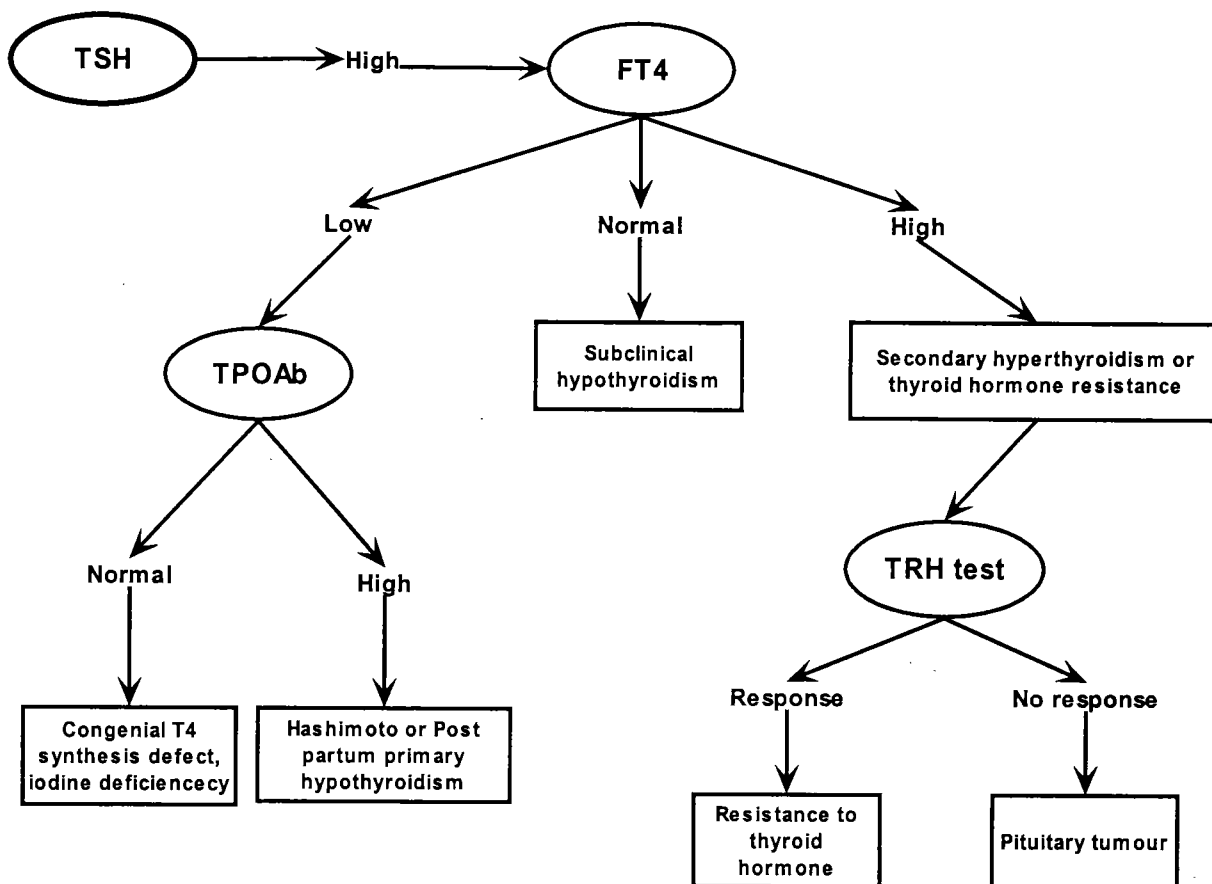
TRH stimulation test is valuable to investigate the capability of the pituitary gland to secrete TSH. This may be important for the diagnosis of secondary hypothyroidism or secondary hyperthyroidism. Cost effectiveness of this investigation should be considered in each case.

A rational approach for the diagnosis of thyroid disorders starts with TSH measurement. If the results are below or above the reference interval of TSH, FT4 should be measured to further characterise a diseased stage (Figures 3 and 4). The FT3 is not required for the diagnosis of hypothyroidism if TSH is increased (Figure 4). FT3 can be of value in monitoring situations with simultaneously low TSH and FT4 (Figure 3). Further investigations may be decided by the laboratory (reflex testing) based on the outcome of the initial TSH measurement. Reflex testing cannot reasonably go beyond measuring FT4 without consultation with the clinician.

TRH stimulation tests are useful for assessing conditions that may be caused by a dysfunction of the pituitary gland.

Investigation at a later time (after 3 -5 years) are advisable, if the patient belongs to a risk group, or shows unclear symptoms, even if TSH concentrations were found to be 'normal'. In some countries screening with TSH of women above 50 years of age is recommended.

Figure 4 Diagnostic strategy with elevated S-TSH



6. FURTHER READING

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