

Diagnostic methods of TSH in thyroid screening tests

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Abstract

Introduction: Reliable and quick thyreologic diagnostics, as well as verification of the effectiveness of the therapy undertaken, is of great importance for the state of health of society. The measurement of plasma TSH is the commonly accepted and most sensitive screening test for primary thyroid disorders, which are the most frequent diseases related to the endocrine glands. At present, the available methods for the determination of TSH are characterized by high sensitivity ≤ 0.01 $\mu\text{IU/ml}$ and lack of cross-reactivity. However, many drugs and substances, as well as pathological conditions, may affect the TSH level.

Objective: evaluation of contemporary laboratory methods for the determination of TSH and the principles of interpretation of screening tests.

State of knowledge: In many countries, the TSH test is the only test performed in the diagnostics of thyroid function; nevertheless, it seems that for genuine and objective assessment of thyroid status the TSH level, together with FT4 level, should be absolutely determined, which allows the differentiation and assessment of the intensity of thyroid function disorders and foresee its consequences. The interpretation of TSH results in screening tests is different in such population groups as: children aged under 14, pregnant women, the elderly, and patients with non-thyroidal illnesses.

Conclusions: From among currently used laboratory methods for determination of TSH levels, third generation non-isotopic methods are most frequently recommended, especially the method of immunochemiluminescence.

Key words

thyroid disorders, screening laboratory tests, TSH

INTRODUCTION

Thyroid diseases are the most frequent endocrine disorders, among which the diseases on the autoimmune background (AITD, Autoimmune Thyroid Diseases) occupy the primary position, and concern approximately 5% of the population. Thyroid diseases are 5–10 times more often diagnosed among females than males, and the frequency of their occurrence increases with age. In the case of hyperthyroidism in children morbidity is 10 times rarer compared to adults [1]. Quick thyreologic diagnostics, as well as verification of the effectiveness of the therapy undertaken, is of the utmost importance for the state of health of society.

Thyrotropin (TSH – Thyroid Stimulating Hormone) stimulates the production and secretion of the metabolically-active thyroid hormones, thyroxine (T4) and triiodothyronine (T3), by interacting with a specific receptor on the thyroid cell surface. TSH is composed of two non-covalently linked subunits, designated alpha and beta. Although the alpha subunit of TSH is common to luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG), the beta subunits of these glycoproteins are hormone specific and confer biological as well as immunological specificity. The synthesis and secretion of TSH is stimulated by the thyrotropin releasing hormone (TRH), the hypothalamic tripeptide, in response to low

levels of circulating thyroid hormones. Elevated levels of T3 and T4 suppress the production of TSH via a classic negative feedback mechanism. Recent evidence also indicates that somatostatin and dopamine exert inhibitory control over TSH release, suggesting that the hypothalamus may provide both an inhibitory and stimulatory influence on pituitary TSH production [1].

The measurement of plasma TSH is the commonly accepted and most sensitive screening test for primary thyroid disorders, because the pituitary gland responds with great changes in its secretion, even to slight changes in the levels of free thyroid hormones. The sensitivity of its measurement in the diagnostics of tissue hormone excess is estimated to be higher than 95%, and the specificity – approximately 90%, while its daily fluctuations are very small and are of no importance for the interpretation of results [2]. The determination of TSH serves not only as a preliminary test in the differentiation of the thyreologic state of the population, but also plays the role of a predictive factor of the occurrence of malignant changes within the nodules [3]. In many countries, the TSH test is the only test performed in the diagnostics of thyroid function; however, it seems that for a genuine and objective assessment of the thyreologic state, the level of TSH, together with FT4 level, should absolutely be determined, which allows the identification of patients with pathology of the hypothalamo-pituitary system with respect to thyroid axis. At the same time, an abnormal TSH level makes it necessary to determine the peripheral hormone levels, and form of free thyroid hormones FT4 and FT3, which enables evaluation of the intensity of thyroid function disorders and foresee its consequences (Fig. 1) [1, 2].

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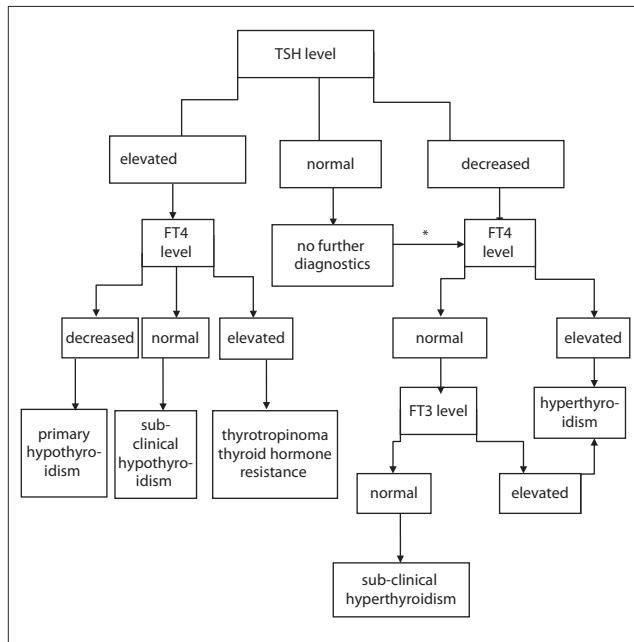


Figure 1. Algorithm for diagnostic procedure in thyroid diseases [1,2].
*If secondary hypothyroidism is clinically suspected, FT4 should be assessed.
TSH – thyroid stimulating hormone; FT4 – free thyroxine; FT3 – free triiodothyronine.

Review of laboratory tests of thyroid function. Studies evaluating the thyroid function have changed, together with the progress of diagnostic methods, from classic studies, such as an assessment of basic metabolism, protein-bound iodine and serum cholesterol level, through studies *in vivo* with isotopes (determination of iodine uptake, test of suppression of iodine uptake by the thyroid gland, Werner's test and bovine TSH stimulation test, Ambinon test, to isotope tests *in vitro*, or modern non-isotope methods). The methods for determination of TSH which were used many years ago were characterised by low sensitivity, because they detected only the normal and elevated levels of TSH (1.0 mIU/l), and by low specificity. The main drawback of these methods was cross-reactivity with other glycoprotein hormones with a structure similar to TSH, such as gonadotrophic hormones; FSH and LH, or hCG.

The currently applied methods for the determination of TSH are characterized by a much higher sensitivity (3rd generation methods, even up to ≤ 0.01 μ IU/ml, (μ IU/mL equivalent to mIU/L) and specificity, due to the use of two monoclonal antibodies identifying two different epitopes of the TSH, which allowed the elimination of cross-reactivity [4]. Current guidelines for TSH assays recommend a functional sensitivity of ≤ 0.01 μ IU/ml for 'third' generation performance. The protocol for determining the functional sensitivity of TSH assays specifies analyses of serum samples with two reagent lots over a 6 – 8-week period. Functional sensitivity has replaced analytical sensitivity as a means of assessing low concentration accuracy [5]. Table 1 presents currently used biochemical methods applied in thyreological diagnostics.

Radioimmunological methods are the conventional isotope methods consisting in the measurement of radioactivity of the substance labelled with a radioactive isotope (antigen or antibody) participating in the antigen-antibody reaction. The RIA method uses the competition between the antigen labelled with a radioisotope (at a known concentration) and

Table 1. Methods of determination of TSH level [5, 6, 7].

Isotope methods	Non-isotope methods
RIA – Radio-Immuno Assay (radioimmunologic)	EIA – Enzyme Immuno Assay (immunoenzymatic)
IRMA – Immuno-Radio-Metric Assay (immunoradiometric)	ELISA – Enzyme linked Immunosorbent Assay
CPB – Competitive Protein Binding (radiocompetitive)	MEIA – Microparticle Enzyme Immuno Assay
RRA – Radio-Receptor Assay (radioreceptor)	FIA – Fluoro Immuno Assay (immunofluorometric)
	LIA, Lumino Immuno Assay (immunochemiluminescence)

a non-labelled (examined) antigen for the antibody binding site with the production of antigen-antibody complexes, which are subsequently separated. By measuring the activity of these complexes and knowing the amount of the added antibody and labelled antigen the level of non-labelled, i.e. the examined antigen may be calculated. The results of these determinations exert an effect on both the clinical status of the patient, drugs administered, type of diet, as well as the levels of insulin and renin in blood, or time of the day. The method of collecting blood samples and their storage is also of great importance. The limitations of this method result both from the possibilities of the occurrence of cross-reactivity with other substance of a structure similar to that of the substance examined, and the sensitivity of the method, because the lowest TSH value determined is 1uIU/ml.

Further progress in the methodology of TSH determination was the introduction of sensitive 2nd generation radioimmunologic methods. The Immuno-Radio-Metric Assay (IRMA) consists in the incubation of TSH antigen and two monoclonal antibodies, one of them labelled with radioisotope iodine 125 (marker), while the other is immobilized on the inner surface of the test tube (a coated tube system) and production of 'sandwich'-like complexes. After washing out the excess marker, the measurement of radioactivity is performed. The radioactivity measured is directly proportional to the level of TSH in a respective sample. Analytical sensitivity read from the optimum curve is 0.04 μ IU/ml. Functional sensitivity of the test is 0.07 mIU/L. Cross-reactivity is for HCG <0.1%, FSH <0.01%, LH <0.1%. The limitations in the use of this method mainly concern lipemic serum, because lipemia decreases the measured values (triglycerides > 700 mg/dL). However, the values of haemoglobin (<600ng/dL) or bilirubin (<10mg/dL) do not exert an effect on the result of determination.

Other isotope radioimmunologic methods for the determination of TSH are rarely used today. The Competitive Protein Binding radioassay (CPB) uses the reaction between the substance examined and specific antibody, while the Radio-Receptor Assay (RRA) uses cell receptors for the hormones examined instead of antibodies. The determinations cover the substances which show biological activity, and the labelled antigen competes with that unlabelled for a limited number of binding sites [4, 5, 6].

Among non-isotope methods, an equally sensitive 2nd generation method is the Enzyme Immuno Assay (EIA), in which an antigen or antibody is linked to an enzyme, a colour reaction occurs, and the intensity of colour indirectly depends on the concentration of the antigen or antibody determined, and measured with the use of spectrophotometric methods. Similarly, the Enzyme Linked Immunosorbent

Assay (ELISA) is a sensitive and very specific method which allows the qualitative and quantitative detection of antigens or antibodies. This is a method for the detection of specified proteins in the material examined with the use of polyclonal or monoclonal antibodies conjugated with a suitable enzyme, most often peroxidase. The essence of the test consists in the introduction of biological material containing antibodies linked to enzyme, specific for the immobilized antigen, which produce an immune complex. After the addition of a suitable substrate, the enzyme linked to the specific antibody catalyses the reaction, the product of which may be spectrophotometrically determined. Within this method, three tests are distinguished: a quicker, so-called direct ELISA test, where an antigen is bound to the antibodies on a microtiter plate and then detected by the subsequent enzyme-linked antibodies, and indirect ELISA test, in which the antigen-specific monoclonal antibody, so-called primary antibody is unlabelled, while labelled secondary antibody binds to the primary antibody. Both immunoenzymatic methods, EIA and ELISA, as well as immunofluorometric method (FIA, Fluoro Immuno Assay), are characterized by high sensitivity in detecting TSH, i.e. the lowest value determined being 0.01 μ IU/ml [6, 7].

Further progress in the methodology of the determination of TSH is the development of 3rd generation tests, where the lowest measurable value remains within the range 0.01 μ IU/ml, whereas the immunochemiluminescence (direct chemiluminescence) technique (LIA, Lumino Immuno Assay) uses constant amounts of two antibodies, and has a high sensitivity. The first – in the labelled reactant, monoclonal mice anti-TSH antibodies labelled with acridine ester, and the second – in the solid phase, labelled with acridine ester, polyclonal sheep anti-TSH antibodies covalently linked to paramagnetic particles. There is a direct relationship between a patient's TSH level, and the relative luminescence units (RLU) measured by photodetector. However, there are some limitations with this method: if heterophilic antibodies are found in a serum sample they may react with immunoglobulins in the reactants, and affect the results of immunodiagnostic tests *in vitro*. Patients who have a constant contact with animals or animal serum may be susceptible to such interferences, and show abnormal TSH values. Analytical sensitivity of the test is 0.01 mIU/ml. Functional sensitivity is 0.019 mIU/ml. An equally sensitive test of the 3rd generation is MEIA, i.e. improved EIA. Microparticle enzyme immunoassay (MEIA) is a technique in which the solid-phase support consists of very small particles covalently bound to the microparticles. Antigen, if present, is then 'sandwiched' between bound small microparticles in liquid suspension: specific reagent antibodies and antigen-specific, enzyme-labelled antibodies. Antigen-antibody complexes are detected and quantitated by analysis of fluorescence from the enzyme-substrate interaction [6, 7].

There are also certain limitations while applying the above-mentioned methods, due to the heterogeneity of the TSH particle and the occurrence of its different isoforms. The specificity of tests is still insufficient in the case of an abnormal TSH structure, and in consequence, its alternated biological activity, which may be the case in the diseases of the hypothalamus and pituitary gland, when the TSH molecule may be abnormally glycosylated (an excessive amount of sialic residues) and, therefore, may possess a decreased thyrotropic activity. This leads to the development of central

hypothyroidism, despite the normal or slightly elevated serum TSH level. It was noted that in 35% of patients with central hypothyroidism the TSH level is decreased, in 41% – normal, and in 25% – elevated [8].

The reliability of TSH determinations in approximately 10% of patients is also affected by the presence of heterophilous antibodies which interfere with the methodology of some analytical tests and cause falsely extortionate results. Two classes of such antibodies have been distinguished: polyreactive antibodies to which belong, among others, IgM class rheumatoid factor, and antibodies produced as a result of infection or contact with animal antigen, defined as HAMA (Human Anti-Mouse Antibodies) and HAAA (Human Anti-Animal Antibodies) [4, 9].

Interpretation of laboratory test results in thyroid diseases.

During the last two decades the upper normal limit for TSH has decreased to the present value of 4.0–4.5 mIU/ml in adults, but values vary slightly among laboratories. In the UK, guidelines issued by the Association for Clinical Biochemistry suggest a reference range of 0.4–4.5 mIU/ml [10]. The National Academy of Clinical Biochemistry (NACB) stated that it expected the normal range for adults to be reduced to 2.5 μ IU/mL, because research had shown that adults with an initially measured TSH level of over 2.0 μ IU/mL had 'an increased odds ratio of developing hypothyroidism over the [following] 20 years, especially if thyroid antibodies were elevated [4]. In addition, the NACB refers to the fact that over 95% of healthy volunteers without personal and family medical history taking for thyroid diseases, goiter, seronegative to antiperoxidase and anti-thyroglobuline antibodies and who do not take medicines, have a TSH level within the range of values 0.4–2.5 mIU/ml [4]. Simultaneously, many experts in thyrology, based on the results of population studies, agree concerning the lower normal limit of 0.2–0.4 mIU/ml [11, 12, 13].

Interference of drugs and other substances, as well as diseases and pathological conditions with thyrotropic axis, is also an important problem (Tab. 2). Moreover, the interpretation of the TSH level in population groups, such as: 1) children aged under 14; 2) pregnant women; 3) the elderly; 4) patients with non-thyroidal illnesses, should be performed in a different way than among the general population.

The first group in which the specific criteria should be applied are children, in whom both TSH and fT4 levels are

Table 2. Factors affecting TSH level [1, 2, 6].

Factors causing increased secretion of TSH		Factors causing decreased secretion of TSH	
Drugs and other substances	Diseases	Drugs and other substances	Diseases
dopamine receptor antagonists		dopamine and dopamine receptor agonists	
haloperidol		somatostatin and its analogues	
chlorpromazine	Addison's disease	thyroid hormones	endogenous depression
amphetamine	cirrhosis	glucocorticosteroids	Cushing's disease
lithium compounds	malaria	opioids	acromegaly
sulfapyridine	malignant cancer	pimozide	severe renal failure
H ₂ receptor blockers		fentolamina	malnutrition
clomifene		cyproheptadine	
iodine and iodine compounds in RTG		klofibrat	
		salicylates	
		9-cis-retinoic acid	
		interferon	

higher in the first year of life, especially during the first week, and the upper normal TSH limit is slightly higher than in adults and remains so until the age of 14 [4].

The subsequent special period of life is pregnancy, when the physiological TSH level decreases due to the thyrotropic effect of hCG. According to the researchers, during the 1st and 2nd trimesters, the lower normal limit of TSH is within the range 0.01–0.03 mIU/ml, and in the 3rd trimester reaches higher values within 0.1 mIU/ml. However, the upper normal limit for the individual trimesters is by approximately 30% lower than the producer's norms. An unequivocal determination of the upper normal limit for individual trimesters of pregnancy is preferred within the following ranges: 1st trimester – 2.5 mIU/ml, and maximum 3 mIU/ml in the 2nd and 3rd trimesters [4, 14, 15].

Conventionally, as a cut off point, 0.2–0.4 mIU/ml is used for the lower normal limit, paying attention to the elderly in whom the values between 0.1 – 0.4 may increase the risk of occurrence of heart rhythm disorders [16, 17]. Although the clinically obvious form of the disease brings about neither diagnostic nor therapeutic difficulties, the sub-clinical form remains a controversial problem in the circles of endocrinologists. Biondi and Cooper indicated a considerable and versatile risk of complications related with sub-clinical hyperthyroidism [18]. Even mild suppression of the TSH level – TSH < 0.3 mIU/ml, brings about the risk of cardiovascular complications (most often atrial), as well as an increased mortality risk, especially in patients at the old age and/or with a medical history of cardiovascular diseases [19, 20]. Nevertheless, these results are not unequivocal, because studies by German researchers did not confirm at all the relationship between sub-clinical hyperthyroidism and cardiovascular risk in an adult population [21].

However, in postmenopausal women, even in the condition of sub-clinical hyperthyroidism, an additional complication is the possibility of decrease in the mineral bone density as a result of accelerated bone turnover, with the domination of bone resorption [22]. Thus, in the group of old age patients the diagnostic and therapeutic interpretation should always be considered individually, taking into account all coexisting risk factors [23].

Patients with non-thyroidal illnesses, low T3 syndrome, low T3 and low T4 syndrome, sick euthyroid syndrome, require a different interpretation of TSH determinations in combination with free fractions of hormones fT3 and fT4. The disorders observed are associated with the suppressed TSH secretion and decreased serum fT3, and during the period of convalescence may take a course with an increase in TSH level, without the necessity for substitutive treatment [2, 24, 25].

At the same time, it should be emphasized that the presence of an abnormal TSH level makes it necessary to determine the level of peripheral hormones and forms of free thyroid hormones FT4 and FT3, which allows evaluation of the intensity of thyroid function and foresee its consequences (Fig. 1).

CONCLUSIONS

From among currently used laboratory methods for the determination of TSH level, non-isotope methods are most frequently recommended, especially the

immunochemiluminescence technique (LIA), because it is characterized by very high sensitivity ≤ 0.1 mIU/l (for 3rd generation method) and specificity (lack of cross-reactivity). Among isotope methods, only the immunoradiometric assay (IRMA) maintains comparable analytical parameters, as well as concerning its cost. However, it should be kept in mind that many factors, including age, medicines administered and other conditions (pregnancy, some diseases), may affect TSH level. The interpretation of the TSH test results differs in such population groups as children aged under 14, pregnant women, as well as patients at old age and those with non-thyroidal illness. This fact should be considered not only in the clinical diagnostics but also in screening population studies.

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TSH TESTS The best way to initially test thyroid function is to measure the TSH level in a blood sample. Changes in TSH can serve as an "early warning system" often occurring before the actual level of thyroid hormones in the body becomes too high or too low. A high TSH level indicates that the thyroid gland is not making enough thyroid hormone (primary hypothyroidism). The opposite situation, in which the TSH level is low, usually indicates that the thyroid is producing too much thyroid hormone (hyperthyroidism). Occasionally, a low TSH may result from an abnormality in the pituitary gland,