Thyroid Function

TSH

Analyte Information

Thyroid-stimulating hormone (TSH)

Introduction

Thyroid-stimulating hormone (thyrotropin, TSH) is a glycoprotein with molecular weight of approximately 28 kDa. The hormone is released by the anterior pituitary gland (adenohypophysis) in response to thyrotropin-releasing hormone (TRH).

It consists of two noncovalently linked subunits – alpha and beta. The alpha-subunit contains 92 amino acids, and it is almost identical with the alpha-subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG). The beta-subunit, composed of 118 amino acids, is unique for TSH and it is responsible for its specific interaction with TSH receptor.

Its main biological function is to stimulate thyroid gland to produce and release thyroid hormones thyroxine (T4) and triiodothyronine (T3). Thyroid hormones control the basal metabolism and are necessary for neural development, normal growth and for sexual maturation.

Biosynthesis

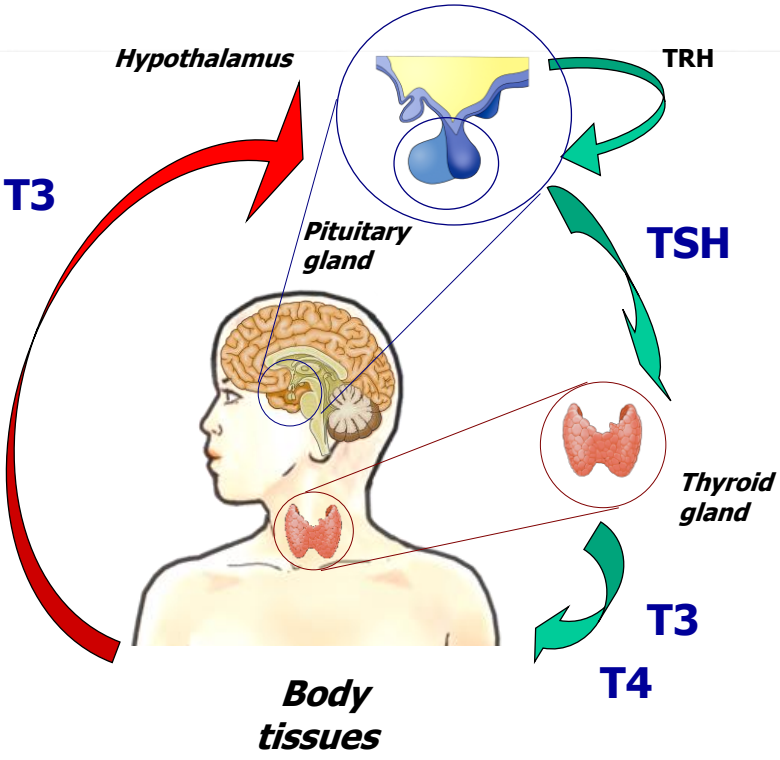
Production of TSH is induced by the hypothalamic hormone TRH and it takes place in thyrotrope cells of anterior pituitary gland.

TSH is released into circulation and stimulates thyroid gland to produce thyroid hormones T4 and T3. High T3 and T4 levels act by the negative feedback mechanism (see Fig.1) and diminish pituitary response to TRH. On the contrary, low T3 and T4 levels increase secretion of both TRH and TSH.

There are other factors playing certain role in stimulation and inhibition of TSH synthesis, including emotions, stress, immune system, nutrition state of the organism, or other hormonal systems (adrenal hormones, estrogens, somatostatin, dopamin).

The biological half-life of TSH is approximately 1 hour.

Fig.1: Hypothalamo-pituitary-thyroid axis



Physiological Function

The main function of TSH is regulation the endocrine function of the thyroid. It interacts with specific cell receptors on the thyroid cell surface and stimulates two actions:

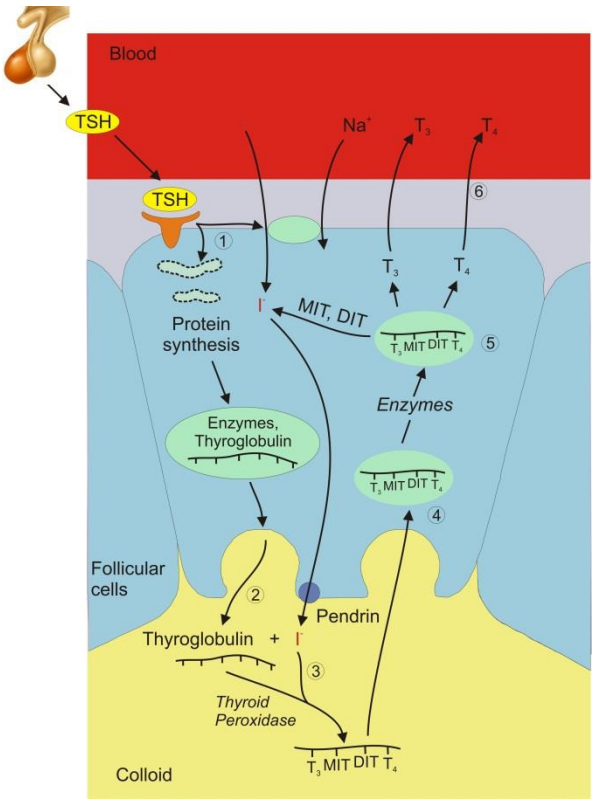
- Reproduction of thyroid cells and thyroid hypertrophy
- Production and secretion of thyroid hormones – T3 and T4

TSH binding to thyroid receptor can be mimicked by receptor stimulating antibodies in autoimmune Graves' disease. Thyroid receptor is also stimulated, in certain extend, by hormone hCG that increases significantly in pregnancy. This can provoke a transient condition termed gestational hyperthyroidism.

Production of thyroid hormones starts by absorption of iodide from the blood into follicular cells, against its concentration gradient. Transport is mediated by an intrinsic membrane protein called the Na+/I− symporter (NIS), stimulated by TSH. On the other side of the cell, a second I−transport protein called pendrin moves iodide into the colloid, where it is involved in hormonogenesis (see Fig.2 and 3).

As iodide is taken in, TSH stimulates the synthesis of thyroglobulin. Thyroglobulin is a big dimeric protein that serves as a reservoir and substrate for thyroid hormone production, and its transport into the follicular colloid. Simultaneously, TSH stimulates synthesis and transport of enzymes participating in thyroid hormone creation.

Fig.2: Follicular cell and thyroid hormone synthesis



1. TSH binds to its receptor and stimulates intake of iodide and synthesis of thyroglobulin

2. Enzymes and thyroglobulin are transported into the colloid by exocytosis

3. Iodide is bound to the thyroglobulin molecule to create T3 and T4

4. Thyroglobulin is taken back into the cells by endocytosis of the colloid

5. Globules with colloid merge with lysosomes; lysosomal proteases release T3 and T4 from Tg

6. T3 and T4 are transported across the cell membrane and enter circulation

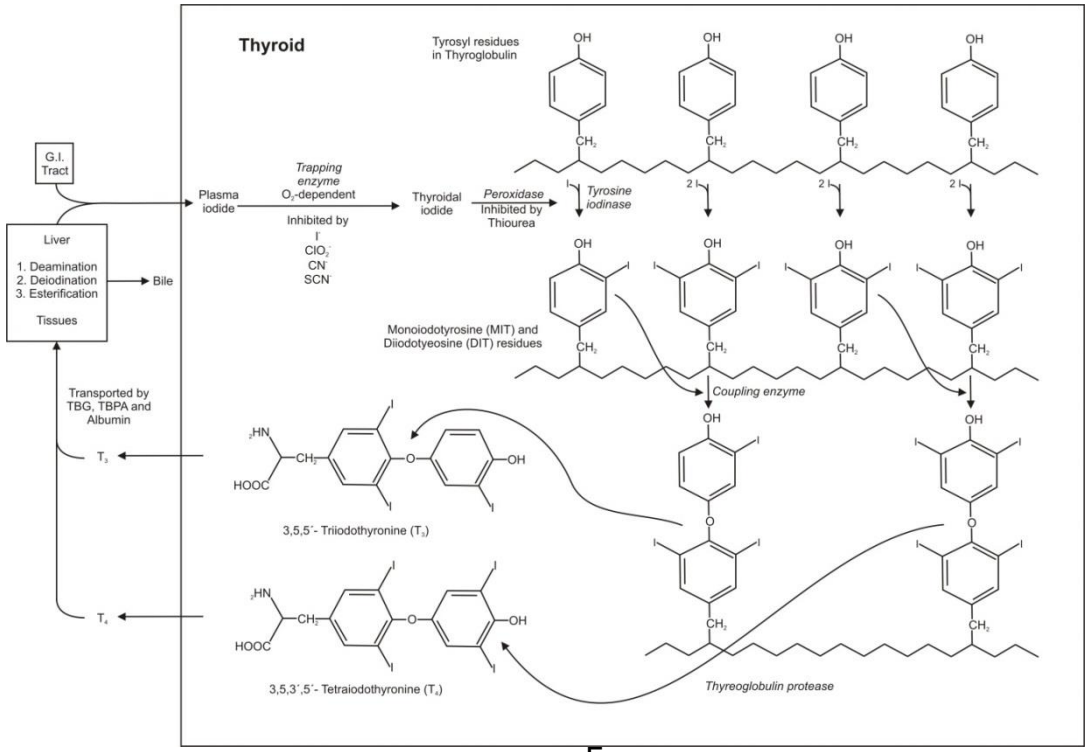
The enzyme called thyroid peroxidase catalyses covalent binding of iodine to tyrosine residues in the thyroglobulin molecule, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Thyroxine is created by combining two molecules of DIT; triiodothyronine is created by combining one molecule of MIT and one molecule of DIT. This occurs within the colloid, but mainly at the interface between the follicular cell and the colloid.

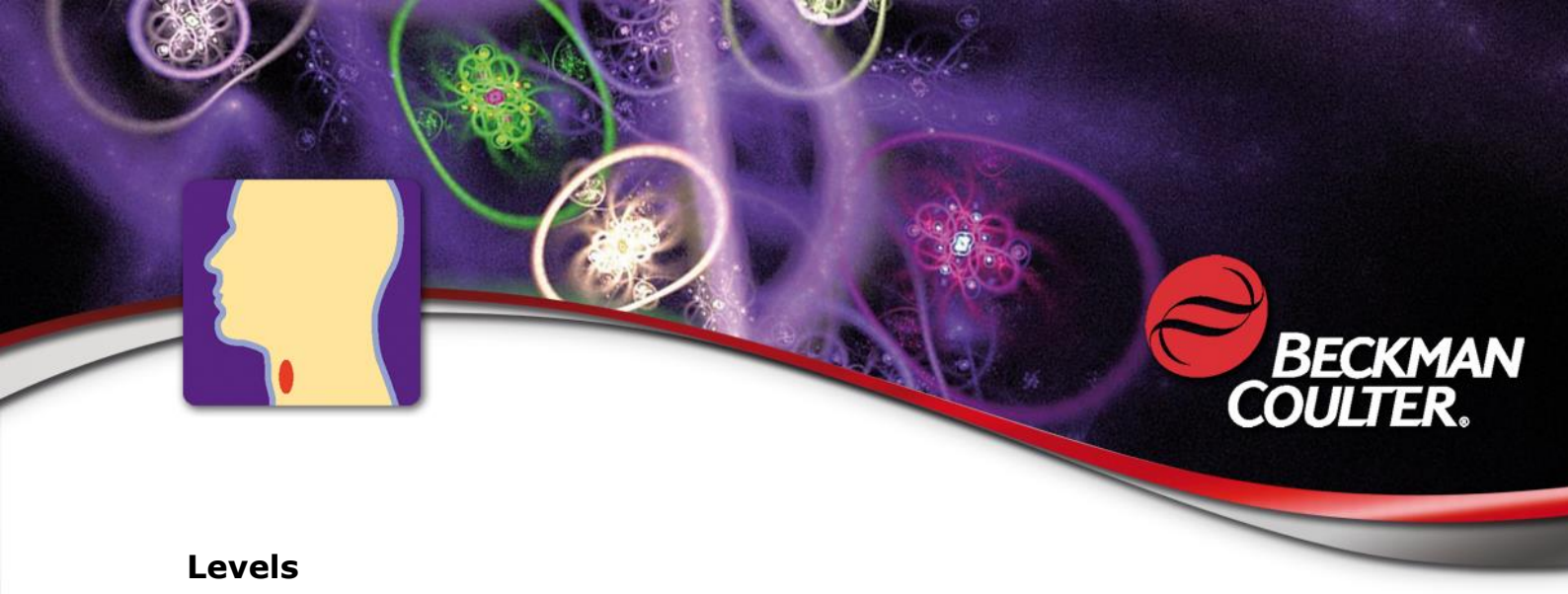
Small globules of follicular colloid are endocytosed, again under the influence of TSH. These globules merge with lysosomes. Proteases present in lysosome digest iodinated thyroglobulin and release T3 and T4 from binding. TSH also mediates the transport of T3 (10%) and T4 (90%) across the thyrocyte membrane into circulation, while the lysosome is recycled back into the follicular lumen.

Thyroid hormones enter the cells and binds to a nuclear receptor, causing transcription of specific thyroid hormone responsive genes.

There are two main functions of the thyroid hormones. The first role is to increase metabolism, and the second role is to maintain normal growth and development in children, including mental development and attainment of sexual maturity.

Fig.3: Formation of thyroid hormones[1]





Levels

The TSH levels are relatively stable through the life, with two exceptions:

- TSH levels increase significantly with birth, peaking at 30 minute, but they normalize to adult values within a few weeks.
- TSH levels are increased during first trimester of pregnancy. It is caused by increased concentrations of placental hormone hCG. As the receptors for hCG and TSH have 85 % analogy, TSH receptor is, in certain extend, stimulated by hCG. It leads to increase of thyroid hormone level and consequent suppression of TSH by negative feedback mechanism. TSH level normalizes in the second trimester.

Certain increase of expected values during the life is reported, but it reflects increasing prevalence of thyroid gland disorders with age rather than real physiological increase.

TSH has diurnal rhythm, with the lowest values at 5-6 p.m. and highest at 2-4 a.m.

Typical TSH levels[2] of children and adult males and females are given in Tab.1.

For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Tab.1: Typical TSH levels in serum[2]

Specimen (serum)	Reference interval (mIU/L)
Children	
Premature infants (28-36 gestation week)	0.7-27
1-4 days	1.0-39
2-20 weeks	1.7-9.1
5 months-20 years	0.7-6.4
Adults	
21-54 years	0.4-4.2
55-87 years	0.5-8.9
Pregnancy	
First trimester	0.3-4.5
Second trimester	0.5-4.6
Third trimester	0.8-5.2

Diagnostic utility

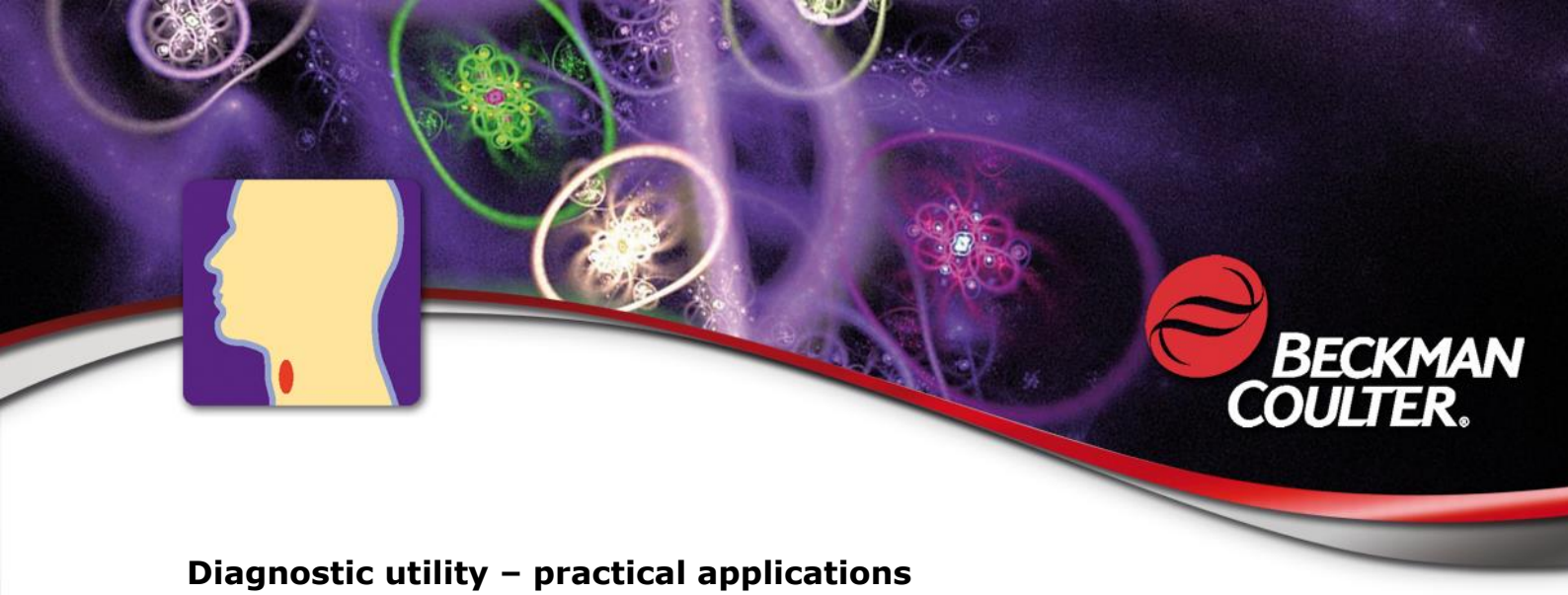
As thyroid diseases are often presented with vague and subtle symptoms, the assessment of thyroid hormones values is a key to the proper diagnosis of thyroid disorders. The determination of TSH is the test of the first choice. The change of TSH level is much more pronounced than the changes in T3 or T4 levels, e.g. change of FT4 twice can elicit 100-times changed serum TSH value. TSH is used for diagnosis of hypo- and hyperthyroidism and their subclinical forms, when the TSH value is altered but thyroid hormones still remain within the range. It is also very useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypo- and hyperthyroidism.

Elevated TSH levels

- primary hyporthyroidism
- secondary hyperthyroidism
- subclinical hypothyroidism
- physical stress
- diagnostics using ^{131}I
- ectopic TSH secretion (lung, breast tumors)
- thyroid hormone resistance
- euthyroid sick syndrome (recovery phase)
- drug administrations - amiodarone, benserazid, clomiphene, chlorpromasine, haloperidole, lithium, methimazole, metoclopramide, phenothiazine, propylthiouracilmorphine, drugs containing iodine

Decreased TSH levels

- primary hyperthyroidism
- secondary and tertiary hypothyroidism
- subclinical hyperthyroidism
- euthyroid sick syndrome
- acromegaly
- Cushing's syndrome
- 1st trimester of pregnancy
- mental anorexia
- secondary amenorrhea
- Klinefelter's syndrome
- chronic kidney insufficiency
- liver cirrhosis, serious illness,
- drug administrations - corticoids,bromocriptine, carbamazepine, cyproheptadine, levodopa, metergoline, phentolamine, somatostatin, apomorphine, dopamine, verapamile, diphenylhydantoine, heparin



Diagnostic utility – practical applications

Diagnosis, differential diagnosis of primary and secondary hyperthyroidism and monitoring of hyperthyroidism treatment

Primary hyperthyroidism

TSH is suppressed, T4 and T3 increased. Patients with hyperthyroidism typically have serum TSH concentration less than 0.05 mIU/L. A serum TSH within euthyroid reference interval almost always eliminates the diagnosis of hyperthyroidism. Finding a low TSH concentration and elevated FT4 level is usually sufficient to diagnose **primary hyperthyroidism**.

If the TSH concentration is low and FT4 concentration within the normal reference interval, a T3 measurement should be performed, because serum T3 level is often elevated to a greater extent than T4 in early phases of **Graves' disease and in some cases of solitary or multinodular toxic Goiters** (called T3 thyrotoxicosis).

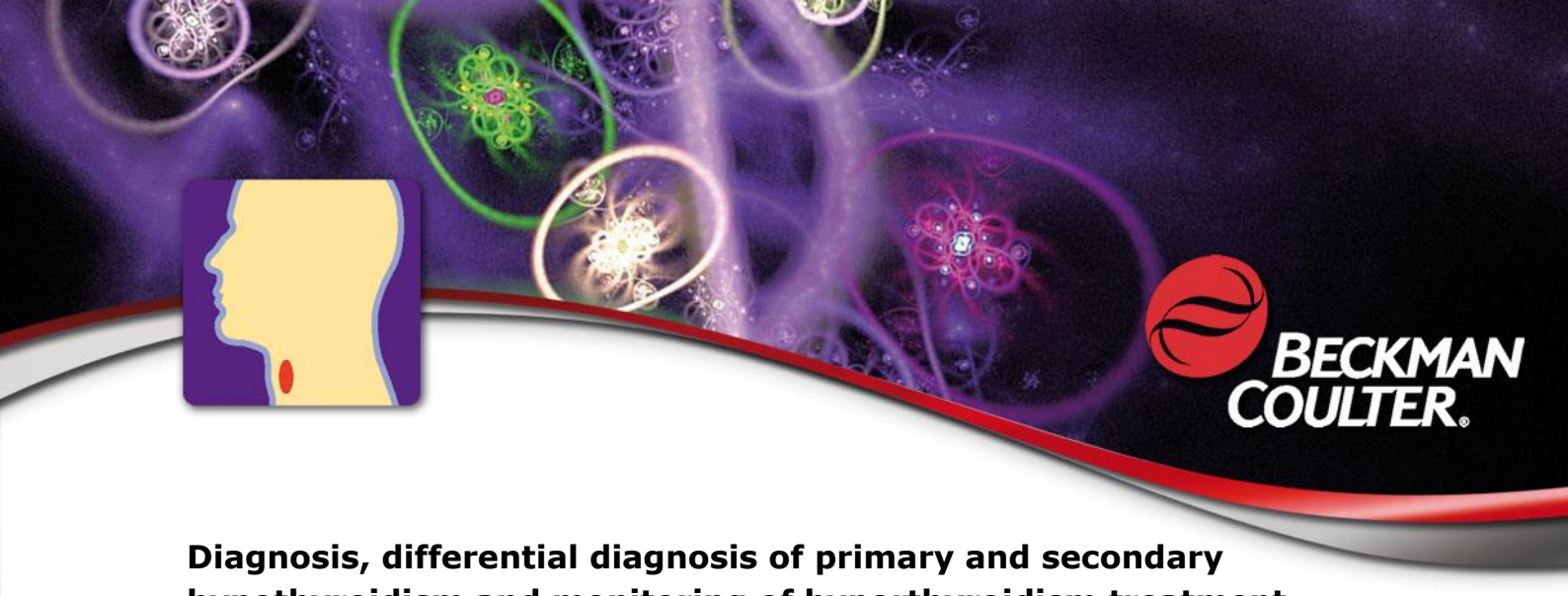
A persistently suppressed TSH serum concentration of normal FT4 and FT3 levels could indicate **subclinical hyperthyroidism**.

Secondary hyperthyroidism

In rare cases of increased T4, T3 levels together with TSH, thyroid hormone rise is mediated by TSH due to either TSH-secreting pituitary adenoma, or pituitary resistance to thyroid hormones, or mutation of thyroid hormone receptor gene.

Monitoring of hyperthyroidism treatment

At the time treatment is initiated, measurements of serum FT4 are recommended every few weeks until symptoms abate and serum values normalize. Continuous monitoring after successful therapy is recommended, either with TSH, or with FT4, or both, in dependence of the type of treatment.



Diagnosis, differential diagnosis of primary and secondary hypothyroidism and monitoring of hyporthyroidism treatment

Primary hypothyroidism

Synthesis of T4 and T3 is impaired, what leads to increase in TSH concentrations and consequent stimulation of thyroid enlargement (goitre). Primary nongoitrous hypothyroidism is characterized by loss or atrophy of thyroid tissue, resulting in decreased production of thyroid hormones despite maximal stimulation of TSH. **Hashimoto's thyroiditis** is the most frequent cause of primary hypothyroidism. This is frequently associated with circulating anti-thyroid antibodies. Reduced levels of T4 and T3 lead to hypersecretion of pituitary TSH. The elevated TSH concentration is an important factor. In mild of **subclinical form**, thyroid hormone concentrations remain within euthyroid interval, but TSH is already elevated.

Secondary and tertiary hypothyroidism

Secondary hypothyroidism occurs as a result of pituitary disease, tertiary hypothyroidism as a result of hypothalamic disease. TSH levels are decreased, as well as concentration of thyroid hormones T3 and T4. Thyrotropin-releasing hormone (TRH) stimulation test helps to differentiate between secondary and tertiary hypothyroidism. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism.

Congenital hypothyroidism

Congenital hypothyroidism is a common cause of preventable mental retardation. It affects approximately 1 of 3 000–4 000 infants. Congenital hypothyroidism may be caused by congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion.

Neonatal screening tests determine the level of TSH, sometimes in combination with FT4, to detect congenital hypothyroidism already few days after the birth. Drop of blood is collected to filtration paper from a heel of the newborn. High TSH levels and low FT4 level suggest congenital hypothyroidism.

Monitoring of hypothyroidism treatment

Adequacy of administered dose is evaluated by the determination of TSH. If it is within the normal range, optimally at lower part of reference range, the treatment is considered satisfactory.

Diagnosis of hypothyroidism in pregnancy

Hypothyroidism in pregnancy is usually caused by Hashimoto's disease. There are recommendation to determine TSH, FT4 and anti-TPO during 1st trimester. Cut-off levels of parameters should be adjusted on the bases of healthy pregnant women.

The affected women should be sent to endocrinologist and treatment by thyroxine should start.

Confirmation of TSH suppression in thyroid cancer patients

In patients on TSH suppression therapy of differentiated thyroid cancer, TSH is monitored to confirm that the dose of levothyroxine is sufficient to suppress the TSH to the desirable value (usually <0.1 mIU/L, lower in case of high risk patients).

Thyroid screening in elderly

Frequency of thyroid diseases increases significantly with age and symptoms of hyperthyroidism and hypothyroidism can be manifested only in a subtle way among older people, or the symptoms may be considered as the manifestation of another disorder. Therefore, establishment of a screening program seems to be desirable. Determination of TSH, FT4, and Anti-TPO in all women over 50 is one of the possible strategies, but no clear consensus has been achieved yet.

References

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