Thyroid Function

Free and Total Thyroxine

Analyte Information

Free and Total Thyroxine (FT4/TT4)

Introduction

Thyroxine (T4), together with triiodothyronine (T3), are two biologically active thyroid hormones.

Both, T4 and T3, play a crucial role in biology of human body. Derived from the amino acid tyrosine, and bedecked with four iodines, thyroxine is the ultimate metabolism regulator. It influences carbohydrate metabolism, protein synthesis and breakdown, and cardiovascular, renal, and brain function. Untreated babies with low T4 are sentenced to cretinism, adults will suffer from mental slowness, weight gain, depression, and fatigue.

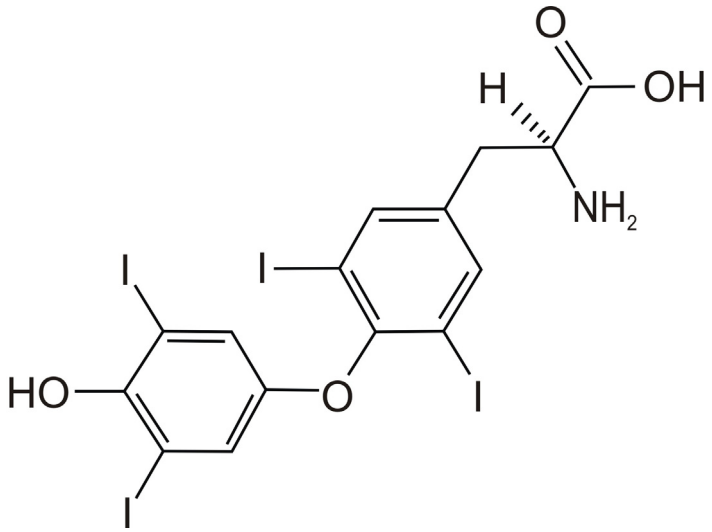
T4 together with T3 act on virtually every cell in the body to alter gene transcription. Disorders associated with changed thyroid hormone secretion are common and affect about 5% of women and 1% of men.

T4 makes up more than 80% of circulating thyroid hormones and serves as pro-hormone for T3 in target tissues. Only free form (not bound to plasma proteins) is biologically active, but only 0.02-0.05% of free form is found in circulation.

Thyroxine; 3,5,3', 5'-L-tetraiodothyronine, is mainly called as T4 (TT4 total or FT4 free form).

Its summary formula is $C_{15}H_{11}I_4NO_4$ and its molecular weight (Mr) is 776.87 Da.

Fig.1: Structural formula of Thyroxine



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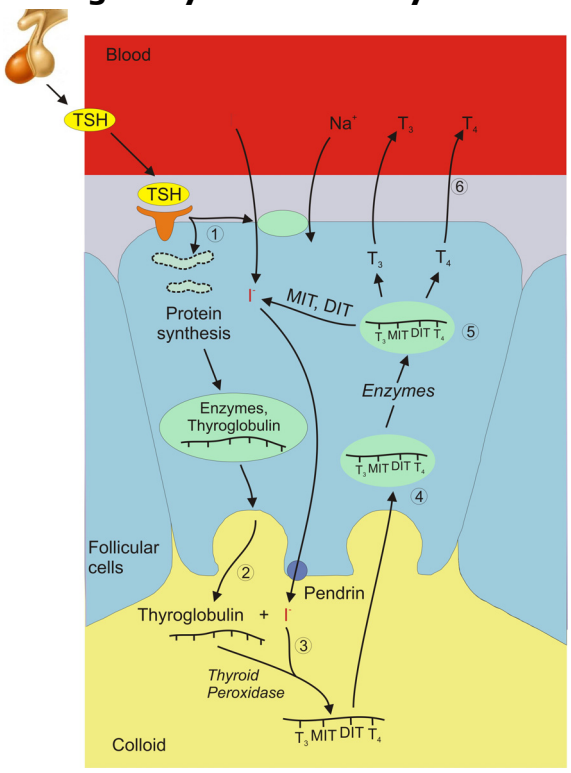
Biosynthesis

T3 and T4 are produced in thyroid gland under regulation of hypothalamic-pituitary–thyroid axis. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to produce thyroid stimulating hormone (TSH) and TSH stimulates the thyroid gland to produce thyroid hormones T4 and in lesser extent T3. A fall in thyroid hormone concentrations causes an increase in both TRH and TSH secretion. Conversely, a rise in the thyroid hormone concentration provokes an inhibitory effect on the pituitary response to TRH (negative feedback). The synthesis and storage of thyroid hormones occurs in thyroid gland which is butterfly-shaped and is located in the front of the neck above trachea. The functional unit of this gland is the follicle, a roughly spherical group of cells arranged around a protein-rich storage material called colloid. The biosynthesis of T3 and T4 is complex and involves steps as the trapping of circulating iodide by the thyroid gland, incorporation of iodine into tyrosine, the coupling of iodinated tyrosyl residues to form T3 and T4 within the protein thyroglobulin (Tg) backbone, and endocytosis, followed by proteolytic cleavage of Tg, releases thyroid hormones into circulation. TSH, a crucial regulator in T3 and T4 synthesis, mediates many steps as stimulation of the iodide pump, Tg synthesis in follicular cells, colloidal uptake by follicular cells, and the regulation of Tg proteolysis rate for T3 and T4 liberation. It also induces an increase in the size of the thyroid follicular cells. The mechanism of thyroid hormone synthesis is shown on Fig.2 and 3.

Fig.2: Synthesis of thyroid hormones



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

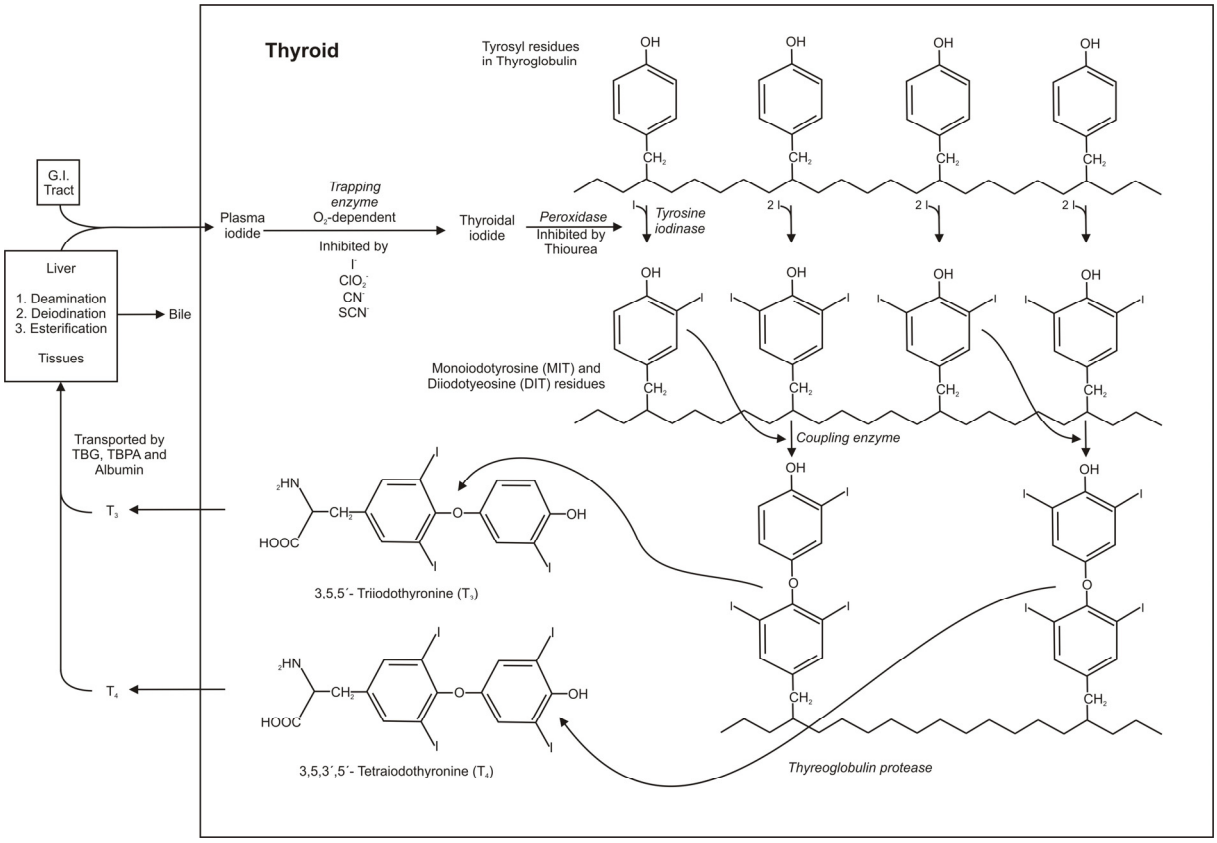
4. Thyroglobulin is taken back into the cells by endocytosis of the colloid

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

Iodide transport to the follicles is the first and rate limiting step in the synthetic process. Iodide is oxidized to active iodine by hydrogen peroxide inside the follicular cell. This reaction is catalyzed by the enzyme thyroid peroxidase (TPO). Iodine is then actively transported across the apical surface of the follicular cell and is immediately incorporated into the tyrosine residues of the Tg molecules. Tg and other enzymes are also synthesized in the follicular cell and transported into colloid, where covalent binding of iodine forms monoiodotyrosine (MIT) and diiodotyrosine (DIT). A coupling reaction between pairs of these iodinated tyrosine molecules occurs. Two tyrosine residues, when iodinated at two positions (DIT), produce T4, whilst the combination of DIT and MIT produces T3. Such coupling can occur within a single molecule of thyroglobulin or between dimerized molecules of the protein. This coupling is also catalyzed by TPO. Thyroid hormones are stored in this state and are released when the thyroglobulin molecule is taken back up into the follicular cells.

Fig.3: Formation of thyroid hormones[1]

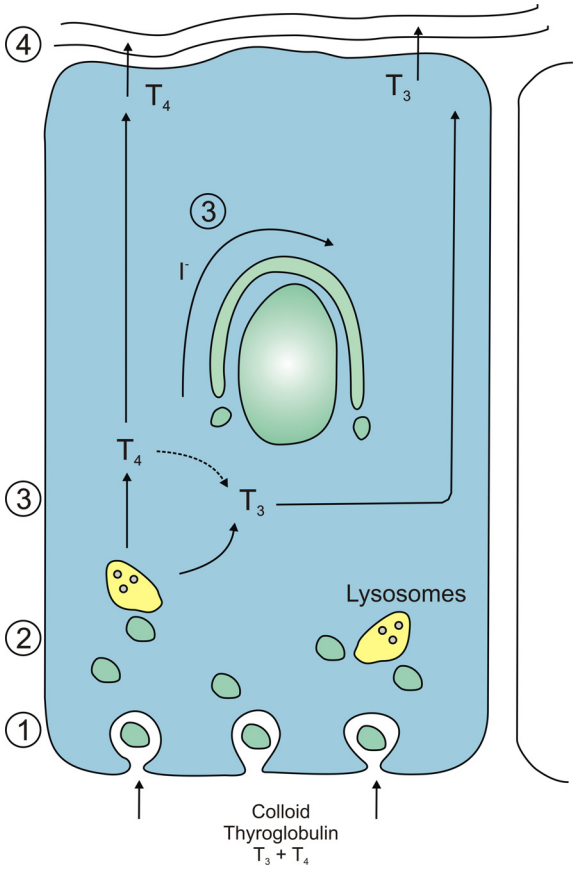


Stimulated by TSH, thyroglobulin droplets are captured by the follicular cells by a process of pinocytosis. Fusion of the droplets with lysosomes results in hydrolysis of the thyroglobulin molecules and release of T4 and T3. About 10% of T4 undergoes mono-deiodination to T3 before it is secreted, the released iodine is recycled. The secretion of thyroid hormone synthesis is shown on Fig.4.

Approximately 100 µg of thyroid hormones are secreted from the gland each day, mostly in the form of T4 with about 10% as T3. 80% of T4 undergoes peripheral conversion to the more active T3 in the liver and kidney or to reverse T3 (rT3) that has little or no biological activity. Very small quantities of other iodinated molecules, such as MIT and DIT are measurable in the circulation as well.

T4 and T3 hormones are in the circulation bound to carrier proteins. Approximately 65-70% of T4 is bound to thyroid-binding globulin (TBG), 10-15% to pre-albumin (TBPA), 15-20% to albumin and 3-6% to T4 binding lipoprotein (T4 BL). Only 0.02-0.05% of T4 is found in free form and only free hormone is biologically active. The protein bound hormone acts as a reservoir for T4 to maintain a constant concentration of free T4. Bound and free fractions are in equilibrium. The equilibrium with pre-albumin and albumin is rapid. By contrast, TBG binds hormones very tightly and equilibrium dissociation is slow.

Fig.4: Secretion of thyroid hormones from the thyroid gland[3]



1. Under the influence of TSH, colloid droplets consisting of thyroid hormones within the thyroglobulin molecules are taken back up into the follicular cells by pinocytosis

2. Fusion of colloid droplets with lysosomes causes hydrolysis of thyroglobulin and release of T3 and T4

3. About 10% of T4 undergoes mono-deiodination to T3 before it is secreted. The released iodide is reutilized

4. On average approximately 100 µg T4 and about 10 µg T3 are secreted per day

Metabolism[1]

T4 is metabolized by a series of deiodinations which are divided into three types (Fig.5).

Type 1: deiodinates at both the 5‘and 5 carbon atoms and is found in the liver, kidney, thyroid, pituitary gland and central nervous system, with a high K_m for T4. Its activity is increased in hyperthyroidism and reduced in hypothyroidism.

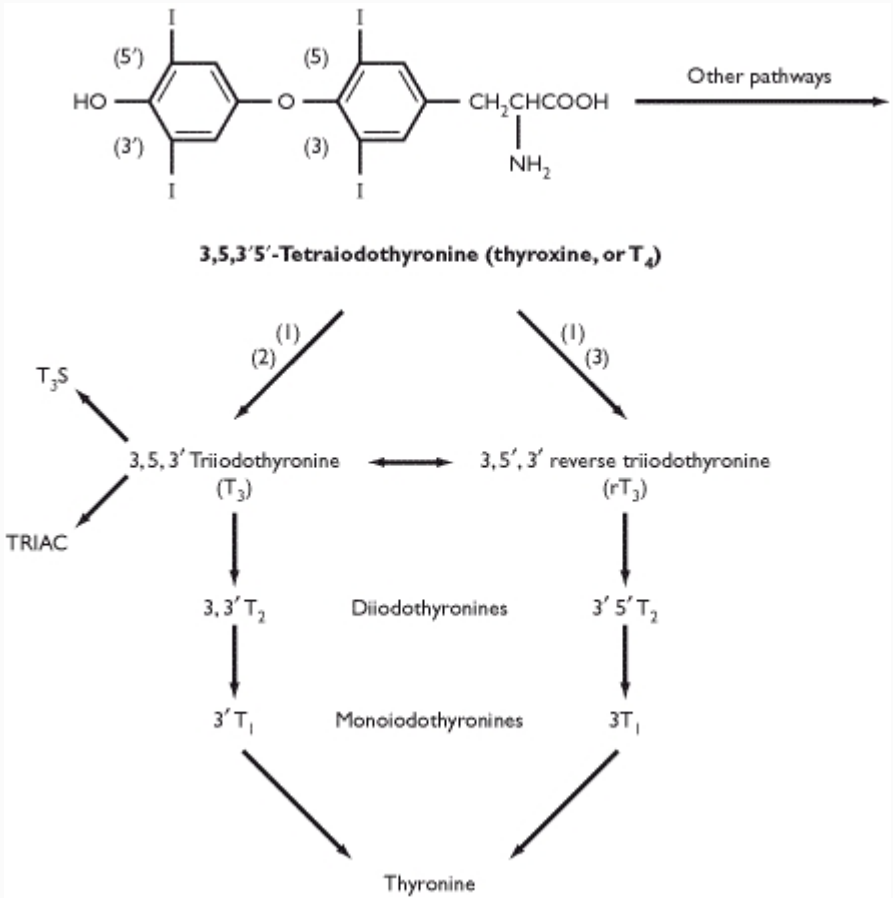
Type 2: deiodinates only at the 5‘position and is found in brain, brown fat, placenta and pituitary gland. With a lower Km than Type 1, it is considered to maintain intracellular concentrations of T3. This is important in the negative feedback actions of T4 on the pituitary gland. Its activity is decreased in hyperthyroidism and increased in hypothyroidism.

Type 3: deiodinates only at the 5 position and is found only in brain and placenta. As it is incapable of converting T4 to the active T3, it may protect the brain and fetus from excess active T3.

Some T4 and T3 are also metabolized by oxidative deamination, which produces pyruvic acid analogues that are ultimately converted to thyroacetates by a decarboxylation reaction. These analogues have some residual biological activity, but there is no evidence that they are physiologically active. In the liver, T4 and T3 are conjugated to form sulphates and glucuronides. These conjugates enter the bile and pass into the intestine. These conjugates are then hydrolyzed some are reabsorbed or excreted in the stools. The amounts of thyroidal substances in the urine are very small.

The serum half-life of T4 is 7 days.

Fig.5: Metabolism of thyroid hormones[3]



Physiological function

The thyroid hormones T4 and T3 are essential for proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism. They influence growth and development of all the body tissues. Their optimal levels are crucial for proper bone growth, development of brain and nervous system in children. Thyroid hormones also help maintain normal blood pressure, heart rate, digestion, muscle tone, and reproductive function.

Thyroxine is believed to be a pro-hormone and a reservoir for the most active and main thyroid hormone T3. Within cells, T4 is either converted to T3, which is about 3-4 times more potent than T4, or reverse T3, which is biologically inactive. Deficiency of deiodinase can mimic an iodine deficiency. Ultimately, T3 and to a lesser degree T4 binds to the nuclear thyroid hormone receptor, altering gene expression pattern in a tissue-specific fashion.

Levels

The FT4 and TT4 levels are constant through the life. They are on the highest level after birth but drop quickly during several weeks.

Values of free T4 are independant of the binding protein concentrations. Nevertheless, the total levels are influenced by the wide variation in the concentration of binding proteins. Consequently, total T4 concentartions may differ significantly among euthyroid individuals. When the values of total T4 are measured, knowledge of possible changes in binding proteins are very important.

Typical FT4 and TT4 levels[2] of children and adult males and females are given in Tab.1 and 2.

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

Tab.1: Typical FT4 levels in serum[2]

Specimen (serum)	**Reference interval (pmol/L)**
Newborn (1-4 days)	28-68
Children (20 weeks-20 years)	10-26
Adult (21-87 years)	10-35
Pregnancy	
1st trimester	9-26
2nd and 3rd trimester	6-21

Equation for the conversion of units for FT4: 1 ng/dLx12.9 = pmol/L

Tab.2: Typical TT4 levels in serum[2]

Specimen (serum)	Reference interval (nmol/L)
Cord	95-168
Newborn	
(1-3 days)	152-292
1-2 weeks	126-214
Children	
1-4 months	93-186
4-12 months	101-213
1-5 years	94-194
5-10 years	83-172
10-15 years	72-151
Adult	
Male	59-135
Female	71-142
>60 years	65-138
Maternal serum	
15-40 weeks	117-181

Equation for the conversion of units for TT4: 1 µg/dLx12.9 = nmol/L

Free thyroxine index, FT_4I (also called T7)

FT4 levels in serum can be also estimated by calculation of FT_4I on the basis of a T3 Uptake and TT4 tests. The uptake of labeled triiodothyronine (T3) is measured in this test. T3 is less strongly bound by serum proteins, so it is used instead of T4. The free T4 index is then obtained by multiplying the T3 uptake value by the total concentration of T4 in serum.

Diagnostic utility — prospects and possibilities[4]

As thyroid diseases are often presented with vague and subtle symptoms, the assessment of FT4 or TT4 values is a key to the proper diagnosis of thyroid disorders. Measurement of FT4 with TSH represents the best methods to determine thyroid function status. Hypothyroidism and hyperthyroidism are the two primary pathological conditions that affect the thyroid gland. Measurement of FT4 and TSH allows to distinguish whether hyperthyroidism (increased FT4) or hypothyroidism (low FT4) are primary (the majority of cases, TSH altered in the opposite direction as FT4) or secondary/tertiary (pituitary/hypothalamic origin, TSH altered in the same direction as FT4). Total T4 and also T3 levels can vary widely due to changes in binding protein levels, without any change in free thyroid hormone levels, hence, actual thyroid function status.

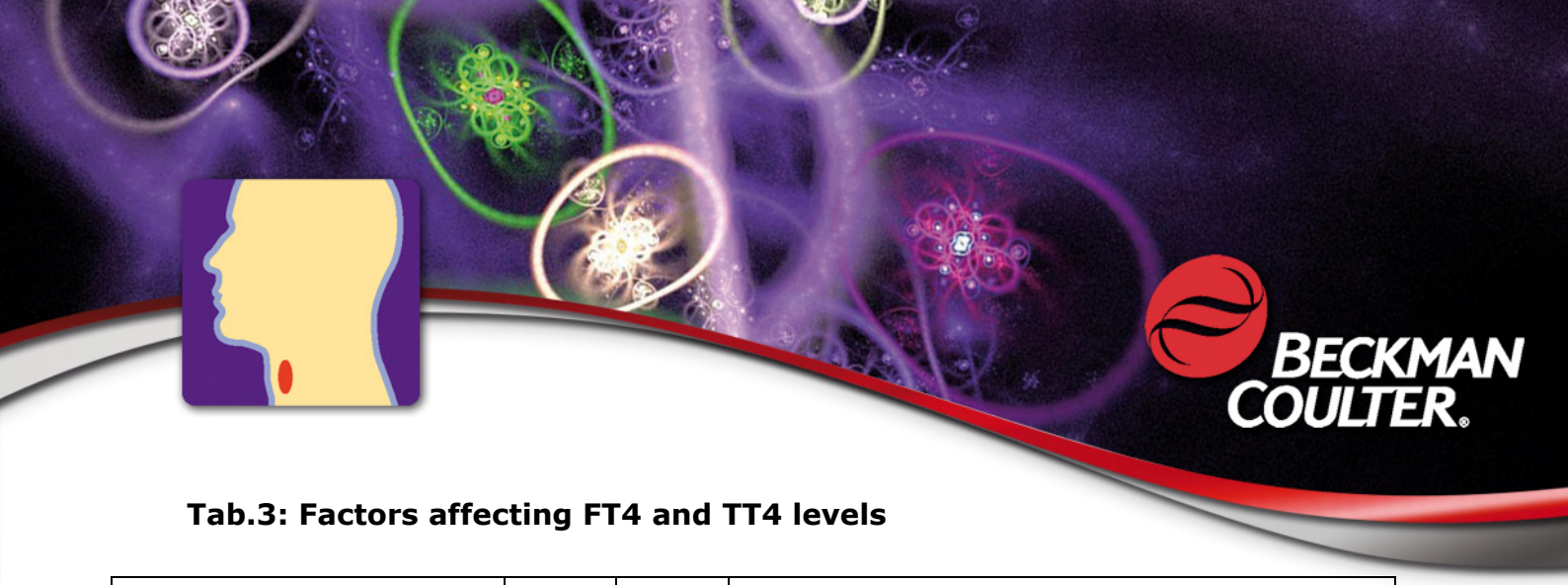
Elevated FT4/TT4 levels are associated with:

- hyperthyroidism
    - **Primary**
        - Graves'disease (diffuse toxic hyperplasia)
        - Plummer's disease (toxic multinodular goitre)
        - Toxic solitary adenoma
        - Acute or subacute thyroiditis (viral or bacterial etiology) - onset
        - Hashimoto's (autoimmune) thyroiditis (initial phase)
        - De Quervain's thyroiditis (subacute)
        - Thyroid carcinoma (papillary, follicular, anaplastic)
    - **Secondary**
        - TSH secreting pituitary tumor (secondary hyperthyroidism)
    - Postpartum thyroiditis
    - hCG secreting trophoblastic tumor
    - Exogenous intake of thyroxine
    - Excess iodide

Decreased FT4/TT4 levels are associated with:

- hypothyroidism
  - **Primary**
    - **Loss of functional tissue**
      - Chronic lymphocytic Hashimoto's thyroiditis
      - Radioation injury of the neck (I^{131} therapy, radiotherapy)
      - Postoperative hypothyroidism
      - Thyroid gland dysgenesis, developmental defects (neonatal)
    - **Infiltrative disease of the thyroid**
      - Infective disease of thyroid gland (viral, bacterial)
    - **Defects in thyroid hormone synthesis**
      - Congenital biosynthesis defects
      - Endemic iodine deficiency
      - Drug induced defects (lithium, glucocorticoids, iodine,..)
      - Iodiopathic primary hypothyroiditism (TSH receptor defect)
      - Antithyroid agents
      - Thyroiditis with autoantibodies
  - **Secondary (hypothyrotropic)**
    - **Pituitary disease – TSH deficiency**
    - **Hypothalamic disease – TRH deficiency**

There are many states when free and total T4 levels are affected differently. The Tab.3 shows the examples of such conditions.



Tab.3: Factors affecting FT4 and TT4 levels

Cause	TT4	FT4	Comment
TBG amplification			
-oral contraceptives	+	N	Can remarkably elevate TT4 concentration, but not FT4 and FTI
-genetic amplification	+	N	Incidence 1:40000
-pregnancy	+	-	FT4 decrease is not affected by TBG increase
-newborns	+	(+)	FT4 slight increase due to increased TSH levels
-active hepatitis	+	+/N	Lowered TBG degradation
TBG reduction			
-genetic	-	N	Rarely
-liver cirrhosis	N /+	+/(-)	TBG drop, proportional of degree decompensation
Albumin changes			
-euthyroid excess of T4	+	N	Familiar binding abnormality of thyroid hor. with approximately 50 times higher affinity
-glomerular protein loss	(-)	N	TBG normal, albumin lowered
Binding competitors			Interferes with the binding of thyroid hormones to plasma proteins
-heparin therapy	N	+	Heparin therapy releases protein lipase in plasma with consequent increase of free fatty acids, which interfere with this binding. Free fatty acids also elevated during diabetic keto-acidosis and starving
-diabetic keto-acidosis	-	+	
-starving	N	+	
-acetylsalicylic acid	N/(-)	+	Interferes with T4 binding to TBPA
-phenytoin, phenobarbital, karbamasepine	-	-	Interferes with T4 binding to TBG and supports its degradation in liver
-amiodarone	+/N	+	Prevents thyroid hormone degradation

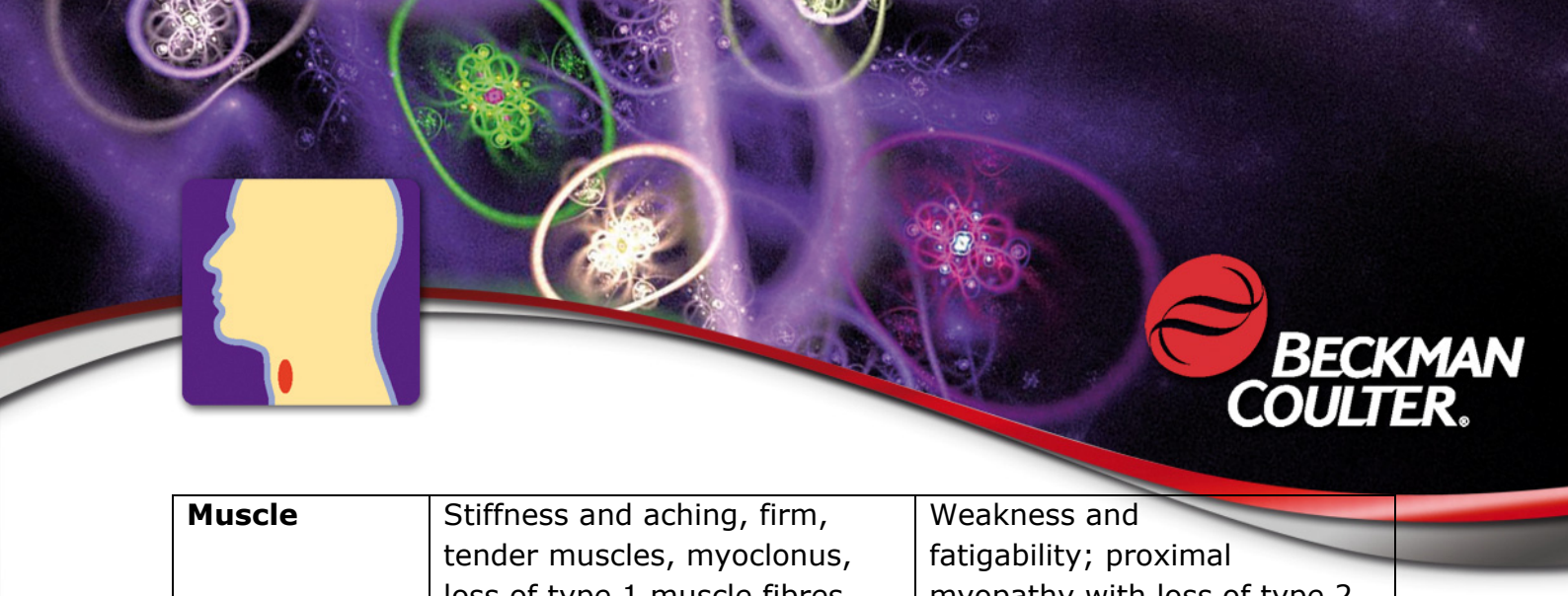
N- normal; + increased; - decreased

Hyperthyroidism is defined as a hypermetabolic condition caused by excessive production of thyroid hormones. Some clinicians prefer general term thyrotoxicosis rather than hyperthyroidism to define the hypermetabolic state associated with increased amount of thyroid hormones in circulation. The prevalence of hyperthyroidism is fairly low in the general population (0.3-0.6%) and women are more prone to this disease, with the ration of females to males with Grave's disease being 5:1.

Hypothyroidism is defined as a deficiency in thyroid hormone secretion and action. It is a common disorder that occurs in mild or severe forms in 2-15% of the population. Women are again affected more than men, and both sexes are affected more often with increasing age. Clinical symptoms (see Tab.4) can range from obvious and easy to recognize lethargy, fatigue, and cold intolerance to more subtle, subclinical disease with general symptoms that escape detection. Myxedema is a severe form of hypothyroidism in which there is an accumulation of mucopolysaccharides in the skin and other tissues, leading to a thickening of facial features and a doughy induration of skin. Cretinism is the term used to describe severe hypothyroidism that develops in the newborn period.

Tab.4: Clinical manifestation of thyroid hormone deficiency and excess[3]

Tissue/organ	Deficiency	Excess
Skin/hair	Pale, dry puffy skin (myxedema), dry brittle hair, nails	Pink, warm, moist skin Onycholysis of nails
Cardiovascular	Decreased blood volume and cardiac output; dilated pale poorly contractile myocardium; pericardial effusion; sinus bradycardia	Increased cardiac output, decreased peripheral resistance; supraventricular tachycardia/atrial fibrillation
Respiratory	Pleural effusion (small), alveolar hypoventilation in severe hypothytoidism, obstructive sleep apnoe	Decreased vital capacity (myopathy of respiratory muscles)
Gut	Modest weight gain, decreased motility (ileus or constipation), small ascites, associated pernicious anemia and achlorhydria	Increased appetite, weight loss, increased motility (loose motions), nausea and vomiting (especially in pregnancy), associated pernicious anemia and achlorhydria or celiac disease
CNS	In childhood: poor neural development and myelination (cretinism) Adults: slowed intellectual function, paranoid or depressive psychiatric disorder, perceptive deafness, night blindness, cerebellar ataxia, carpal tunnel syndrome	Nervousness, emotional lability, hyperkinesia, tremor



Muscle	Stiffness and aching, firm, tender muscles, myoclonus, loss of type 1 muscle fibres	Weakness and fatigability; proximal myopathy with loss of type 2 myocytes; may be associated with myasthenia gravis; hypokalemic periodic paralysis may be seen especially in Chinese
Skeleton	Poor growth and maturation of bone, decreased urinary excretion of Ca^{2+}	Demineralization of bone; increased urinary excretion of Ca^{2+} and PO_4^{3-}; hypercalcemia
Kidney	Renal blood flow, glomerular filtration rate and tubular resorption and secretory functions all decreased; decrease in urinary free water excretion	Renal blood flow, glomerular filtration rate and tubular resorption and secretory functions all increased
Bone marrow	Decreased red cell mass; normochonic normocytic anemia; associated pernicious anemia and macrocytic anemia	Increased red cell mass; associated pernicious anemia and macrocytic anemia
Gonad	In childhood: delayed puberty but occasional paradoxical precocious sexual development Adults: menorrhagia, decreased libido, erectile dysfunction, infertility	In childhood — delayed puberty, though physical development is normal In adulthood — increased libido, oligomenorrhea, pregnancy loss
Metabolic	Low resting metabolic rate. Decreased appetite, weight gain, cold intolerance, reduced body temperature, flat glucose tolerance curve with delayed insulin response; increased insulin sensitivity; decreased synthesis and degradation of lipids	Increased RMR, and appetite; weight loss; decreased glucose tolerance; increased synthesis and degradation of both lipids and proteins

Diagnostic utility – practical applications

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

Primary hyperthyroidism

T4 and T3 are increased, TSH suppressed. 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 information 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 degree than T4 in early phases of **Graves' disease and in some cases of solitary or multinodular toxic Goitres** (called T3 thyrotoxicosis).

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

Secondary hyperthyroidism

In rare cases when all T4, T3 and TSH levels are increased, thyroid hormone rise is mediated by TSH due to e.g. TSH-secreting pituitary adenoma or pituitary resistance to thyroid hormones.

Monitoring of hyperthyroidism treatment

At the time when treatment is initiated, measurements of serum FT4 are recommended every few weeks until symptoms abate and serum values normalize. Continuous monitoring for recurrence of disease is suggested 2-3 times a year after successful therapy.

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

Primary hypothyroidism

Synthesis of T4 and T3 is impaired, either due to of extrinsic of intrinsic factors. Stimulation by hypersecretion of TRH and TSH causes compensatory 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 antithyroid antibodies. Reduced levels of T4 and T3 lead to hypersecretion of pituitary TSH. The elevated TSH concentration is an important factor. In mild or **subclinical form**, thyroid hormone concentrations remain within euthyroid interval, but TSH is elevated.

Secondary hypothyroidism

Secondary hypothyroidism occurs as a result of pituitary or hypothalamic disease that produces a deficiency in either TSH or TRH, or both.

Congenital hypothyroidism

Congenital hypothyroidism is found at the birth and may be caused by the complete absence of the thyroid gland or can occur due to defect in thyroid hormone synthesis. Early detection and treatment are crucial to avoid irreversible neurological damage. North American screening program is based on T4 measurement followed by TSH measurement in the case of low T4 values. Alternatively e.g. European program favor screening of TSH followed by T4 determination. Primary hypothyroidism is easily treated by oral thyroxine administration. FT4 concentrations adjust quickly, but TSH levels remain high. 4-8 weeks are needed to reach normal TSH values. Periodic monitoring of TSH 1-3 times a year is recommended.

Thyroid status in pregnancy[5]

A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. These changes mean that laboratory tests of **thyroid function must be interpreted with caution during pregnancy**. Thyroid function tests change during pregnancy due to the influence of two main hormones: human chorionic gonadotropin (hCG), and estrogens. HCG can weakly turn on the thyroid and the high circulating hCG levels in the 1st trimester may result in a slightly low TSH and then return to normal throughout the duration of pregnancy. Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone. However, measurements of free hormones usually remain normal. The normal thyroid status during pregnancy is shown in the Tab.5.

Tab.5: The normal thyroid status during pregnancy

	1st trimester	**2nd trimester**	**3rd trimester**
TSH	Normal or decreased	Normal	Normal
FT4	Normal	Normal	Normal
FT3	Normal	Normal	Normal
TT4	High	High	High
TT3	High	High	High
T3 Uptake	Low	Low	Low
Free T4 index	Normal	Normal	Normal

But both states hyperthyroidism and hypothyroidism can be found or exacerbated during pregnancy. Both mother and baby can be severely jeopardized.

Overall, the most common cause (80-85%) of **maternal hyperthyroidism** during pregnancy is Graves' disease and occurs in 1 in 1500 pregnant patients. Graves' disease often improves during 3rd trimester of pregnancy and may worsen during the postpartum period.

Uncontrolled maternal hyperthyroidism has been associated with fetal tachycardia (fast heart rate), small for gestational age babies, prematurity, stillbirths and possibly congenital malformations.

Extremely high levels of thyroid stimulating immunogloblulins (TSI) do cross the placenta and can interact with the baby's thyroid. Although uncommon (2-5% of cases of Graves' disease in pregnancy), high levels of maternal TSI's, have been known to cause fetal or neonatal hyperthyroidism.

The other problem is that anti-thyroid drug therapy usually cross the placenta and can potentially impair the baby's thyroid function and cause fetal goitre.

Mild hyperthyroidism is often monitored closely without therapy as long as both the mother and the baby are doing well. When hyperthyroidism is severe enough to require therapy, anti-thyroid medications are the treatment of choice. The goal of therapy is to keep the mother's free T4 and free T3 levels in the high-normal range on the lowest dose of anti-thyroid medication

Hypothyroidism in pregnancy is usually caused by Hashimoto's disease. Hypothyroidism can occur during pregnancy due to the initial presentation of Hashimoto's thyroiditis, inadequate treatment of a woman already known to have hypothyroidism from a variety of causes, or over-treatment of a hyperthyroid woman with anti-thyroid medications. Untreated, or inadequately treated, hypothyroidism has been associated with maternal anemia, myopathy (muscle pain, weakness), congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage (bleeding). Additionally, thyroid hormone is critical for brain development in the baby. Children born with congenital hypothyroidism (no thyroid function at birth) can have severe cognitive, neurological and developmental abnormalities if the condition is not recognized and treated promptly.

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 adequate treatment should start as soon as possible.

Diagnosis, differential diagnosis of non-thyroid illness (NTI)[3]

Many disorders are associated with thyroid hormone excess or deficiency in the absence of thyroid disease and are found in patients with acute illness. Such a condition was determined as **non-thyroid illness**. It is considered to result from the effects of acute illness and/or the drugs treating illness on the synthesis, transport and metabolism of thyroid hormones.

According to thyroid hormone levels several groups can be found:

-Low serum T3, normal T4. The most common biochemical abnormality, it is seen in approximately 70% hospitalized patients. T3 reduced by about 50%, rT3 increased (except in renal failure) due to its decreased clearance as a result of reduced activity/production of 5' mono-deiodinase Type 1.

-Low serum total T3 and T4. Usually is seen in severely ill patients. Free T4 is normal owing to inhibition of T4 binding or production of altered TBG.

-High serum total T4, normal total T3. It is seen in patients with liver disease producing increased quantities of TBG. Free T3 low or low-normal, rT3 high.

-Increased serum total-T4 and TBG, normal T3 and paradoxical decreases in rT3. It is seen in patients with HIV infection.

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