

Thyroid Disorders

DISORDERS OF THE THYROID GLAND

THYROID DEVELOPMENT AND PHYSIOLOGY

- Fetal development:-
 - Hypothalamic neurons synthesize Thyrotropin-Releasing Hormones (TRH) by (6-8) wk, the pituitary portal vessel system begins development by 8-10 weeks, and thyroid stimulating hormones (TSH) secretion is evident by 12 weeks of gestation.
 - Maturation of the hypothalamic pituitary-thyroid axis occurs over the second half of gestation but normal feed back relationships are not mature until approximately 3 months of postnatal life.

THYROID PHYSIOLOGY:

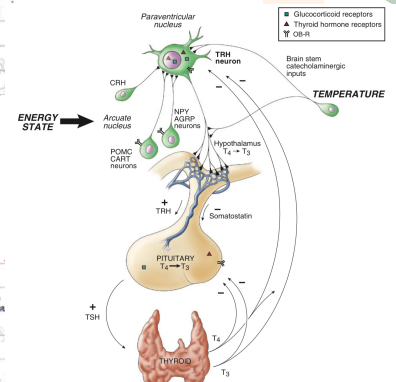
- The main function of the thyroid gland is to synthesize T4 and T3.
- The recommended dietary allowance of iodine is 30 mcg/kg/d for infants. 90-120 mcg/24h for children, and 150 mcg/24 h for adolescents and adults.
- Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as iodide.
- Iodination of tyrosine forms moniodotyrosine and diiodotyrosine ; 2 molecules of diiodotyrosine then couple to form 1 molecule of T4 , or 1 molecule of diiodotyrosine and 1 of moniodotyrosine to form T3.
- Once formed, hormones are stored as thyroglobulin in the lumen of the follicle (colloid).
- The metabolic potency of T3 is 3-4 times that of T4.
- Only 20 % of circulating T3 is secreted by the thyroid, the remainder is produced by deiodination of T4 in the liver, Kidney and other peripheral tissues by type I 5' - deiodinase.
- In the pituitary and brain, approximately 80% of required T3 is produced locally from T4 by a different enzyme, type 2 5' - deiodinase.
- The level of T3 in blood is 1/50th that of T4 but T3 is the physiologically active thyroid hormone.
- Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation and affect carbohydrate, lipid and vitamin metabolism.
 - About 70% of circulating T4 is firmly bound to thyroxine-binding globulin (TBG)
 - Only 0.03% of T4 in serum is not bound and comprises free T4.
 - 0.3% of T3 is unbound or free T3.

Handwritten notes in Arabic discussing thyroid physiology and development. Key points include:

- Development of the hypothalamic-pituitary-thyroid axis.
- Role of TRH and TSH.
- Thyroid development timeline (6-12 weeks gestation).
- Thyroid hormone synthesis steps: iodination of tyrosine, coupling to form T4 and T3.
- Storage of hormones as thyroglobulin.
- Metabolic effects of T3 and T4.
- Deiodination of T4 to T3 in various tissues.
- Binding of T4 to TBG.

Handwritten notes in Arabic detailing the biochemical synthesis of thyroid hormones. Key steps include:

- Iodide (I⁻) transport into the thyroid gland via Na⁺/I⁻ cotransporter.
- Oxidation of iodide to I₂ by thyroid peroxidase (I₂ peroxidase).
- Organification of I₂ on tyrosine residues.
- Coupling of moniodotyrosine (MIT) and diiodotyrosine (DIT) to form T4 and T3.



Handwritten notes in Arabic discussing the clinical implications of thyroid disorders. Key points include:

- Effects of thyroid hormone deficiency on growth and development.
- Effects of thyroid hormone excess on metabolism and body weight.
- Diagnosis of thyroid disorders using T4 and T3 levels.
- Treatment options for thyroid disorders.

A. Thyroid physiology

1. **Hypothalamic–pituitary–thyroid axis** is regulated by a feedback loop between T_4 , triiodothyronine (T_3), thyrotropin-releasing hormone (TRH), and thyroid-stimulating hormone (TSH).
2. Both T_4 and T_3 circulate bound to **thyroid-binding proteins**, including thyroid-binding globulin (TBG) and thyroid-binding prealbumin (TBPA).
3. The **free (unbound) forms** of T_4 and of T_3 are the biologically active forms of each hormone.

FETAL AND NEWBORN THYROID

- Approximately 1/3 of maternal T_4 crosses the placenta to the fetus.
- Maternal T_4 may play a role in fetal development, especially of the brain, before the synthesis of fetal thyroid hormone begins.
- At birth, there is an acute release of TSH; peak serum concentrations reach 60mU/L in 30min in full term infants.
- A rapid decline occurs in the ensuing 24hrs and a more gradual decline within the next 5 days to less than 10mU/L.

Hypothyroidism

B. Hypothyroidism

- Hypothyroidism results from deficient production of thyroid hormone or a defect in thyroid hormone receptor activity.

1. Clinical presentation in children and adolescents

- a. **Suboptimal growth velocity** (less than 5 cm per year or 2 inches per year) with a **delayed bone age**
- b. **Goiter** may sometimes be detected on palpation of the thyroid.
- c. **Myxedema**, or “puffy skin,” dry skin, or occasionally, **orange-tinged skin**
- d. **Amenorrhea** or **oligomenorrhea** in adolescent girls
- e. **Fatigue** or **decreased energy levels**. **Sleep** may be altered.
- f. **Constipation**

2. Causes are extensive.

a. Congenital hypothyroidism

1. **Epidemiology.** This condition is **one of the most common disorders for which newborns are screened**. It is evaluated on newborn screening and has an incidence of 1 in 4000 births.
2. **Etiology**

- a. **Thyroid dysgenesis.** This is the **most common cause (85%) of congenital hypothyroidism**. Ectopic thyroid gland (failure of the gland to properly descend from the base of the tongue during development) is the most common cause (~80% of cases), followed by agenesis.
- b. **Thyroid dysmorphogenesis.** This refers to multiple **inborn errors** of thyroid hormone synthesis, which account for about 10–15% of all cases of congenital hypothyroidism. These conditions are **autosomal recessive** and **usually present with a goiter**. **Pendred syndrome**, an **organification defect**, is the most common of these defects and is associated with **sensorineural hearing loss**.
- c. Use of **propylthiouracil (PTU)** during pregnancy for maternal Graves disease may result in transient hypothyroidism in the newborn, because PTU crosses the placenta and may temporarily block fetal thyroid hormone synthesis.
- d. **Maternal autoimmune thyroid disease** may also result in transient hypothyroidism, as maternal thyroid-blocking antibodies may cross the placenta and block TSH receptors on the newborn thyroid gland.

3. **Clinical features.** Most newborns are **asymptomatic at birth** and have an unremarkable physical examination. However, **thyroid hormone is essential for normal brain growth during the first 3 years of life**, and with time, the following clinical features become more apparent if the patient goes untreated:

- a. **Classic historical features** include a history of prolonged jaundice and poor feeding.
- b. **Classic symptoms** include lethargy and constipation.

TABLE 175.2 Causes of Hypothyroidism in Infancy and Childhood

AGE GROUP	MANIFESTATION	CAUSE
Newborn	No goiter	Thyroid gland dysgenesis or ectopic location Exposure to iodides TSH deficiency TRH deficiency
	± Goiter	Inborn defect in hormone synthesis* or effect Maternal goitrogen ingestion, including propylthiouracil, methimazole, iodides Severe iodide deficiency (endemic)
Child	No goiter	Thyroid gland dysgenesis Cystinosis Hypothalamic-pituitary insufficiency Surgical after thyrotoxicosis or other thyroid surgery
	Goiter	Hashimoto thyroiditis: chronic lymphocytic thyroiditis Inborn defect in hormone synthesis or effect Goitrogenic drugs, infiltrative (sarcoid, lymphoma)

c. **Classic physical examination findings** include large anterior and posterior fontanelles, protruding tongue, umbilical hernia, myxedema, mottled skin, hypothermia, delayed neurodevelopment, and poor growth.

- Serum levels of prolactin are elevated.
- Retardation of osseous development can be shown radiographically at birth in about 60%. The distal femoral epiphysis, normally present at birth is often absent.

- Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of the thyroid gland.
- Birth weight and length are normal, but head size may be slightly increased because of myxedema of the brain.
- Prolongation of physiologic jaundice.
- Feeding difficulties, lack of interest, somnolence and choking spells during nursing are often present during first month of life and respiratory difficulties.
- Affected infants cry little, sleep much, have poor appetites and are generally sluggish.
- Constipation, abdomen is large, umbilical hernia.
- The temperature is subnormal; skin may be cold and mottled.
- Edema of the genital and extremities may be present.
- The pulse is slow, heart murmurs, cardiomegaly and asymptomatic pericardial effusion.
- Macrocytic anemia is often present.
- 10% of infants with congenital hypothyroidism have associated congenital anomalies.
- Without treatment retardation of physical and mental development becomes greater by 3-6m of age. The child growth will be stunted, the extremities are short, and the head size is normal or even increased.
- The anterior and posterior fontanels are open widely.
- The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen.
- The mouth is kept open, and the thick broad tongue protrudes. Dentition will be delayed.
- The neck is short and thick. The hands are broad and the fingers short.
- The skin is dry and scaly.
- The scalp is thickened and the hair is coarse, brittle and scanty. The hairline reaches far down the forehead.
- Development is delayed
- The muscles are usually hypotonic.

TABLE 175.3 Symptoms and Signs of Hypothyroidism

ECTODERMAL
Poor growth
Dull facies: thick lips, large tongue, depressed nasal bridge, periorbital edema
Dry scaly skin
Sparse brittle hair
Diminished sweating
Carotenemia
Vitiligo
CIRCULATORY
Sinus bradycardia/heart block
Cold extremities
Cold intolerance
Pallor
ECG changes: low-voltage QRS complex
NEUROMUSCULAR
Muscle weakness
Hypotonia: constipation, potbelly
Umbilical hernia
Myxedema coma (carbon dioxide narcosis, hypothermia)
Pseudohypertrophy of muscles
Myalgia
Physical and mental lethargy
Developmental delay
Delayed relaxation of reflexes
Paresthesias (nerve entrapment: carpal tunnel syndrome)
Cerebellar ataxia
SKELETAL
Delayed bone age
Epiphyseal dysgenesis, increased upper-to-lower segment ratio
METABOLIC
Myxedema
Serous effusions (pleural, pericardial, ascites)
Hoarse voice (cry)
Weight gain
Menstrual irregularity
Arthralgia
Elevated CK
Macrocytosis (anemia)
Hypercholesterolemia
Hyperprolactinemia
Precocious puberty in severe cases

Congenital hypothyroidism	
Clinical manifestations	• Initially normal at birth • Symptoms develop after maternal T₄ wanes: ◦ Lethargy ◦ Enlarged fontanelle ◦ Protruding tongue ◦ Umbilical hernia ◦ Poor feeding ◦ Constipation ◦ Dry skin ◦ Jaundice
Diagnosis	• ↑ TSH & ↓ free T₄ levels • Newborn screening
Treatment	• Levothyroxine



b. **Hashimoto disease (chronic lymphocytic thyroiditis [CLT])**. This autoimmune disorder is characterized by lymphocytic infiltration of the thyroid gland, resulting in varying degrees of follicular fibrosis and atrophy and follicular hyperplasia.

1. **Epidemiology**

- a. **Most common cause of acquired hypothyroidism with or without a goiter**
- b. More common in girls

2. **Etiology**. Thyroid autoantibodies develop because of a disturbance in immunoregulation, resulting in a state of thyroid cell cytotoxicity or stimulation. There is often a genetic predisposition.

3. **Clinical features**. Presentation is variable.

- a. Asymptomatic
- b. Goiter, which is classically firm and pebbly in nature
- c. **Short stature**
- d. **Transient hyperthyroidism ("Hashitoxicosis")** may occur in some patients.

4. **Management**. Thyroid hormone replacement with L-T₄ to normalize the TSH level.

3. **Diagnosis of hypothyroidism**

- a. **Neonatal screening tests** for congenital hypothyroidism (TSH is measured)
- b. **Increased TSH**, which is usually the first sign of thyroid failure
- c. **Low T₄ level**
- d. **Antithyroid antibodies** (especially **thyroid antiperoxidase antibodies**) as a marker for autoimmune thyroid disease

TABLE 175.1 Laboratory Test Results in Various Types of Thyroid Function Abnormalities in Children*

ABNORMALITY	SERUM			
	TOTAL T ₄	FREE T ₄	SERUM TSH	SERUM TBG
Primary hypothyroidism	↓	↓	↑	N
Hypothalamic (TRH) tertiary hypothyroidism	↓	↓	↓	N
Pituitary (TSH) secondary hypothyroidism	↓	↓	↓	N
TBG deficiency	↓	N	N	↓
TBG excess	↑	N	N	↑

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Hyperthrodism

C. Hyperthyroidism

1. Clinical features

- a. **Eye** examination may demonstrate lid lag and **exophthalmos**.
- b. **Thyroid gland** is enlarged and usually smooth in texture. A thyroid bruit may be appreciated in untreated patients.
- c. **Cardiac examination** demonstrates tachycardia, and patients may complain of palpitations.
- d. **Skin** is warm and flushed. (Key point: The presence of vitiligo or alopecia suggests the possible coexistence of other autoimmune polyendocrinopathies, including Addison disease and DM.)
- e. **CNS** evaluation may be remarkable for nervousness and fine tremors with a history of fatigue and difficulty concentrating in school.

TASK		TABLE 175.4 Clinical Manifestations of Hyperthyroidism		DONE	
		ASSOCIATED CHANGE	SIGN/SYMPTOM		
.....		Increased catecholamine effects	Nervousness		
.....			Palpitations		
.....			Tachycardia		
.....			Atrial arrhythmias		
.....			Systolic hypertension		
.....		Hypermetabolism	Tremor		
.....			Brisk reflexes		
.....			Increased sweating		
.....			Shiny, smooth skin		
.....			Heat intolerance		
.....			Fatigue		
.....			Weight loss—increased appetite		
.....		Myopathy	Increased bowel movement (loose stools)		
.....			Hyperkinesia		
.....			Weakness		
.....			Periodic paralysis		
.....		Miscellaneous	Cardiac failure—dyspnea		
.....			Proptosis, stare, exophthalmos, lid lag, ophthalmopathy		
.....			Hair loss		
.....			Inability to concentrate		
.....			Personality change (emotional lability)		
.....			Goiter		
.....			Thyroid bruit		
.....			Onycholysis		
.....			Painful gland*		
.....			Acute thyroid storm (hyperpyrexia, tachycardia, coma, high-output heart failure, shock)		

f. **Pubertal** evaluation may be notable for **delayed menarche** and **gynecomastia** in **boys**.

2. **Graves disease (diffuse toxic goiter).** This **autoimmune disorder** is characterized by autonomous production of excessive thyroid hormone by the thyroid gland, mediated by a TSH receptor-stimulating antibody.

a. **Epidemiology.** Graves disease is the most common cause of hyperthyroidism in childhood. Females predominate (male:female = 1:3).

b. Etiology

1. Strong genetic factors

2. **Thyroid-stimulating immunoglobulin (TSI)**, an IgG antibody, cross-reacts with the TSH receptors in the thyroid gland and stimulates T_4 production.

c. **Laboratory findings.** Increased T_3 and T_4 levels with suppressed TSH level in the presence of TSI.

d. Management

1. **Antithyroid medications.** The two most commonly used antithyroid medications are **PTU** and **methimazole**. Methimazole is the preferred first-line agent given the risks of hepatotoxicity with PTU therapy.

2. **Subtotal thyroidectomy** may be considered if antithyroid medication fails or if there is a particularly large goiter.

3. **Radioactive iodine** can be used in older children and adolescents.

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