
بسم الله الرحمن الرحيم

HYPOTHYROIDISM

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Organification, Coupling, Storage, and Release

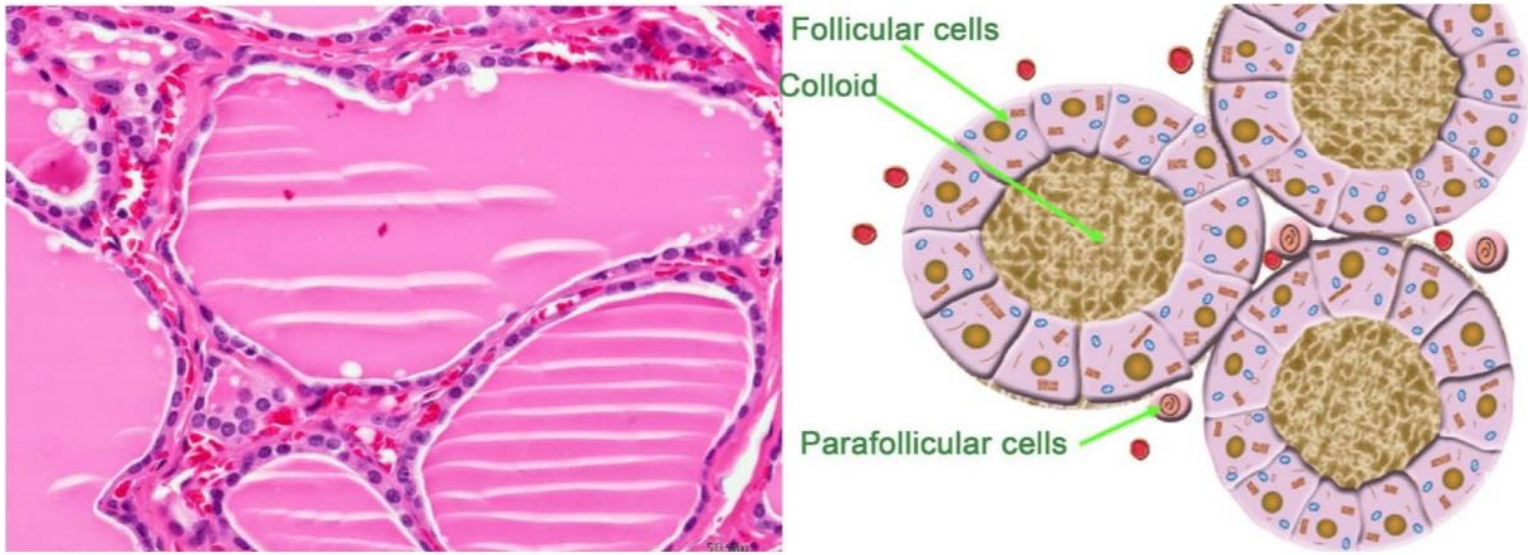

Figure 2. Thyroid Follicles and thyroid parafollicular or C cells.

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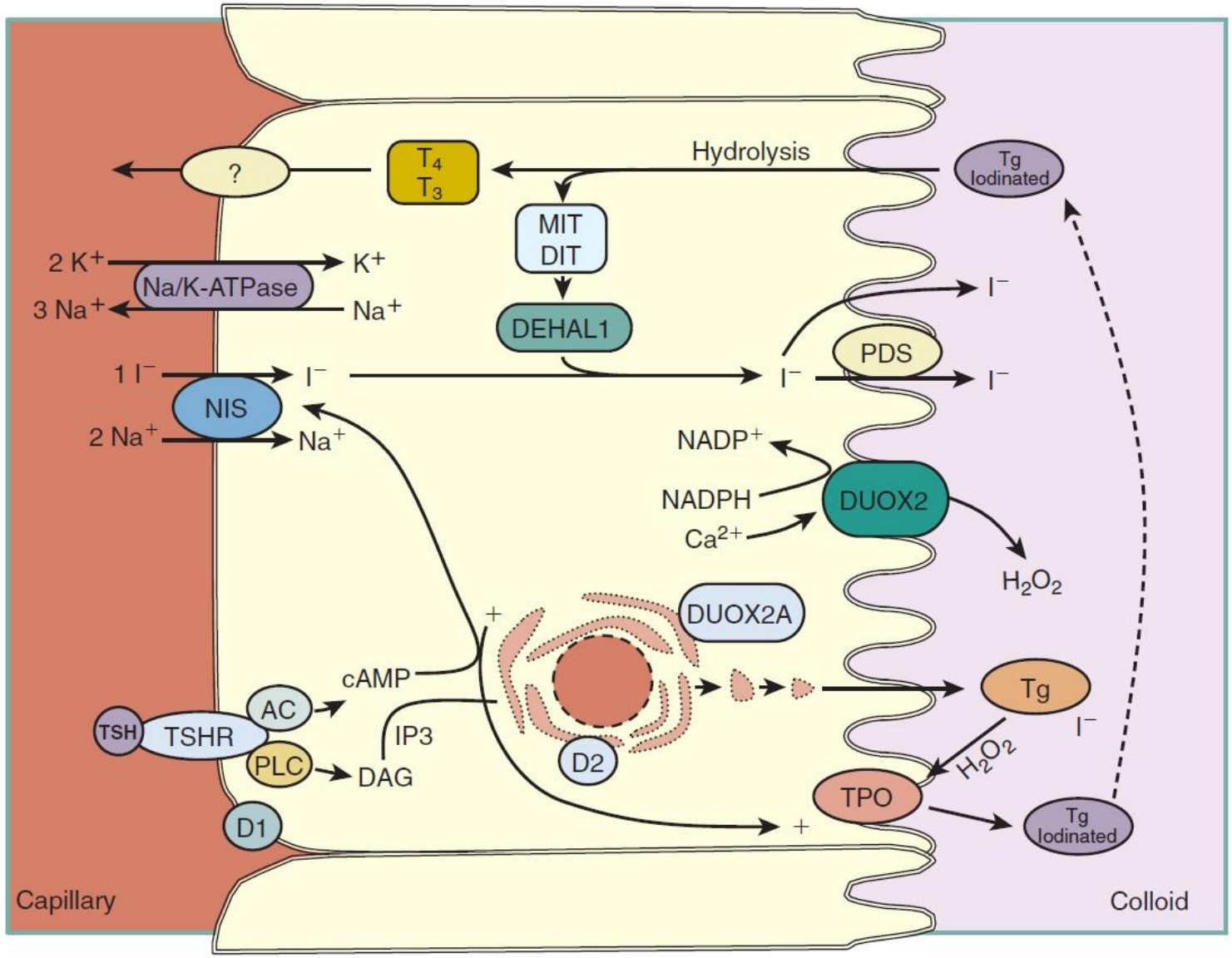

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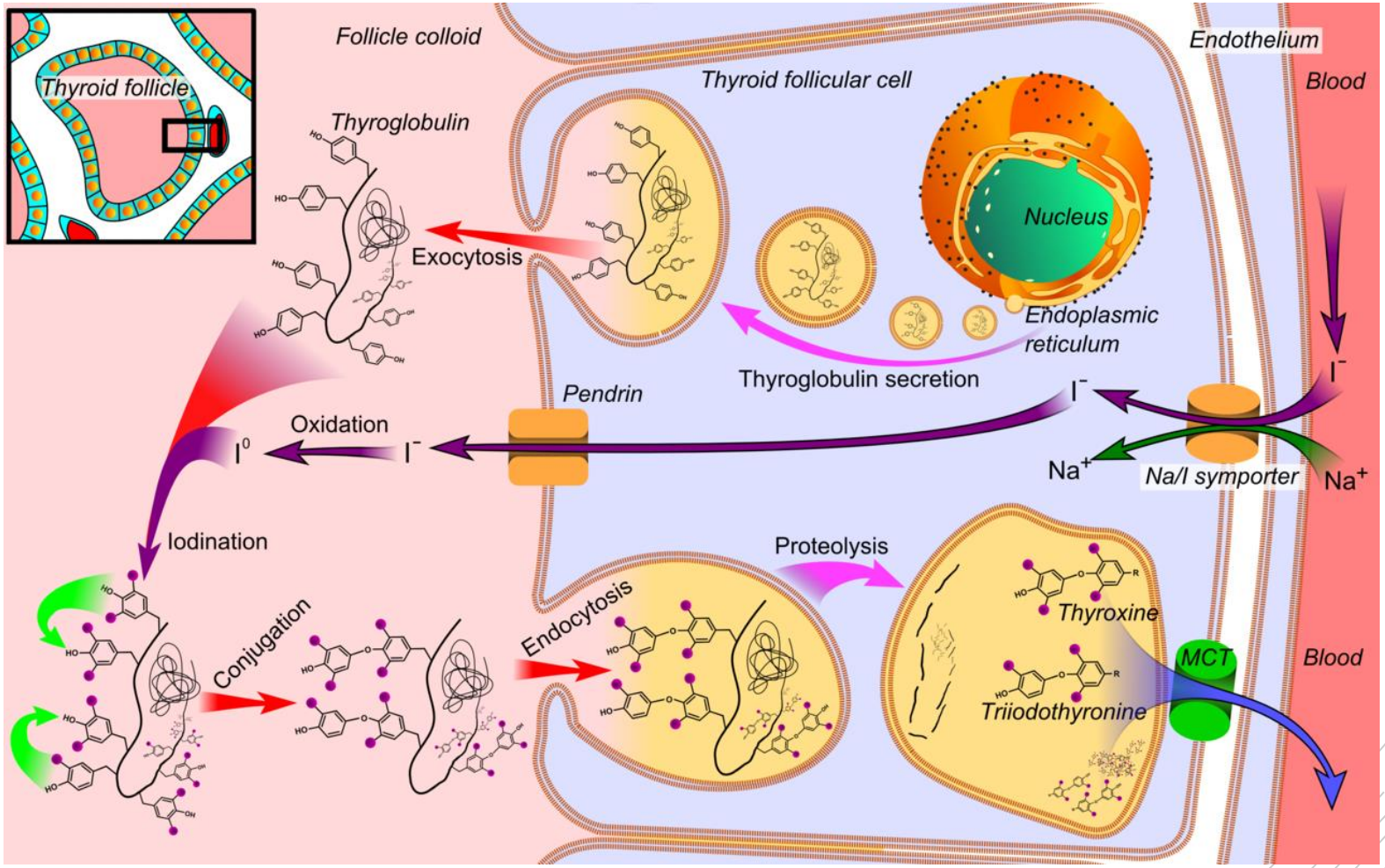

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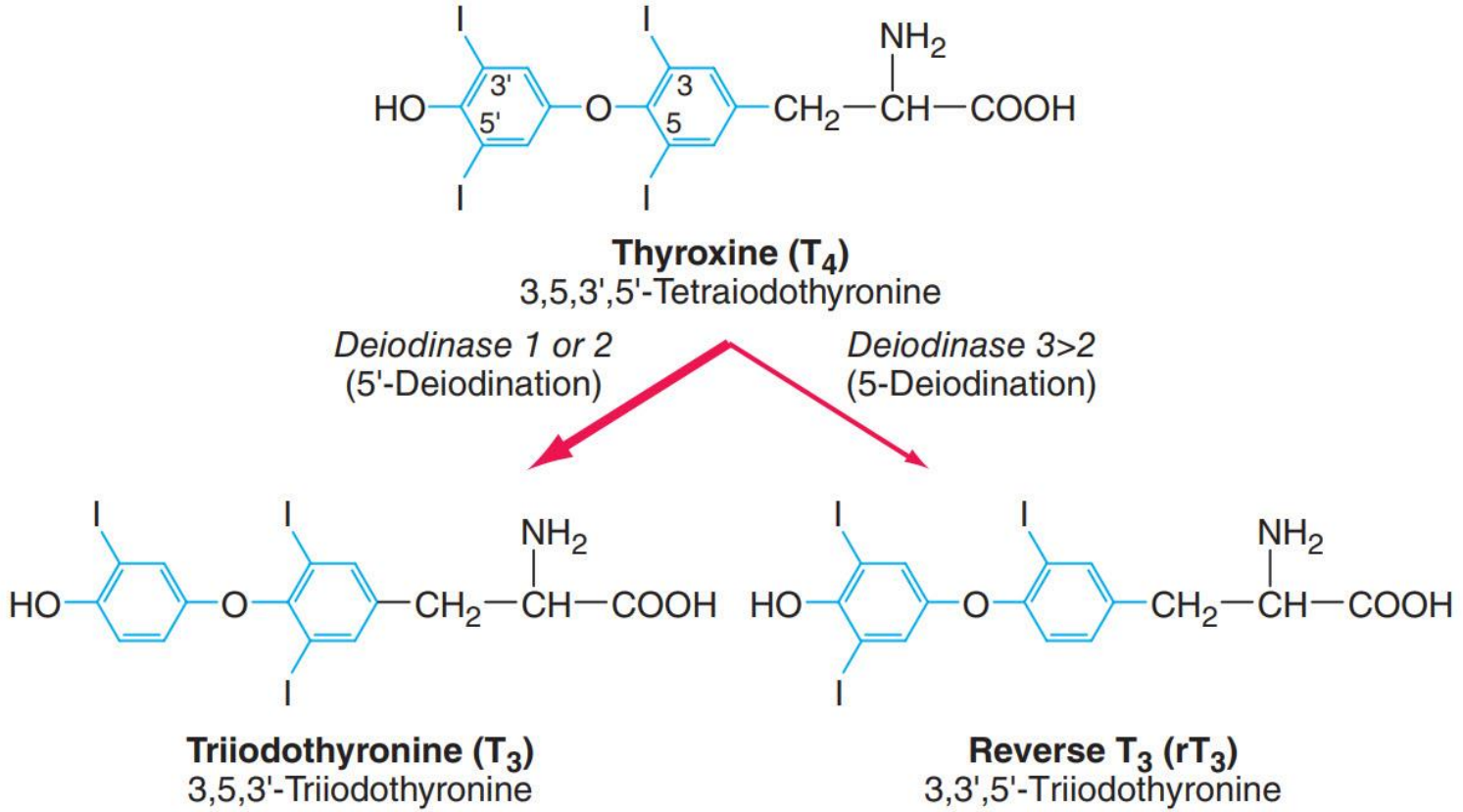


FIGURE 375-1 Structures of thyroid hormones. Thyroxine (T_4) contains four iodine atoms. Deiodination leads to production of the potent hormone triiodothyronine (T_3) or the inactive hormone reverse T_3.

Causes of Hypothyroidism

Primary:

- Iodine deficiency
- Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
- Iatrogenic: **131I treatment**, subtotal or total **thyroidectomy**, external **irradiation** of neck for lymphoma or cancer
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs
- Congenital hypothyroidism: absent or ectopic thyroid gland, TSH-R mutation
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Causes of Hypothyroidism

Transient:

- Subacute thyroiditis
- Silent thyroiditis, including postpartum thyroiditis
- After **131I treatment** or **subtotal thyroidectomy** for Graves' disease

Secondary:

- Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma
- Isolated TSH deficiency
- Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Iodine deficiency

In areas of relative **iodine deficiency**, there is an increased prevalence of **goiter** and, when deficiency is severe, **hypothyroidism** and **cretinism.**

Cretinism is characterized by **mental and growth retardation** and occurs when children who **live in iodine-deficient regions** are **not treated** with iodine or thyroid hormone to restore normal thyroid hormone levels **during early life.**

In addition to overt cretinism, **mild iodine deficiency** can lead to **subtle reduction of IQ.**

The recommended average daily intake of iodine is:

- **150–250 µg/d for adults**
- **90–120 µg/d for children**
- **250 µg/d for pregnant and lactating women**

Autoimmune hypothyroidism

Antibodies to **TPO** and **Tg** are **clinically** useful **markers** of thyroid autoimmunity.

Up to 20% of patients with autoimmune hypothyroidism have antibodies against the **TSH-R**, which, **prevent the binding of TSH**. These **TSH-R-blocking antibodies**, therefore, cause **hypothyroidism** and, **thyroid atrophy**.

About **5–15% of euthyroid women** and up to **2% of euthyroid men** have **thyroid antibodies**; such individuals are at **increased risk of developing thyroid dysfunction**.

Oversupply of iodine, through supplements or foods enriched in iodine, is associated with an **increased incidence of autoimmune thyroid disease.**

Almost **all** patients with **autoimmune hypothyroidism**, and **up to 80%** of those with **Graves' disease,** have **TPO antibodies,** usually at high levels.

Autoimmune hypothyroidism

Autoimmune hypothyroidism may be associated with a goiter (Hashimoto's) or, at the later stages of the disease, minimal residual thyroid tissue (*atrophic thyroiditis*).

Because the **autoimmune process** gradually **reduces** thyroid function, there is a phase of compensation when normal thyroid hormone levels are maintained by a rise in TSH.

Although some patients may have minor symptoms, this state is called ***subclinical hypothyroidism.***

Later, unbound T4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually **TSH >10 mIU/L**), which is referred to as ***clinical hypothyroidism*** or ***overt hypothyroidism***.

Congenital hypothyroidism

TABLE 376-2 Genetic Causes of Congenital Hypothyroidism

DEFECTIVE GENE PROTEIN	INHERITANCE	CONSEQUENCES
PROP-1	Autosomal recessive	Combined pituitary hormone deficiencies with preservation of adrenocorticotropic hormone
PIT-1	Autosomal recessive Autosomal dominant	Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)
TSHβ	Autosomal recessive	TSH deficiency
TTF-1 (TITF-1)	Autosomal dominant	Variable thyroid hypoplasia, choreoathetosis, pulmonary problems
TTF-2 (FOXE-1)	Autosomal recessive	Thyroid agenesis, choanal atresia, spiky hair
PAX-8	Autosomal dominant	Thyroid dysgenesis, kidney abnormalities
NKX2-1	Autosomal dominant	Thyroid dysgenesis, brain, lung abnormalities
NKX2-5	Autosomal dominant	Thyroid dysgenesis, heart abnormalities
TSH-receptor	Autosomal recessive	Resistance to TSH
$G_{s\alpha}$ (Albright hereditary osteodystrophy)	Autosomal dominant	Resistance to TSH
Na^+/I^- symporter (SLC5A5)	Autosomal recessive	Inability to transport iodide
DUOX2 (THOX2)	Autosomal dominant	Organification defect
DUOXA2	Autosomal recessive	Organification defect
Thyroid peroxidase	Autosomal recessive	Defective organification of iodide
Thyroglobulin	Autosomal recessive	Defective synthesis of thyroid hormone
Pendrin (SLC26A4)	Autosomal recessive	Pendred syndrome: sensorineural deafness and partial organification defect in thyroid
Dehalogenase 1 (IYD)	Autosomal recessive	Loss of iodide reutilization

Congenital hypothyroidism

The **majority of infants appear normal at birth**, and <10% are diagnosed based on **clinical features**, which include:

- prolonged jaundice
- feeding problems
- Hypotonia
- enlarged tongue
- delayed bone maturation
- umbilical hernia

Importantly, **permanent neurologic damage** results **if treatment is delayed**.

Subacute and Silent thyroiditis

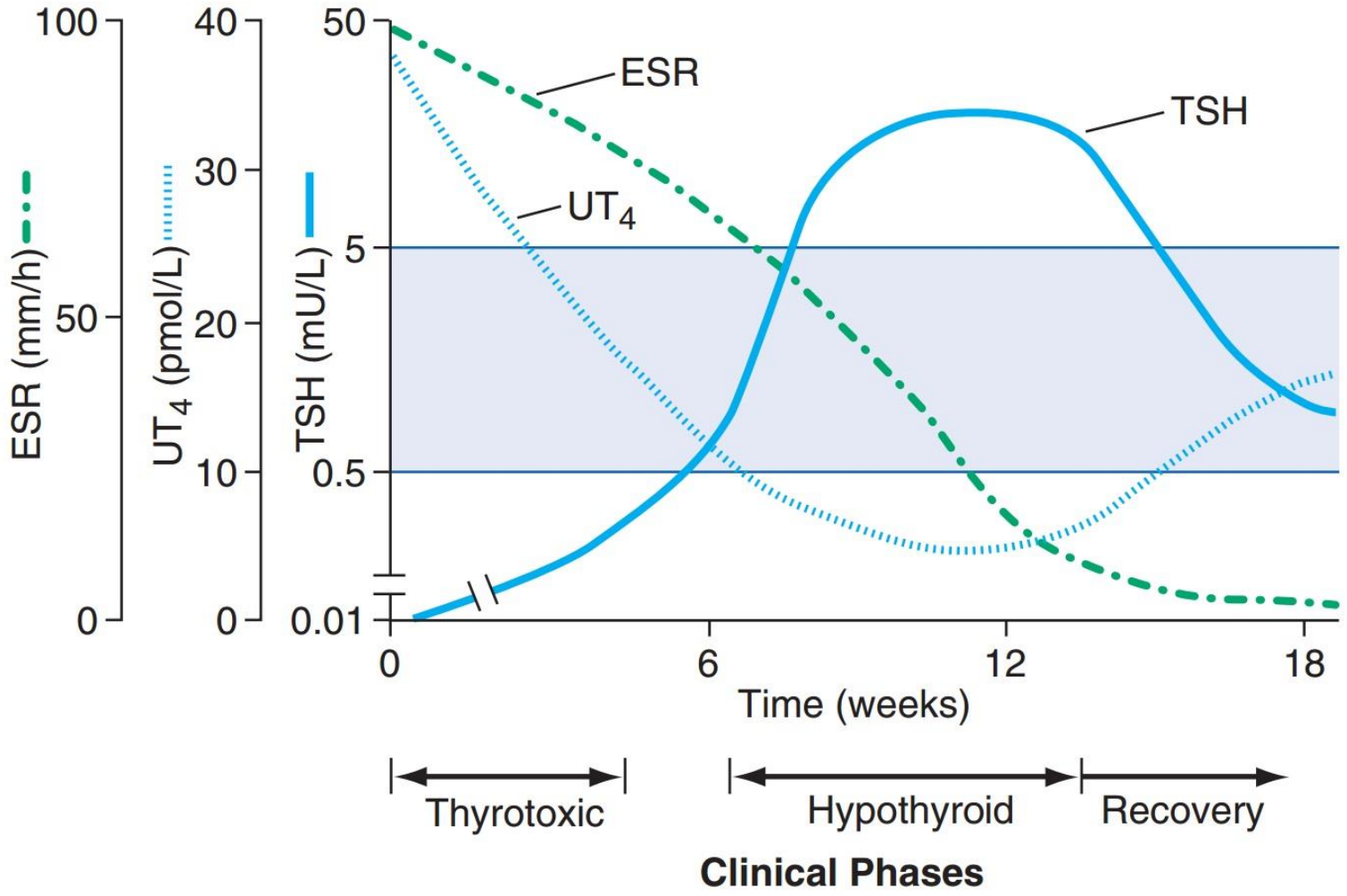
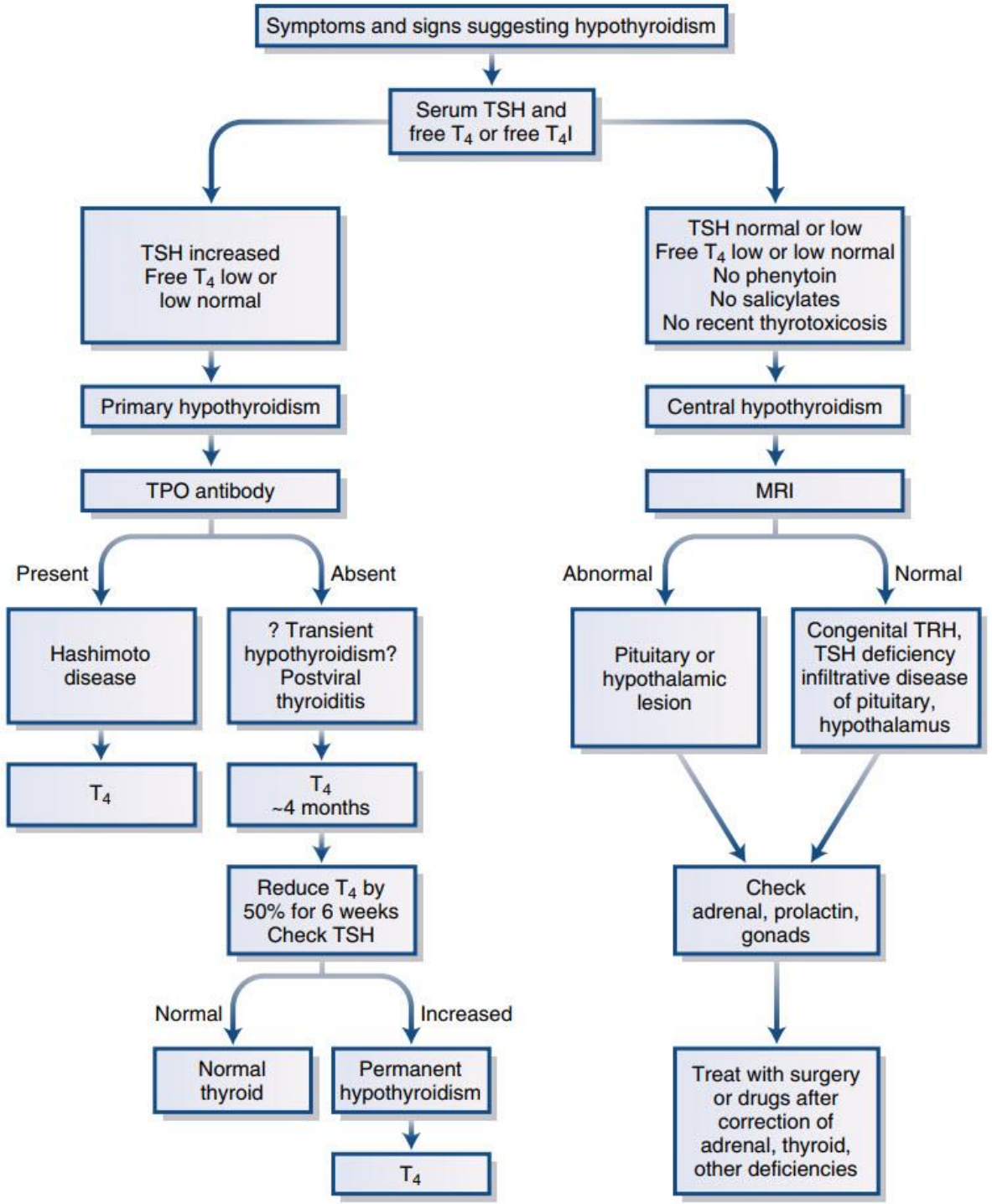


TABLE 376-3 Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

SYMPTOMS	SIGNS
Tiredness, weakness	Dry coarse skin; cool peripheral extremities
Dry skin	Puffy face, hands, and feet (myxedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia
Difficulty concentrating and poor memory	Peripheral edema
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Carpal tunnel syndrome
Dyspnea	Serous cavity effusions
Hoarse voice	
Menorrhagia (later oligomenorrhea or amenorrhea)	
Paresthesia	
Impaired hearing	

Diagnosis


Symptoms and signs suggesting hypothyroidism
Serum TSH and free T_4 or free T_4I
TSH increased Free T_4 low or low normal
Primary hypothyroidism
TPO antibody
Present
Absent
Hashimoto disease
T_4
? Transient hypothyroidism? Postviral thyroiditis
T_4 ~4 months
Reduce T_4 by 50% for 6 weeks Check TSH
Normal
Increased
Normal thyroid
Permanent hypothyroidism
T_4
TSH normal or low Free T_4 low or low normal No phenytoin No salicylates No recent thyrotoxicosis
Central hypothyroidism
MRI
Abnormal
Normal
Pituitary or hypothalamic lesion
Congenital TRH, TSH deficiency infiltrative disease of pituitary, hypothalamus
Check adrenal, prolactin, gonads
Treat with surgery or drugs after correction of adrenal, thyroid, other deficiencies

Levothyroxine

If there is **no residual thyroid function**, the daily replacement dose of levothyroxine is usually **1.6** μg/kg body weight (typically 100–150 μg).

Adult patients **under 60** years old **without** evidence of **heart disease** may be started on **50–100** μg levothyroxine (T4) daily.

The dose is **adjusted** on the basis of **TSH** levels, with the **goal of treatment being a normal TSH,** ideally in the **lower half** of the reference range.

TSH responses are gradual and should be measured about **2 months** after **instituting** treatment or after **any subsequent change** in levothyroxine dosage.

Levothyroxine

levothyroxine be consistently taken 60 minutes before breakfast.

levothyroxine should be separated from other potentially interfering medications and supplements

(e.g., calcium carbonate and ferrous sulfate)

4-hour separation

Because **T4 has a long half-life (7 days)**, patients who **miss a dose** can be advised to take two doses of the skipped tablets at once.

Patients with a **suppressed TSH of any cause**, including T4 overtreatment, have an **increased risk of atrial fibrillation and reduced bone density.**

Levothyroxine

Switches between levothyroxine products could potentially result in variations in the administered dose and should generally be avoided for that reason.

Because **use of different levothyroxine products** may sometimes be associated with altered serum TSH values, a change in an identifiable formulation of levothyroxine (brand name or generic) should be followed by **re-evaluation of serum TSH**.

Levothyroxine

In patients of **normal body weight** who are taking **≥200 µg of levothyroxine per day**, an **elevated TSH** level is often a sign of **poor adherence to treatment.**

In patients in whom levothyroxine **dose requirements are much higher than expected**, evaluation for gastrointestinal disorders such as Helicobacter pylori–related gastritis, atrophic gastritis, or **celiac disease** should be considered.

reassessment of TSH after Initiation or discontinuation of:

- estrogen and androgens
- phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline

Levothyroxine

When deciding on a **starting dose** of levothyroxine,

- the patient's weight
- pregnancy status
- etiology of hypothyroidism
- Age
- **general clinical** context, including the presence of cardiac disease
- the TSH goal appropriate for the clinical situation

should all be considered.

Levothyroxine

Weekly oral administration of the full week's dose of levothyroxine should be considered in individuals in whom adherence cannot otherwise be sustained.

Subclinical Hypothyroidism

Subclinical hypothyroidism, defined as an **elevated serum thyrotropin** (TSH) level with **normal levels of free thyroxine** (FT4) affects up to 10% of the adult population.

General **Therapeutic** Approach to the Management of **Subclinical Hypothyroidism** in **Nonpregnant Adults**

① Diagnosis of an elevated serum thyrotropin (TSH) level in a nonpregnant adult

② Confirmation of persistent subclinical hypothyroidism

- Initial thyrotropin level 4.5-14.9 mU/L, repeat measurement and document normal free thyroxine level in 1-3 months.
- Initial thyrotropin level ≥15 mU/L, repeat measurement and document normal free thyroxine level in 1-2 weeks.

③ Treatment initiation considerations

	Thyrotropin level, mU/L	Patients <65 years	Patients ≥65 years
	0.4-4.4	Normal thyrotropin reference range	
Subclinical hypothyroidism, Grade 1	4.5-6.9	• Measure thyroid peroxidase (TPO) antibodies • Annual follow-up thyrotropin measurement of asymptomatic patients • Consider treatment with levothyroxine (LT_4) in patients with Multiple symptoms of hypothyroidism Positive TPO antibodies Progressively increasing thyrotropin levels A plan for pregnancy Goiter	Treatment is not recommended
Subclinical hypothyroidism, Grade 1	7.0-9.9	Treat with LT_4 to reduce risk of fatal stroke and coronary heart disease (CHD) mortality[a]	Consider treatment with LT_4 to reduce risk of CHD mortality[a]
Subclinical hypothyroidism, Grade 2	≥10.0	Treat with LT_4 to reduce risk of progression to overt hypothyroidism, heart failure, CHD events, and CHD mortality[a]	

④ Treatment follow-up

- If treatment is initiated, measure thyrotropin level in 6 weeks and adjust LT_4 dose if necessary.
- Once target thyrotropin level is reached, perform annual measurement to confirm that it remains within the target range.

Secondary Hypothyroidism

Secondary hypothyroidism is usually diagnosed in the context of other anterior pituitary hormone deficiencies; **isolated TSH deficiency** is **very rare.**

TSH levels may be low, normal, or even slightly increased in secondary hypothyroidism.

The diagnosis is confirmed by detecting a **low FT4 level.**

The **goal of treatment** is to maintain **T4 levels** in the **upper half** of the **reference range**, because **TSH levels cannot be used to monitor therapy.**

Thank you

For you attention