The Islamic University
College of Pharmacy
Pharmacology & Toxicology Dep.

Applied Therapeutics–II

Thyroid Disorders

Level: 5th
Semester: 2nd

Lecture-2

By
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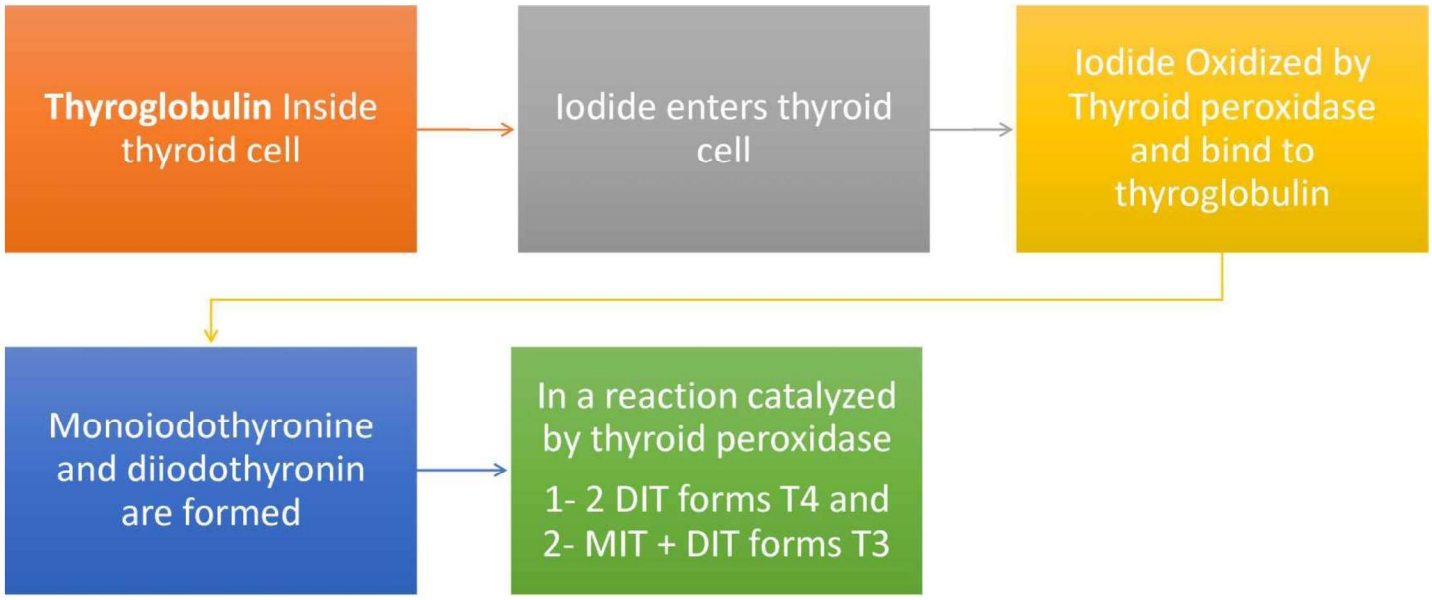
Background

- **Thyroid disorders** involve thyroid hormone *production* or *secretion* and result in **alterations in metabolic stability**.
- The thyroid hormones **thyroxine** (T_4) and **triiodothyronine** (T_3) are formed within thyroglobulin, a large glycoprotein synthesized in the thyroid cell. **Inorganic iodide** enters the thyroid follicular cell and is oxidized by thyroid peroxidase and covalently **bound** (organified) to **tyrosine residues** of **thyroglobulin**.
- Iodinated tyrosine residues **mono**iodotyrosine (MIT) and **di**iodotyrosine (DIT) combine (couple) to form **iodo**thyronines in reactions catalyzed by thyroid peroxidase. Thus, **two molecules of DIT** combine to form T_4, and **MIT and DIT** join to form T_3.
- T_4 and T_3 are transported by **thyroid-binding globulin** (TBG), **transthyretin**, and **albumin**.
- **Only the unbound (free) thyroid** hormone can ***diffuse into cells***, elicit ***biologic effects***, and ***regulate*** thyroid-stimulating hormone (***TSH***) secretion from the pituitary.



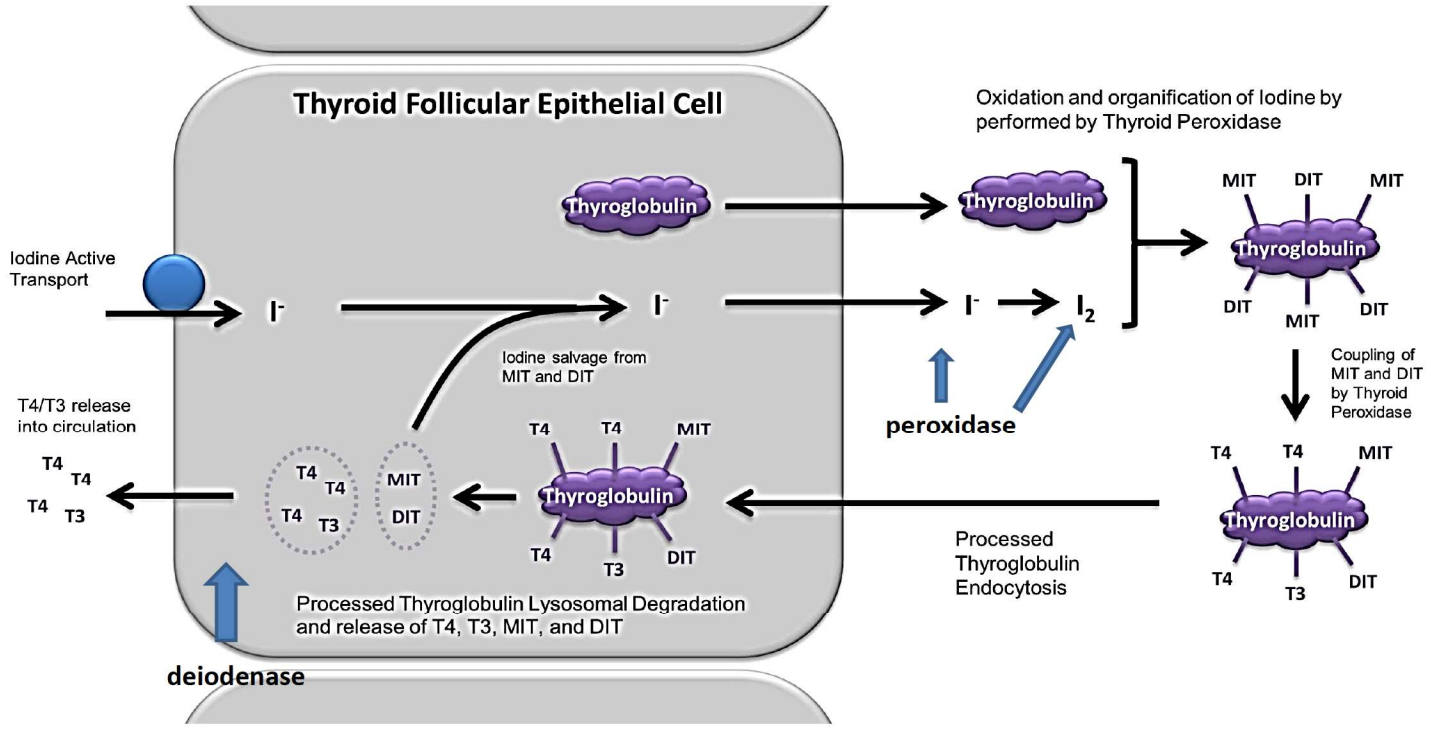
- T_4 is **secreted solely** from the **thyroid**, but **<20% of T_3** is produced there; most T_3 is formed from breakdown of T_4 catalyzed by the **enzyme 5'-monodeiodinase** in **peripheral** tissues.
- **T_3 is five times more active than T_4 .**
- T_3 أكثر نشاطا بخمس مرات من T_4
- **T4 considered a prohormone** that is **converted in the peripheral tissues** (liver, kidney and brain) either to the **active hormone T3** or to the biologically ***inactive* reverse T3** (**rT3**).

Regulation:

- **Thyroid** hormone ***production is regulated*** by **TSH** secreted by the **anterior pituitary**, which in turn is under negative feedback control by the circulating level of ***free thyroid hormone*** and the **positive** influence of hypothalamic **thyrotropin-releasing hormone** (***TRH***).
  - ❑ Thyroid hormone **production is also** regulated by **extrathyroidal deiodination** of **T_4 to T_3**, which can be affected by **nutrition**, **nonthyroidal** hormones, **drugs**, and **illness**.

T4 converted to T3 by peripheral tissue . T4 may be **cleaved** to form **reverse T3**, which has no significant biologic activity.

Biosynthesis of Thyroid Hormones



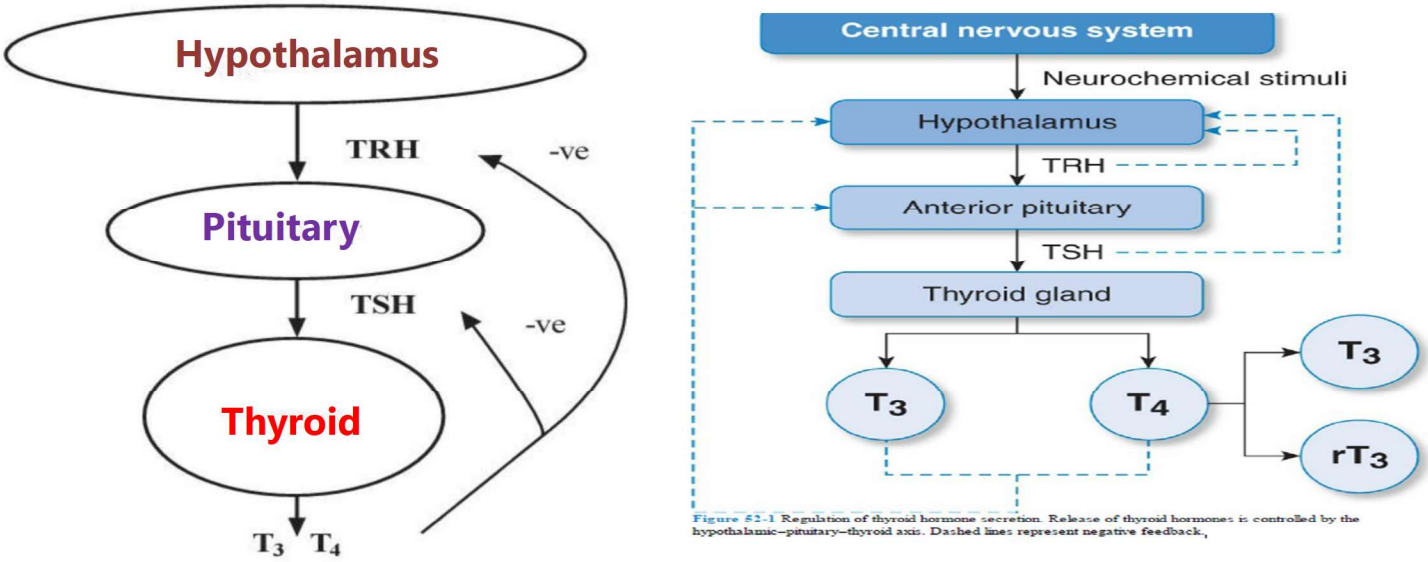


Figure 52-1 Regulation of thyroid hormone secretion. Release of thyroid hormones is controlled by the hypothalamic–pituitary–thyroid axis. Dashed lines represent negative feedback.

biologically ***inactive*** reverse T3 (rT3)

Hypothalamus-pituitary-thyroid <u>axis</u>.

T4 converted to T3 by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.

T_3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; -ve = negative feedback loop

Thyrotoxicosis (Hyperthyroidism)

PATHOPHYSIOLOGY

Thyrotoxicosis results when **tissues are exposed** to **excessive levels of T_4, T_3, or both**. this, **hyperthyroidism** refers to overproduction of **thyroid hormone** by the thyroid gland.

TSH-secreting **pituitary tumors** release biologically active hormone that is unresponsive to normal feedback control. The **tumors may co-secrete prolactin or growth hormone**; therefore, patients may present with **amenorrhea, galactorrhea, or signs of acromegaly**.

Graves' disease is the **most common cause of hyperthyroidism**, which results from the action of thyroid-stimulating **antibodies** (TSAb) directed against the ***thyrotropin receptor*** on the **surface of thyroid cells**. These immunoglobulins **bind** to the **receptor** (*TSH receptors*) and **activate** the enzyme adenylate cyclase in the **same manner as *TSH***. → *++ thyroid hormone*

An **autonomous** thyroid **nodule** (**toxic adenoma**) is a **benign thyroid mass** that ***produces thyroid hormone*** **independent of pituitary and TSH control**. Hyperthyroidism usually occurs with **larger nodules (>3 cm** in diameter).

Hyperthyroidism is defined as **excessive** amounts of thyroid hormones produced by the thyroid gland.
Thyrotoxicosis refers to the **clinical syndrome** associated with **excessive thyroid hormone of any cause.**

In **multinodular goiter**, **follicles with autonomous function** coexist with normal or even nonfunctioning follicles. Thyrotoxicosis occurs when their tissue generate more thyroid hormone than is required.

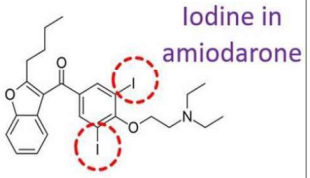
Painful subacute (granulomatous or **de Quervain**) thyroid**itis** often develops after a **viral syndrome**, but **rarely** has a **specific virus** been identified in thyroid parenchyma.

Painless (silent, lymphocytic, or postpartum) thyroid**itis** is **a common cause of thyrotoxicosis**. Its etiology is not fully understood; **autoimmunity** may underlie most cases.

Thyrotoxicosis **factitia** is hyperthyroidism due to ingestion of **exogenous thyroid hormone**. This may occur when thyroid hormone is used for inappropriate indications, excessive doses are used for accepted medical indications, or when there is accidental ingestion. فاكتيشيا

Factitious = artificially created or developed - ingestion of **exogenous thyroid hormone**

* **Amiodarone** may induce **thyrotoxicosis** (**2%-3%** of patients), **overt/apparent hypothyroidism** (**5%** of patients), **subclinical hypothyroidism** (**25%** of patients), or ***euthyroid hyperthyroxinemia***. Because of **amiodarone's** high iodine content (37% by weight), **increased thyroid hormone synthesis** commonly exacerbates thyroid dysfunction in patients with preexisting thyroid disease. Amiodarone also **causes a destructive thyroiditis** with leakage of thyroglobulin and thyroid hormones.



euthyroid = having a normally functioning thyroid gland:

CLINICAL PRESENTATION

- **Symptoms** of thyrotoxicosis include **nervousness**, **anxiety**, **palpitations**, easy fatigability, **heat intolerance**, weight loss concurrent with increased appetite, proximal muscle **weakness**, and **scanty or irregular menses** in **women**.
- **Physical signs** include warm, smooth, moist skin, and unusually fine hair; **onycholysis**; **lid lag**; **tachycardia** **at rest**; occasional **gynecomastia** in **men**; fine **tremor**. **Thyromegaly** is usually present.
- **Graves' disease** is manifested by **hyperthyroidism** + **diffuse** thyroid enlargement + **extrathyroidal findings** of **"exophthalmos**, **pretibial myxedema,** and thyroid **acropachy"**. In ***severe*** disease, a **thrill/excitement** may be **felt** and a **systolic bruit** may be heard over the gland".

In subacute thyroiditis, patients have severe pain in the thyroid region, which often extends to the ear. Systemic symptoms include fever, myalgia, and signs and symptoms of thyrotoxicosis.

Painless thyroiditis has a triphasic course that mimics painful subacute thyroiditis. Most patients present with mild thyrotoxic symptoms; lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged without tenderness (pain on touching).

Thyroid **crisis** (storm) → emergency

علاج هذه الحالة سيأتى بعد

Thyroid storm

- **Thyroid storm** is a ***life-threatening*** medical **emergency** characterized by decompensated **thyrotoxicosis**, high **fever** (often **>39.4°C** [**103°F**]), **tachycardia**, **tachypnea**, dehydration, coma, nausea, vomiting, and diarrhea.

Precipitating factors include **infection**, **trauma**, **surgery**, **radioactive iodine** (***RAI***) treatment, and **withdrawal from anti-thyroid** drugs.

Hyperthyroidism is defined as **excessive** amounts of thyroid hormones produced by the thyroid gland.
Thyrotoxicosis refers to the **clinical syndrome** associated with **excessive thyroid hormone of any cause.**

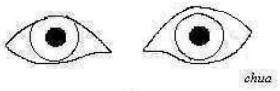
تلخيص

Graves disease is manifested by

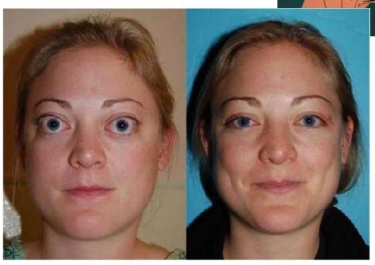
- ❑ hyperthyroidism,
- ❑ diffuse thyroid enlargement,
- ❑ and **extrathyroidal findings of exophthalmos, pretibial myxedema, and thyroid acropachy (**dermopathy) .
  - ✓ In severe disease, a thrill may be felt and a systolic bruit may be heard over the gland.

Thyroid Eye disease

lid lag



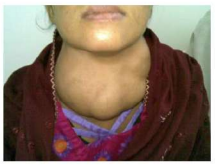
exophthalmos

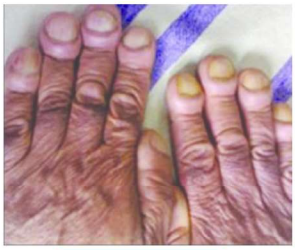


Onycholysis

diffuse thyroid enlargement

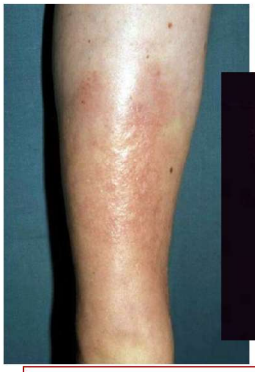
Goiter

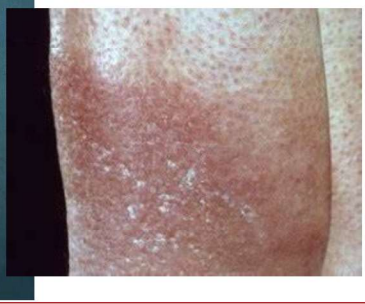




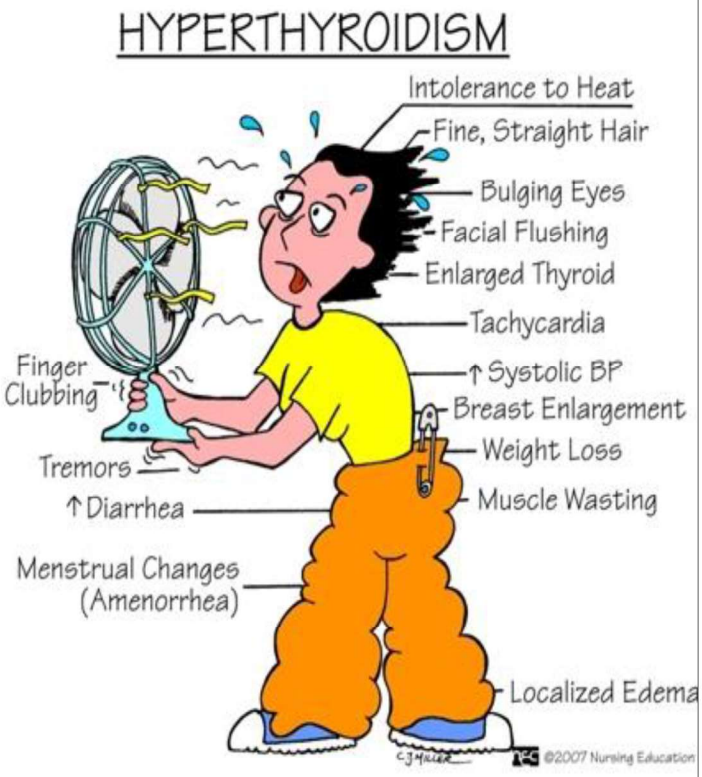
Acropathy

Acropathy is a dermopathy associated with Graves' disease. It is characterized by soft-tissue swelling of the hands and clubbing of the fingers





Graves' Dermopathy Pretibial Myxedema



* LOC = level of consciousness.

DIAGNOSIS:

تقرأ من المرجع لتفاصل أكثر

Thyroid function test involves **T_3, T_4 and TSH** which are important in diagnosis ***in addition*** to patient **history and signs/symptoms**. In patients with **symptomatic disease**, measurement of serum **total & free T4, total T3, and TSH** will **confirm the diagnosis** of thyrotoxicosis.

- **Elevated 24-hour radioactive iodine uptake (RAIU)** indicates **true** hyperthyroidism: the patient's thyroid gland is overproducing T_4, T_3, or both (**normal RAIU 10%-30%**).
  - ❖ **Low RAIU** indicates that excess thyroid hormone is ***not*** *a consequence of thyroid gland hyperfunction,* **but** is likely caused by **thyroiditis**, follicular **cancer**, or **exogenous** thyroid hormone ingestion.
- In **Thyrotoxic Graves' disease, autoimmune disease,** there is an increase in the overall hormone production rate with a **dis**proportionate increase in **T3 relative to T4** ***(Table 20-1)***.
  - The **TSH level** is **undetectable** due to negative feedback by elevated levels of thyroid hormone at the pituitary gland.

TABLE 20-1 Thyroid Function Tests in Different Thyroid Conditions

	Total T_4	Free T_4	Total T_3	TSH
Normal	4.5–10.9 mcg/dL	0.8–2.7 ng/dL	60–181 ng/dL	0.5–4.7 milli-international units/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↓↓*
Hypothyroid	↓↓	↓↓	↓	↑↑*
Increased TBG	↑	Normal	↑	Normal

*Primary thyroid disease.

TREATMENT

- **Goals of Treatment:**
  - Eliminate excess thyroid hormone;
  - minimize symptoms and long-term consequences; and
  - provide individualized therapy based on; the ***type*** and **severity** of disease, patient **age** and **gender**, **existence of nonthyroidal** conditions/comorbidity, and ***response*** to *previous therapy*.
- **NON-PHARMACOLOGIC THERAPY**

Surgical removal of the thyroid gland should be considered in patients with a large gland (>80 g), severe ophthalmopathy, or lack of remission on antithyroid drug treatment.

- ❖ ***If*** **thyroidectomy** is planned: تحضير المريض لعملية استئصال الغدة الدرقية
  1) **Methimazole** is given until the patient is biochemically *euthyroid* (usually **6-8 weeks**),
  2) followed by addition of **iodides** (500 mg/day) for **10-14 days before surgery** to *decrease vascularity of the gland*. (⬇ size, vascularity, & bleeding during Surgery)
  3) **Propranolol** has been used for **several weeks pre-operatively** and **7-10 days after surgery** to maintain *pulse rate <90 beats/min*.

Combined pretreatment with propranolol & 10–14 days of **potassium iodide** also has been advocated/encouraged.

PHARMACOLOGIC THERAPY

1- Thionamides (Methimazole and Propylthiouracil (PTU))

- Methimazole and Propylthiouracil (PTU) **block** thyroid hormone **synthesis** by **inhibiting the peroxidase** enzyme system of the thyroid. PTU (but not methimazole) also inhibits Peripheral conversion of T4 to T3.
- Usual **initial doses** include **methimazole** 30-60 mg daily given in two or three divided doses or PTU 300-600 mg daily (usually in three or four divided doses). Evidence exists that both drugs can be given as a single daily dose. ***Dose modifications should be done monthly.***

Improvement in symptoms and laboratory abnormalities should occur within **4-8 weeks**, at which time a tapering regimen 'to maintenance doses' can be started. •

Doses *can be* changed monthly because the endogenously produced T4 will reach a new steady-state concentration in this interval.

- Typical **daily maintenance doses** are methimazole **5–30 mg** and PTU **50–300 mg**.
- Continue therapy for 12-24 months to induce *long-term remission*.
- **Monitor patients every 6-12 months** *after remission*. **If a relapse occurs,** alternate therapy with **RAI** is preferred over a second course of antithyroid drugs, **because** subsequent courses are *less* likely to induce *remission*.

- **Minor** adverse reactions include pruritic maculopapular **rashes**, arthralgias, **fever**, and benign transient **leukopenia** (*white blood cell count* **<4000/mm³** or **4 x 10^9/L**). The alternate thionamide may be tried in these situations, but cross-sensitivity occurs in about 50% of patients.
- **Major** adverse effects include **agranulocytosis** (with **fever, malaise, gingivitis,** oropharyngeal **infection**, and **granulocyte count <250/mm³ or 0.25 x 10^9/L** (granulopenia), aplastic **anemia**, **lupus-like** syndrome, GI intolerance, **hepatotoxicity**, and **hypo**prothrombinemia. **If** agranulocytosis occurs, it usually develops in the first 3 months of therapy; **routine WBC count** monitoring is **not** recommended because of its **sudden onset**.
- **Because of the risk of serious hepatotoxicity, PTU** should **not** be considered first-line therapy in either adults or children. ***Exceptions*** *to this recommendation* include:
  (1) the **first trimester of pregnancy** (when the risk of methimazole-induced embryopathy may exceed that of PTU induced hepatotoxicity),
  (2) intolerance to methimazole, and
  (3) thyroid **storm**.

Methimazole-induced embryopathy
PTU induced hepatotoxicity

First trimester of pregnancy → PTU

2- Iodides:

- Iodide ***acutely*** **blocks** thyroid hormone **release**, inhibits thyroid hormone **biosynthesis** by interfering with intrathyroidal iodide use, and **decreases size and vascularity** of the gland.
- *Symptom improvement* occurs within 2-7 days of initiating therapy, and serum T4 and T3 concentrations may be reduced for a few weeks.
- **Iodides** are often used as **adjunctive therapy** to:
  1) prepare a patient with ***Graves'*** *disease* for **surgery**,
  2) to **acutely inhibit** thyroid hormone **release** and
  3) quickly attain the **euthyroid** state in severely thyrotoxic patients with **cardiac** decompensation, or
  4) to inhibit thyroid hormone release **after RAI therapy**.

❑ **Potassium iodide** is available as

A. Saturated solution (SSKI) (*38 mg iodide per drop*) **or as**

B. Lugol solution, containing *6.3 mg of iodide per drop*.

- Typical **starting dose** of **SSKI** is **3-10 drops** daily (120-400 mg) in *water or juice*.
  1. When used to **prepare a patient for surgery**, it should be administered **7-14 days preoperatively**. قبل
  2. As an **adjunct to RAI**, ***SSKI should not be used before*** **but** rather ***3-7 days after RAI*** treatment **so that the RAI can concentrate in the thyroid**. بعد

- **Adverse effects of iodide therapy include:**

  A. **hypersensitivity** reactions (skin rashes, drug fever, and rhinitis, conjunctivitis),
  B. **Salivary** gland **swelling**,
  C. **"iodism"** (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea), and
  D. **Gynecomastia**.

- **Iodide is contraindicated in toxic multinodular goiter** because the **autonomous tissue** utilizes the iodine for subsequent thyroid hormone synthesis.

3- Adrenergic Blockers

❖ B-Blockers are used to **ameliorate symptoms** such as palpitations, anxiety, tremor, and heat intolerance.
  ❑ *They have **no effect** on **peripheral** thyrotoxicosis,*
  ❑ ***do not reduce** TSAb, or prevent thyroid **storm**.*

- **Propranolol & Nadolol *partially*** block conversion of T4 to T3, *but* this contribution to overall *effect is small*.
- (β-Blockers are usually used as **adjunctive therapy** with;
  a) **Antithyroid drugs**,
  b) **RAI**, or
  c) **iodides** when treating **Graves'** disease or toxic **nodules**, in preparation for surgery, or in thyroid storm. مع الأيوديد

* The **only conditions** for which **β-blockers** are **primary therapy** for thyrotoxicosis are those associated with **thyroiditis**.

- **Propranolol:** initial dose of 20-40 mg*4 daily is effective for most patients (heart rate <90 beats/min). **Younger** or more **severely toxic patients** may require 240-480 mg/day, perhaps because of increased clearance.

Propranolol and **Nadolol** partially block conversion of T4 to T3, (effect is small).

- β-Blockers are **contraindicated** in decompensated **HF**, **bradycardia**, or with **MAOi** ,**TCA**, and patients with spontaneous **hypoglycemia**. **S/E:** include anxiety, insomnia, lightheadedness الدوار, bradycardia.
- *Centrally acting sympatholytics (eg, **Clonidine**) and calcium channel antagonists (eg, **Diltiazem**) may be useful for symptom control **when contraindications to β-blockade exist***. لو هناك موانع

3- Radioactive Iodine (RAI)**

- **Sodium iodide-131 (I^{131})** is an ***oral liquid*** that concentrates in the thyroid and initially disrupts hormone synthesis. Over a period of **weeks**, **follicles** that have taken up RAI + **surrounding follicles** develop evidence of cellular **necrosis** and **fibrosis** of interstitial tissue.
- Indications: RAI is the **agent of choice** for **Graves' disease, toxic autonomous nodules, and toxic multinodular goiters**.

❖ ***Pregnancy** is an absolute **contraindication** to use of **RAI** because **radiation** would be delivered to the fetal tissue.*

- **β-Blockers** are the **primary adjunctive therapy to RAI** because they may be **given anytime** without compromising RAI therapy.
- If **iodides** are administered (with **RAI**), they (**iodides**) **should** be given **3-7 days after RAI** to prevent interference with uptake of RAI in the thyroid gland.

- Patients with **cardiac disease** and **elderly** patients: are often treated with thionamides prior to RAI ablation *because thyroid hormone* levels transiently **increase** after RAI treatment *due to* release of preformed thyroid hormone.
- Administering antithyroid drug therapy **immediately after RAI** may *result in* a higher rate of post treatment **recurrence** or **persistent** hyperthyroidism.
- **Use of lithium** as adjunctive therapy to RAI has **benefits** of **increased cure** rate, **shortened time** to cure, and **prevention** of **post therapy increases** in thyroid hormone levels.
- The **goal of therapy:** is to ***destroy overactive thyroid cells***, and a **single dose** of 4000-8000 **rad** *results in* a euthyroid state in ***60%*** of patients at **6 months or sooner**. A **second dose** of RAI should be given **6 months after** the first RAI treatment if the patient remains hyperthyroid.
- **Hypothyroidism** commonly occurs **months to years after RAI.**

The **acute, short-term side effects** include: mild thyroid tenderness and dysphagia.

Long-term follow-up has **not** revealed an increased **risk** for development of mutations or congenital defects.

• TREATMENT OF THYROID STORM

Initiate the following therapeutic measures promptly: (1) suppression of thyroid hormone formation and secretion, (2) antiadrenergic therapy, (3) administration of corticosteroids, and (4) treatment of associated complications or coexisting factors that may have precipitated the storm.

- **PTU** in **large doses** may be the **preferred thionamide** because it blocks peripheral conversion of T4 to T3 + interfering with thyroid hormone production. However, ***β-blockers*** and ***corticosteroids*** serve the *same purpose*. **Methimazole** has a *longer duration of action*, which offers a **theoretical advantage**.
- **Iodides**, which rapidly block the release of preformed thyroid hormone, should be ***administered after a thionamide is initiated to inhibit iodide utilization by the overactive gland.***
- **Antiadrenergic** therapy with the short-acting agent **esmolol** is preferred because it *can be used in patients* with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.
- **Corticosteroids** are generally recommended, their **benefits** may be attributed to their antipyretic action and stabilization of blood pressure (BP).
- General **supportive** measures, including **acetaminophen** as an ***antipyretic*** (**avoid aspirin** OR other NSAIDs, which may **displace bound thyroid hormone**), fluid and electrolyte replacement, **sedatives**, **digoxin**, **antiarrhythmics**, **insulin**, and **antibiotics** should be given as indicated.

EVALUATION OF THERAPEUTIC OUTCOMES

- **After therapy** (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, evaluate patients monthly until they reach a **euthyroid** condition.
- Assess for **clinical signs** of continuing thyrotoxicosis or development of hypothyroidism.
- **If T4 replacement is initiated**, the **goal** is to maintain both free T4 level & TSH concentration in the normal range. **Once a stable** dose of T4 is identified, monitor the patient every 6-12 months.

Hypothyroidism

• PATHOPHYSIOLOGY

- **Most hypo**thyroidism cases caused by **chronic autoimmune thyroid**itis (**Hashimoto** disease). A mutating **helper T lymphocytes** directed **against** antigens on the thyroid membrane. The **resulting** *interaction* **stimulates B lymphocytes** to produce **thyroid antibodies**.
  - ❖ **iatrogenic hypothyroidism** follows:
    a) exposure to destructive amounts of radiation,
    b) after total thyroid**ectomy**, or
    c) with **excessive thionamide** doses used to treat hyperthyroidism.

iatrogenic = Illness induced unintentionally by a physician or surgeon or by medical treatment or diagnostic procedures

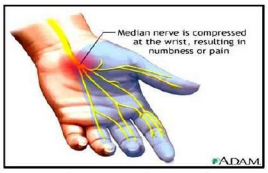
- Other causes of **Primary hypothyroidism** include **iodine deficiency**, enzymatic defects within the thyroid, thyroid **hypo**plasia, and ingestion of goitrogens.
- **Secondary** hypothyroidism due to **pituitary failure** is **uncommon**. pituitary tumors, surgical therapy, external pituitary radiation, *postpartum* pituitary *necrosis* (**Sheehan** syndrome), trauma, and infiltrative processes of the pituitary (eg, metastatic tumors, tuberculosis).

Sheehan syndrome = A condition resulting from the damage to the pituitary gland, due to low levels of oxygen (through **blood loss**), often during childbirth/delivery. It causes difficulty in breast-feeding and failure to resume menstruation after delivery.

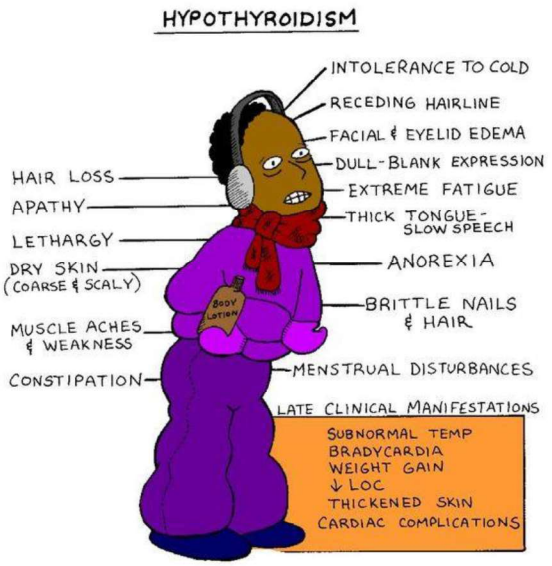
CLINICAL PRESENTATION

- **Symptoms of hypothyroidism include:** dry skin, **cold intolerance**, **weight gain**, **constipation**, weakness, lethargy, **depression**, fatigue, exercise intolerance, loss of energy, muscle cramps, myalgia, and stiffness.
  - **Menorrhagia** and **infertility** are common in **women**.
  - In **children**, thyroid hormone deficiency may manifest as **growth or intellectual retardation.**
- **Physical signs include** coarse skin and hair, cold or dry skin, **periorbital puffiness**, **bradycardia**, and slowed or hoarse speech. *Reversible **neurologic** syndromes* such as *carpal tunnel syndrome*, polyneuropathy, and cerebellar dysfunction may also occur.

Objective **weakness** (with proximal muscles affected more than distal muscles) and slow relaxation of deep tendon reflexes are common.



carpal tunnel syndrome



* LOC = level of consciousness.

Periorbital puffiness = (Eyelid edema)= Mild - severe swelling -around one or both eyes.

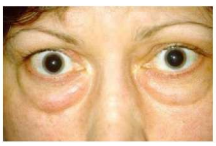
CLINICAL PRESENTATION (Continue ……..)

Most patients with secondary hypothyroidism due to inadequate TSH production have clinical signs of generalized pituitary insufficiency, such as **abnormal menses** and **decreased libido**, or evidence of a pituitary **adenoma**, *such as visual field defects, galactorrhea, or acromegaloid features.*

- **Myxedema coma** is a rare consequence of **decompensated hypothyroidism manifested by** hypothermia, advanced stages of hypothyroid symptoms, and **altered sensorium** ranging from delirium to coma. **Mortality rates' of 60%-70% necessitate immediate and aggressive therapy.**

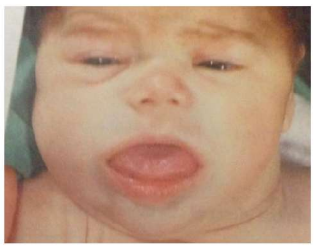
DIAGNOSIS

- A rise in TSH level is the first evidence of primary hypothyroidism. **Many** patients have a **free T4 level within the normal** range (compensated or subclinical hypothyroidism) + (if any) **few symptoms** of hypothyroidism
  - As the disease progresses, the free T4 drops below normal. The **T3 concentration** is often maintained in the **normal range** despite low T4. Eventually, free and/or total T4 and T3 serum concentrations will be low.
- In secondary hypothyroidism in patients with pituitary disease, serum TSH concentrations are generally low or normal.



Periorbital edema
Periorbital puffiness

In children, thyroid hormone deficiency may manifest as growth or intellectual retardation.



Childhood (congenital) hypothyroidism

Treatment of Hypothyroidism

1- Levothyroxine (L-thyroxine, T4) is the drug of choice, *because*:

a) it is chemically ***stable***,
b) relatively ***inexpensive***,
c) ***active*** when given ***orally***,
d) free of antigenicity, and
e) has uniform potency.

Goals of treatment

1- Restore thyroid hormone concentrations in tissue,
2- Provide symptomatic relief,
3- Prevent neurologic deficits in newborns and children, and
4- Reverse the biochemical abnormalities of hypothyroidism

➢ **L-thyroxine** is the drug of **choice** for **pregnant women**, and the goal is to decrease TSH to the normal reference range for pregnancy.

Because T3 (and not T4) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to T3.

Cardiac disease
ronine تأخذ بالإعتبار في حالة العلاج ب

- **Dosing:**

1. In **adult** patients without known cardiac disease, **start therapy** with **levothyroxine 50 mcg** daily and **increase** *after 1 month*.
2. **Older** patients with known cardiac disease:
   - starting dose (initial) is **25** mcg/day ***titrated*** *upward in* ***increments of 25 mcg at monthly*** *intervals* to prevent stress on the cardiovascular system.
3. The average **maintenance dose** for **most adults** is **~125 mcg/day**, but there is a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an appropriate dose.

- Drugs that impair the GI absorption of **levothyroxine**: **Cholestyramine**, calcium **carbonate**, **sucralfate**, **aluminum** hydroxide, **ferrous** sulfate, **soybean** formula, dietary **fiber** supplements, and **espresso coffee** , **histamine blockers** and **PPI**.
- Drugs that **increase T4 clearance**: **rifampin**, **carbamazepine**, and possibly **phenytoin**.
- **Selenium *deficiency*** and **amiodarone** may **block conversion of T4 to T3.**

2- Other preparations:

1- Thyroid USP is usually derived from **pig** thyroid gland. It may be **antigenic** in *allergic or sensitive patients*.

2- Liothyronine (*synthetic* **T3**) has **uniform potency, but** : عيوب

a) has a higher incidence of cardiac adverse effects,
b) higher cost,
c) difficulty in monitoring with conventional laboratory tests.
d) It must be administered three times a day
e) may require a prolonged adjustment period to achieve stable euthyroidism.

3- Liotrix (*synthetic* **T4:T3** in a **4:1** ratio) is chemically stable, pure, and has a predictable potency, **but** is *expensive*. It also *lacks* therapeutic *rationale* because most T3 is converted peripherally from T4.

➢ **Excessive doses** of thyroid hormone may lead to **heart failure**, **angina** pectoris, and myocardial **infarction** (MI). **Hyperthyroidism** leads to **reduced bone density and increased risk of fracture**.

TREATMENT OF MYXEDEMA COMA

1) IV bolus levothyroxine, Immediate and aggressive therapy with **IV bolus levothyroxine 300-500 mcg has traditionally been used** .
   - ❑ **Initial** treatment with **IV liothyronine** or a **combination of both hormones** has also been **advocated** because of **impaired conversion of T4 to T3**.
2) **Glucocorticoid** therapy with **IV hydrocortisone** 100 mg every 8 hours until coexisting **adrenal** suppression is ruled out.
   - **Consciousness**, **lowered TSH** concentrations, and **improvement in vital signs** are expected within *24 hours*.
3) Maintenance **levothyroxine** doses are typically 75-100 mcg IV until the patient stabilizes and oral therapy is begun.
4) Provide **supportive therapy** **to maintain** adequate **ventilation**, **euglycemia**, **BP**, and body **temperature**. ***Diagnose and treat underlying disorders*** *such as sepsis and MI.*

Evaluation of therapeutic outcomes

- **Serum TSH** concentration is the most sensitive and specific monitoring parameter for adjustment of **levothyroxine** dose. Concentrations begin to **fall within hours** and are usually **normalized within 2–6 weeks**.
- Check **both TSH and T4** concentrations **every 6 weeks** *until a* ***euthyroid*** *state* is achieved. An ***elevated TSH level indicates insufficient*** replacement.
- In *patients with* ***hypothyroidism*** caused by hypothalamic or pituitary failure, alleviation of the *clinical syndrome* and restoration of *serum T4 to the normal* range are the only criteria available for estimating the appropriate replacement dose of **levothyroxine**.

Thank You !