King Saud University

MEDICINE
KING SAUD UNIVERSITY

BIOCHEMISTRY TEAM 436

Important Doctors slides
Extra Information Doctors notes

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[Editing file]

Biochemistry

Thyroid Hormones and Thermogenesis

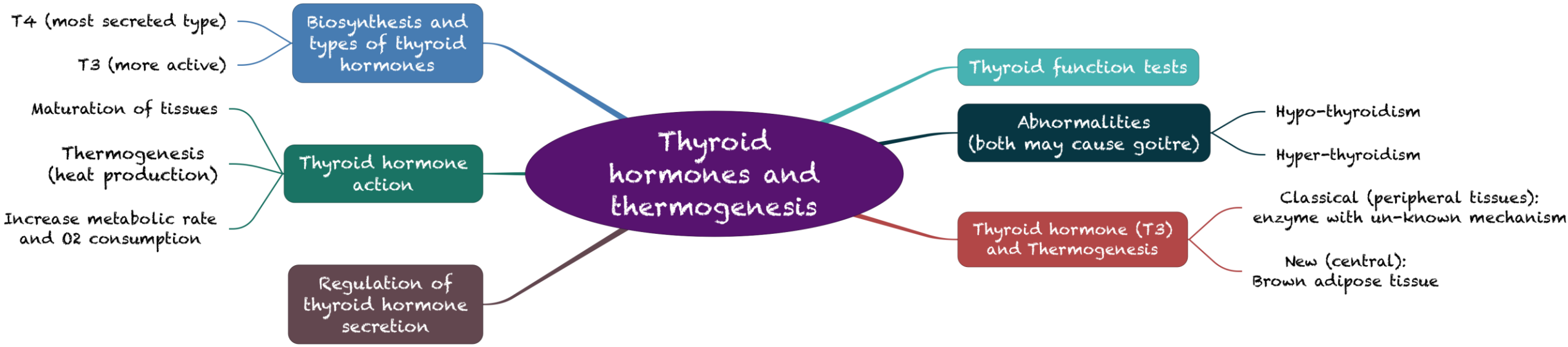
One day you'll be person between the patient and his grief. Please study well ..

OBJECTIVES

By the end of this lecture, the Second Year students will be able to:

- Describe the types and biosynthesis of thyroid hormones
- Discuss the thyroid hormone actions
- Understand the regulation of thyroid hormones
- List and interpret the thyroid function tests
- Define goiter and differentiate between hypo and hyperthyroidism
- Discuss the role of thyroid hormone in thermogenesis

Overview


Thyroid hormones and thermogenesis
Biosynthesis and types of thyroid hormones
T4 (most secreted type)
T3 (more active)
Thyroid hormone action
Maturation of tissues
Thermogenesis (heat production)
Increase metabolic rate and O2 consumption
Regulation of thyroid hormone secretion
Thyroid function tests
Abnormalities (both may cause goitre)
Hypo-thyroidism
Hyper-thyroidism
Thyroid hormone (T3) and Thermogenesis
Classical (peripheral tissues): enzyme with un-known mechanism
New (central): Brown adipose tissue

Types and Biosynthesis of Thyroid Hormones:

❖ Biosynthesis :

1-Synthesized

Synthesized in the **thyroid gland** by:

- Binding to thyroglobulin protein.
  - Iodination and coupling of two tyrosine molecules.

Thyroglobulin is synthesized by follicular cells then released in the lumen. Iodide (comes from the circulation) is oxidized by thyroid peroxidase in the lumen to form Iodine then ,this Iodine binds to tyrosine residues of thyroglobulin to form MIT (Mono-iodotyrosine) and DIT (Di-iodotyrosine) this process is catalyzed by thyroid peroxidase enzyme and it's called (Iodination), after that MIT & DIT get coupled to form T3 & T4 (MIT+DIT=T3 | DIT+DIT=T4).

After forming T3 & T4 the thyroglobulin will go back to follicular cells, TSH will stimulate follicular cells to Endocytose Thyroglobulin that is attached (T4, T3, MIT & DIT) to degrade thyroglobulin by lysosomes and we will be left with T4 & T3 which go to the circulation.
MIT & DIT are degraded to go back to the lumen.

يشرح لك طريقة تكوين الثايروويد هرمون بمراحله في اللومين:
١-تكوين ثايروجلوبيلين (الي راح يساعد على تصنيع الهرمون)
٢-عمل الثايروويد بيروكسيديز على:
أ-يمسك الايوداييد ويسوي له اوكسديشن ويتحول الى ايودين ويرتبط مع التايروزين الي تعتبر جزء من الثايروجلوبلين
ب-يعمل على ربط المكونات الناتجة من هذا الارتباط في تكوين الهرمونات
٣-بعد تكوين الهرمونات يرجع الثايروجلوبلين الى الفلوكلير سيلز ويتم تكسيره (بحيث ما يصنع بشكل زائد).

Types and Biosynthesis of Thyroid Hormones

❖ Biosynthesis :

2-Secretion

Thyroid gland
mostly secretes T4.

3- Deiodination

- Peripheral tissues (liver, kidney, etc.) de-iodinate T4 to T3.
- Deiodination is catalyzed by deiodinase enzyme.
- T4 can be metabolized to **r**T3 (inactive form).

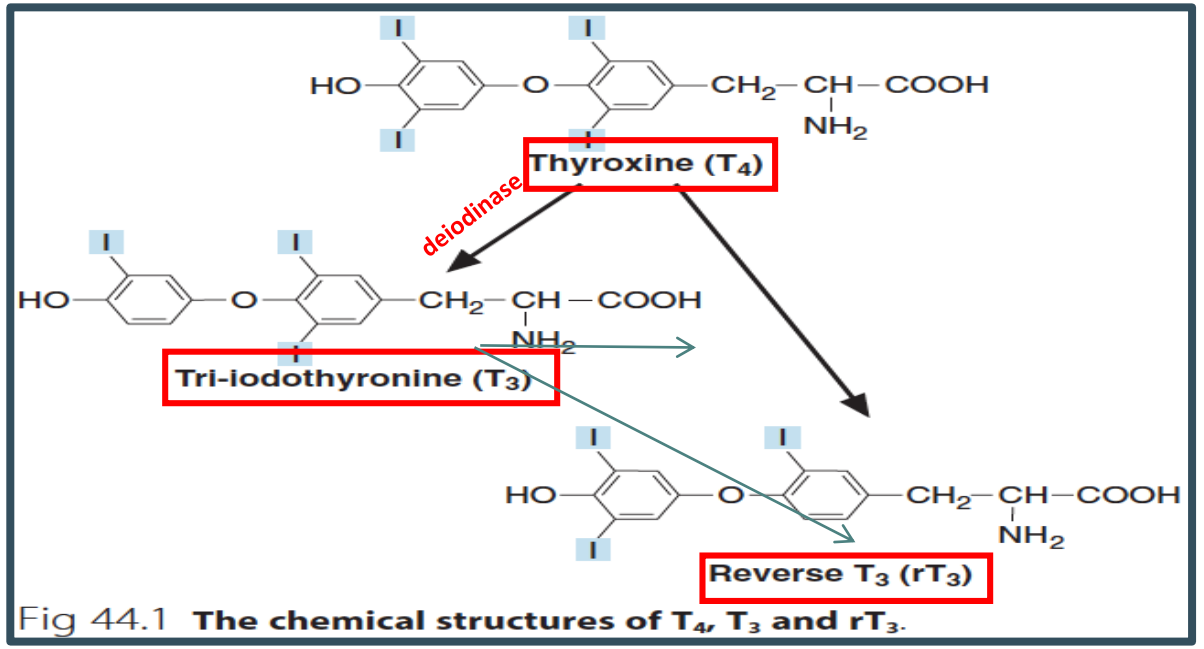


Fig 44.1 **The chemical structures of T_4, T_3 and rT_3.**

T3 & rT3 differ in the position of the iodine (structure)
But they have the same formula.
Pic: Note the difference in the position of Iodine.

- T3 is the most active biological form, less active form is T4 and then the inactive form rT3

Types and Biosynthesis of Thyroid Hormones

❖ Types :

Thyroxine (T4) AKA: tetra-iodothyronin. Number 4 stands for the number of iodine ions. (90%)	Tri-iodothyronine (T3) (10%)
Most of T_4 is transported in plasma as **protein-bound :** ▪ **Thyroxin binding globulin** (TBG)-bound (70%). Don't confuse between thyroglobulin and TBG. ▪ **Albumin-bound** (25%). ▪ **Transthyretin (pre-albumin)-bound** (5%).	T_3 is a more biologically active form.
The **un**bound (free) form of T_4 and T_3 are biologically active. whatever is free is the functional form of hormones	

The percentage of:
- Free T4 = 0.05%
Bound T4 = 99.95%
- Free T3 = 0.5%
Bound T3 = 99.5%

Thyroid hormone action:

- Plays an essential role in **maturation** of all body tissues.
- Involved in **thermogenesis** and metabolic regulation.
- **Increases** cellular oxygen consumption and **stimulates** the metabolic rate.
- Affects the rate of protein, carbohydrate and lipid **metabolism.**

2 Main functions:-
Affects the Metabolism.
Affects Body temperature (Thermogenesis).

❖ Clinical evidence of the wide spectrum of thyroid hormone action:

Case	Consequences
Untreated congenital hypothyroidism:	permanent brain damage. If untreated within the FIRST 3 months, but if you treated it before 3 months you won't see that much of effects. This tells you that thyroid hormones are required for the normal brain development.
Hypothyroid children have:	1. Delayed skeletal maturation ⟶ short stature. (Thyroid hormones Essential for bone maturation) 2. Delayed puberty.
Hypothyroid patients have high serum cholesterol due to: This tells you that thyroid hormones need for lipids metabolism and not only proteins and carbs	1. Down regulation of LDL receptors on liver cells. 2. Failure of sterol excretion via the gut.

❖ Clinical evidence of the wide spectrum of thyroid hormone action:

*hypothyroidism affects the cholesterol level (accumulate in the body and leads to atherosclerosis)
*LDL are particles that carry triglycerides and cholesterol from the liver to the tissue
-So basically they supply triglycerides and cholesterol to your tissues (tissues have receptors for these LDL particles)
-What if you have thyroid deficiency? These receptors will be inactive → less cholesterol uptake by the cells→ cholesterol will accumulate in the serum

Regulation of Thyroid Hormone Secretion:

- The hypothalamic-pituitary-thyroid axis regulates thyroid secretion:

The **hypothalamus senses** low levels of T3/T4 and **releases** thyrotropin releasing hormone (TRH).

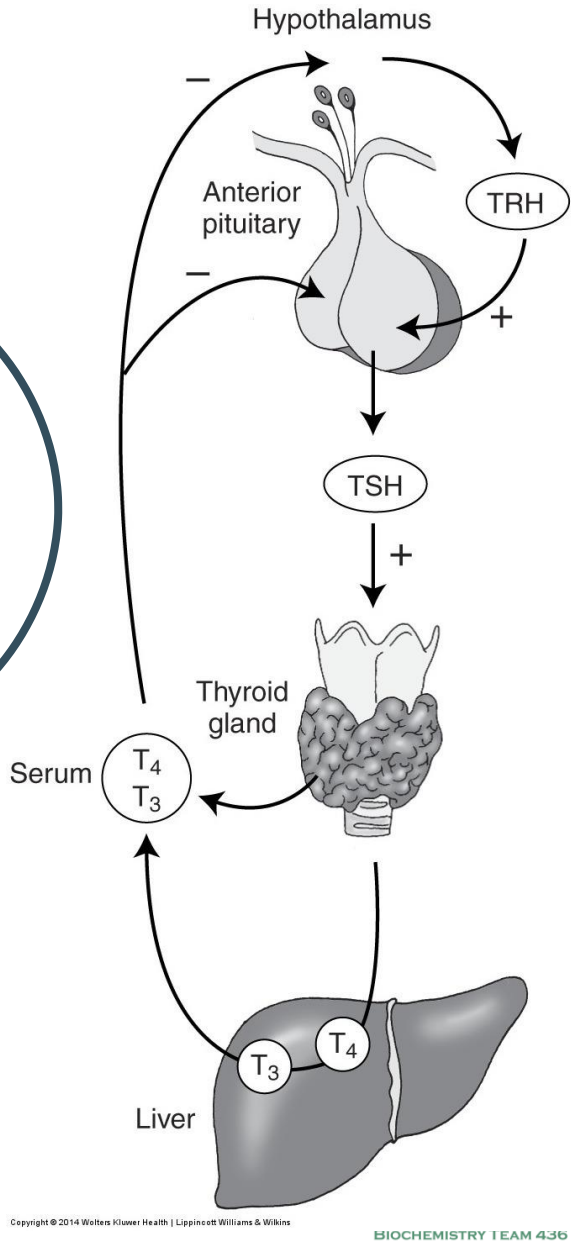
→ TRH **stimulates** the pituitary to produce thyroid stimulating hormone (TSH).

→ TSH stimulates the thyroid to produce T_3/T_4 until levels return to normal.

→ (when they become high) T_3/T_4 exert **negative** feedback control on the hypothalamus and pituitary.

→ Controlling the release of **Both** TRH and TSH.

→ Decrease the amount of Thyroid hormones and cold temp. both stimulate the hypothalamus to release TRH.



- High thyroid hormone levels: suppress TRH, TSH.
- Low thyroid hormone levels: stimulate TRH, TSH to produce more hormone.

Thyroid Function Tests:

TSH measurement:	Total T_4 or free T_4:	Total T_3 or free T_3:	Antibodies:
The most preferred one because its level and the level of T4 & T3 are affecting each other.	-	Not measured unless suspecting hyperthyroidism especially when there is no increase in T4	هاشميتو: انتيبوديز تثبط من عمل الهرمون المثبط عشانه ياكل كثير هاش براون
Assessment of thyroid function.	Assessment of thyroid function.	Useful for assessing hyperthyroidism in which rise in T_3 is independent of T_4 .	Diagnosis and monitoring of autoimmune thyroid disease:
Highly sensitive test (detects very low conc.).	Monitors thyroid treatment (both anti-thyroid and thyroid replacement treatment).	In some patients only T_3 rises (T_4 is normal): T_3 toxicosis.	Hashimoto's thyroiditis (antibodies against TSH receptors that suppress thyroid secretion). Other: Anti-thyroid peroxidase Ab & Anti-thyroglobulin Ab.
If there is small change in the level of T4&T3 (even within the normal range), It will lead to significant change in TSH level, but when TSH level change, it won't much affect in the T4&T3.	TSH may take up to 8 weeks to adjust to new level during treatment. During this time there will be possibility to hypothyroid very fast so you have to measure T4.	For earlier identification of thyrotoxicosis.	Graves' disease (antibodies against TSH receptors that stimulate thyroid secretion). انتي بوديز تثبط من عمل الهرمون المحفز فتدخله القبر (جريف)

Thyroid Function Tests:

We don’t measure the total T4 or T3 because total refers to both bounded and unbounded form of hormones.
The bounded form is bounded to proteins which their levels can be changed (EX: During pregnancy, TBG will increase) which will affect the accuracy of the test. (Total will be high while Free will be in the normal level)

Goitre, Hypo and Hyperthyroidism

Goitre (Enlarged thyroid gland) may be associated with:

- **Hypo**function
- **Hyper**function
- **Normal** thyroid hormone conc. (euthyroid)

Causes:

- Iodine, selenium deficiency — Most common cause
- Hashimoto's thyroiditis
- Graves' disease (hyperthyroidism)
- Congenital hypothyroidism / thyroid cancer

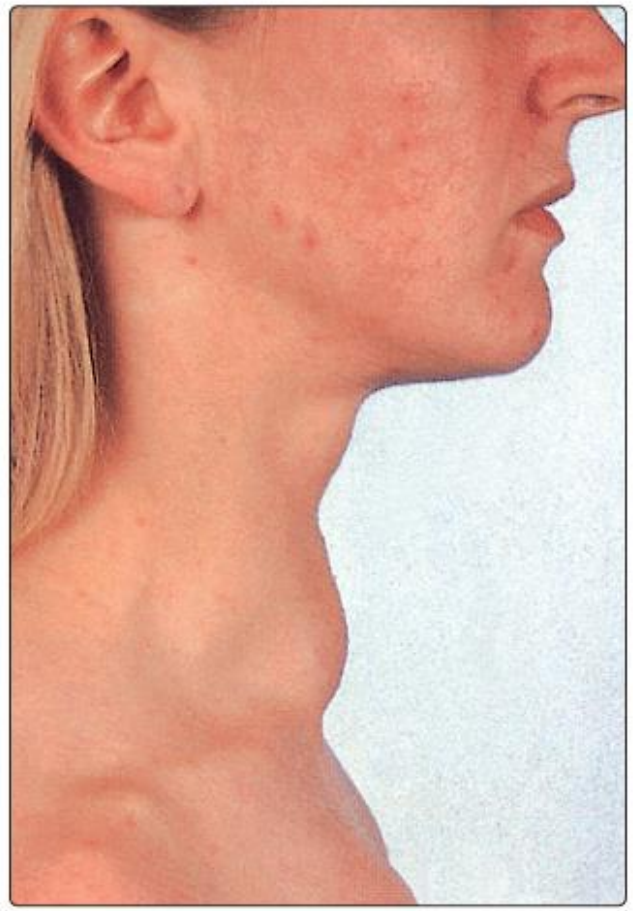


Fig 44.2 **A patient with a goitre.**

Iodine: required for the synthesis of thyroid hormones.
Selenium: co-factor for the synthesis. if selenium is deficient → deficiency of the thyroid hormone

Hypothyroidism

Deficiency of thyroid hormones		
Type	**Primary hypothyroidism:** • Failure of thyroid gland (**Elevated** TSH, **deficiency** of thyroid hormones)	**Secondary hypothyroidism:** • Failure of the **pituitary gland** to secrete TSH (rare) • Failure of the **hypothalamic-pituitary-thyroid axis**
Causes	**1-Hashimoto's thyroiditis.** **2-Radioiodine or surgical treatment of hyperthyroidism.** **3-Drug effects.** **4-TSH deficiency.** **5-Severe iodine deficiency.** **6- Congenital defects in thyroid synthesis / thyroid resistance.**	
Clinical features	**Tiredness / cold intolerance** Most common **/ weight gain / dry skin.**	
Treatment	**Replacement therapy** with levothyroxine (T_4).	

Non-Thyroidal illness

- In some diseases, the normal **regulation** of TSH, T_3 and T_4 secretion and metabolism is **disturbed.**
- Most of T_4 is converted to rT_3 (inactive).
- Causing thyroid hormone deficiency.
- **Secretion** of T_4 and T_3 is **decreased.**

Biochemical investigation of suspected Hypothyroidism

	1	2	3	4
TSH	**Elevated** ↑	**Elevated** ↑	**Within reference range**	**Low** ↓
FT4\T4	**Within or <u>low</u> normal**	**Within reference**	**Low** ↓	**Low** ↓
diagnosis	**Conformed hypo-thyroidism**	**Developing hypo-thyroidism**	**Non-thyroid illness** with the patient who critically ill ex. in ICU	**2ry or central hypo-thyroidism**
Further	Institute T4 Replacement	1-measure thyroid autoantibody titers. 2-Repeat analyses after 2-3 months	1- T3 test **if low** Repeat analyses when non-thyroid illness has resolved (Transist condition)	Check cortisol FSH,LH and prolactin

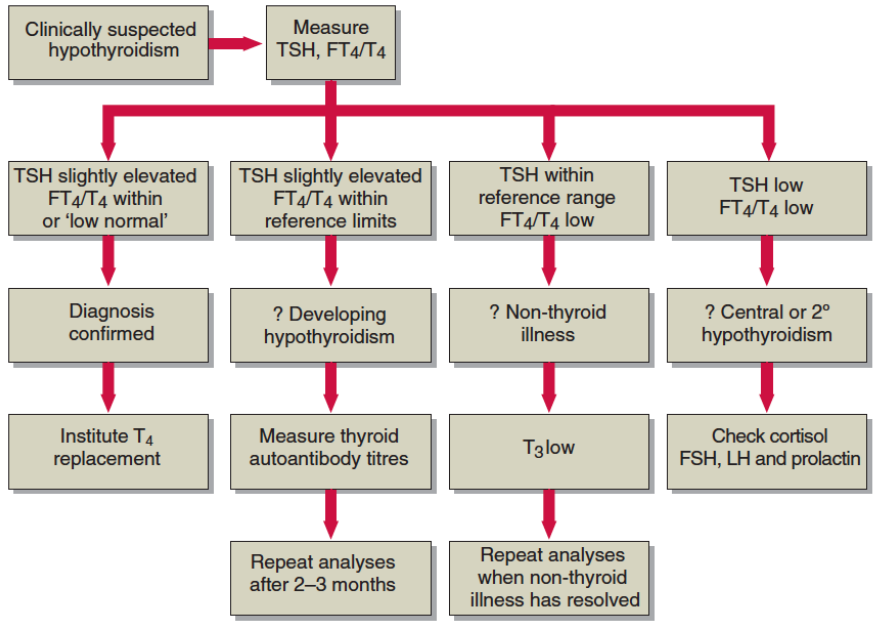


Fig 45.1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

You can't be sure because patient has symptoms of hypothyroidism, so he maybe developing it
At that moment, check for antibodies and if present repeat the test but don't start treating because T4 levels is normal.

Hyperthyroidism

- **Hyperstimulation** of thyroid gland by pituitary gland.
- **Hypersecretion** of thyroid hormones.
- Tissues are exposed to high levels of thyroid hormones (thyrotoxicosis).

- **Causes**:
  - Graves' disease.
  - Toxic multinodular goitre.
  - Thyroid adenoma.
  - Thyroiditis.
  - Excessive intake of iodine / iodine drugs.
  - Excessive intake of T_4 and T_3 .

Cause of Exophthalmos: the auto anti-bodies may attack some of orbital muscles of the eye which will cause inflammation and edema that will lead to Exophthalmos

Fig 46.3 **Lid retraction and exophthalmos in a patient with Graves' disease.**

Graves' disease (Most common)

- Most **common cause** of hyperthyroidism
- An **autoimmune** disease
- Due to **antibodies against** TSH receptors on thyroid gland
- The antibodies mimic the action of pituitary hormone **Causing** hypersecretion of thyroid hormone

Hyperthyroidism

Clinical features Opposite to Hypo-thyroidism	1. Weight loss with normal appetite. 2. Sweating / heat intolerance. 3. Fatigue. 4. Palpitation / agitation, tremor. Thyroid hormones affects sympathetic system greatly. 5. Angina, heart failure. Thyroid hormones affects Ca metabolism which affects heart muscle. 6. Diarrhea. or frequent bowel movements 7. Eyelid retraction and lid lag.
Diagnosis	• Suppressed / undetectable TSH level. • Raised thyroid hormones levels. • Confirms primary hyperthyroidism. Free T_4 and TSH are (not total T4) **first-line tests** for diagnosis of thyroid dysfunction.
Problems in diagnosis	• Total serum T_4 varies due to changes in binding protein levels. • High estrogens in pregnancy increase TBG synthesis. • Total T_4 will be high, free T_4 will be normal. Congenital TBG deficiency can also influence the results.
Treatment	• **Antithyroid drugs:** carbimazole, propylthiouracil. The antibodies act like the TSH exactly • **Radioiodine:** sodium ^{131}I inhibits T_4/T_3 synthesis. it's For the older patient but younger we won't exposer them to radiation so the line of treatment depends on age. • **Surgery:** thyroidectomy.

Biochemical investigation of suspected Hyperthyroidism

	1	2	3
TSH	**Undetectable**	**Detectable**	**Undetectable**
FT4\T4	**Elevated** ↑	**Elevated** ↑	**Within normal limits**
Further	**T3 Levels**	• **Repeat analyses** • **Immunoassay interference**	**T3 Levels**
Diagnosis	If T3 elevated **= Thyrotoxicosis conformed**	-	If T3 elevated **= T3 Thyrotoxicosis**

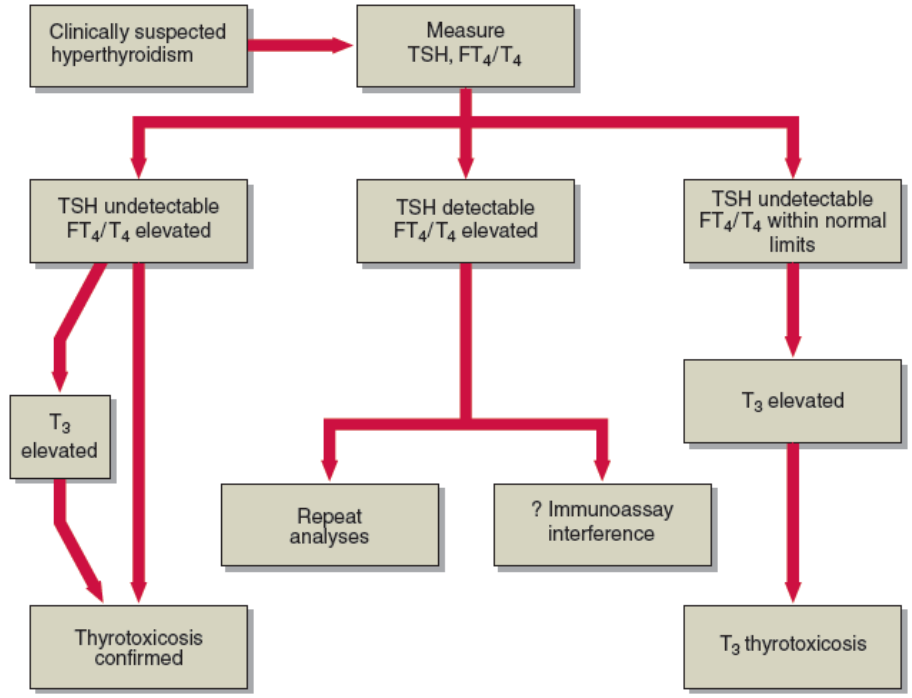


Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Thermogenesis (Heat production)

- Humans are **homeothermic** (keep constant body temp.).
- Tightly controlled **temperature homeostasis.**

Thermogenesis is important in regulation of the metabolism:
*it increases metabolism
*it increases metabolism by increasing cellular oxygen consumption.
Q/ by which process does the thyroid hormone increase cellular oxygen consumption?
A/ Respiratory chain (it increases the respiratory chain)

Thermogenesis is of two types	
Obligatory normal physical activities	Facultative
Heat production due to basal metabolic rate	On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.
-	Facultative thermogenesis in brown adipose tissue (mainly in children, has a lot of mitochondria so, it has ability to synthesize a lot of ATP) is stimulated by sympathetic nervous system

Recall : The amount of energy released when 1 NADH transfer it's electrons to the O2 it produce 52 kcal. And the amount needed to make 1 ATP is 22 kcal. (which means we have a lot of energy that's produced as extra).
- ATP synthesis and breakdown produce heat.
- ATP breakdown : is very efficient process and there is no much release of heat (No much Extra energy).
- ATP synthesis : is not very efficient process (produce a lot of Extra energy) and it releases more of energy as heat.

Brown fat: special form of fat that generates heat, it is rich in sympathetic nerve endings and vessels so, its metabolic activity and development is regulated by norepinephrine, it is normally located in the axillary, subscapular, and interscapular regions.

Thyroid Hormone and Thermogenesis

❖ **Two Concepts of Thyroid Thermogenesis**

1. Classical: peripheral

2. New : Central brown fat

Thyroid hormone (T_3)

It effect Body **tissue cells** (muscle, liver)

↓

Activates certain **Enzymes** by an unknown mechanism

which increase basic metabolic rate (EX: NA/K ATPase etc.)

It directly effects the **Hypothalamus**

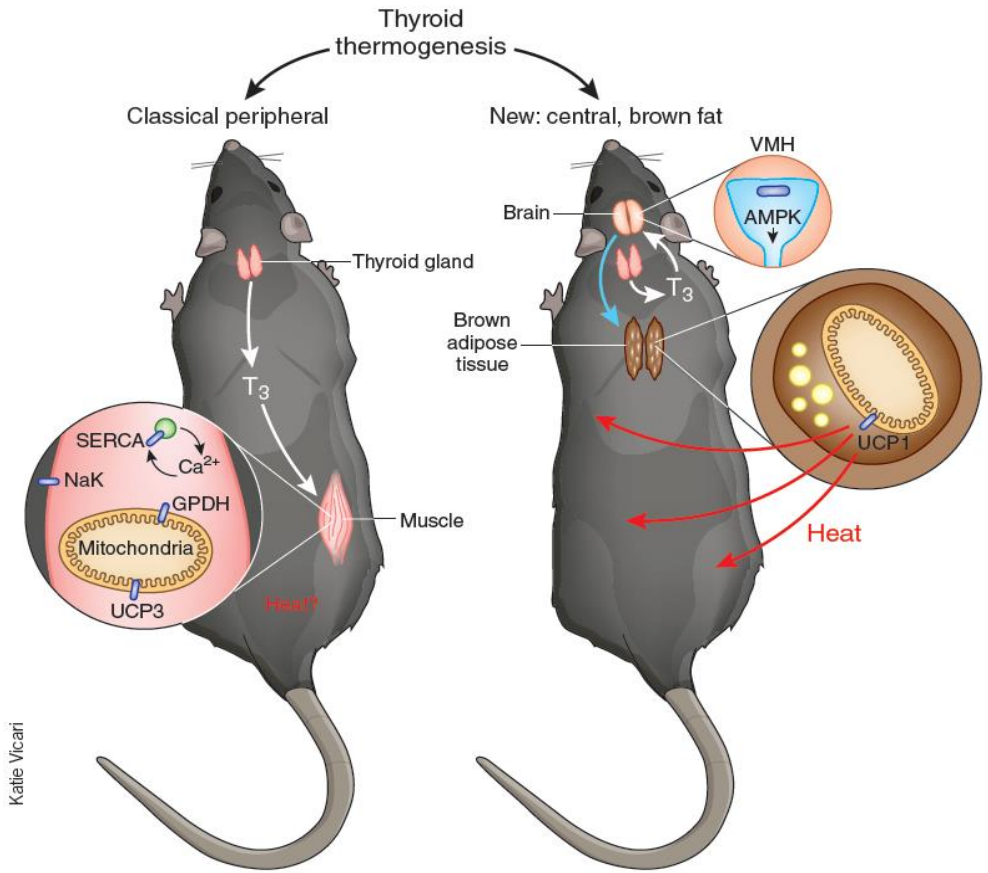
↓

Activates **brown adipose tissue**

↓

Increased body energy expenditure

THERMOGENESIS



Thyroid hormone will affects the hypothalamus where it will inactivate enzyme called AMPK , inactivation of this enzyme will stimulate signals that travel to brown adipose tissues and stimulate the synthesis of UCP1. (see the video in the next slide to know what is the role of UCP1 in thermogenesis).

Thyroid Hormone and Thermogenesis

Brown Fat Thermogenesis

2:55

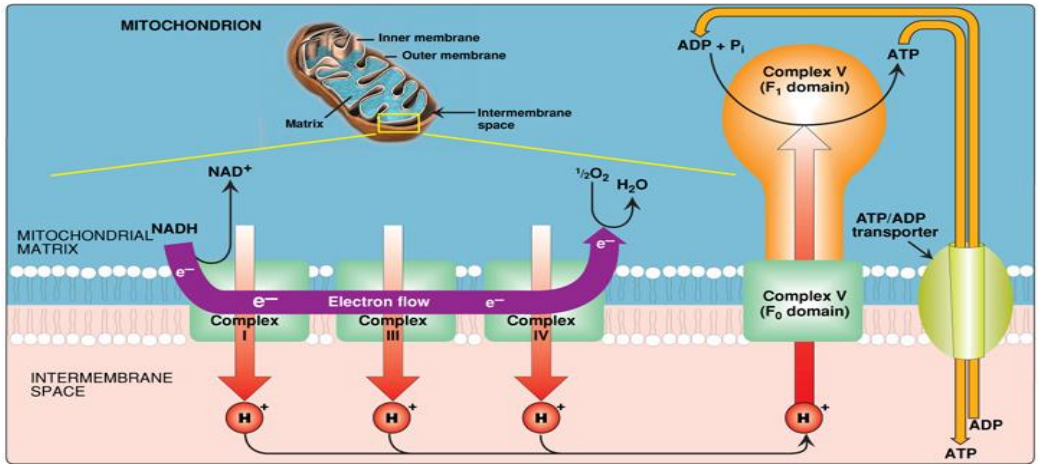
- Thyroid hormone plays essential roles in thermogenesis.
- It **upregulates** body temperature set by the brain.
- It acts centrally on the **hypothalamus** that controls brown adipose tissue for thermogenesis.

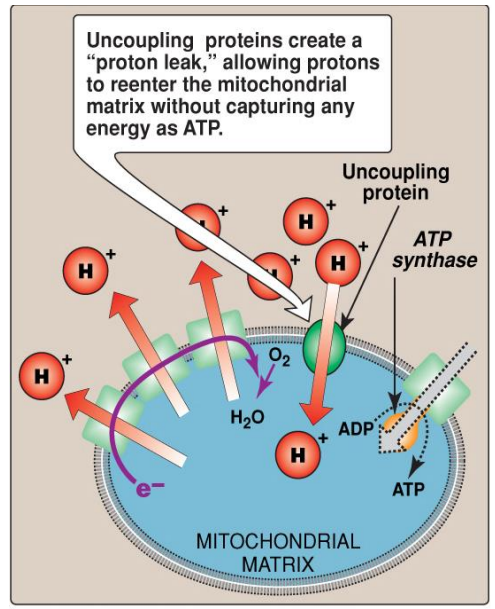
UCP forms leaks in mitochondrial inner membrane allowing protons to fall back into the matrix and energy will be released as heat (non-shivering thermogenesis).

- In respiratory chain, some protons reenter the mitochondrial matrix thru uncoupling proteins (UCPs) without ATP synthesis
- These protons are released as **heat**
- Thyroid hormone regulates mitochondrial UCPs

Examples:

- UCP**1** in brown adipose tissue
- UCP**3** in muscle, other tissues





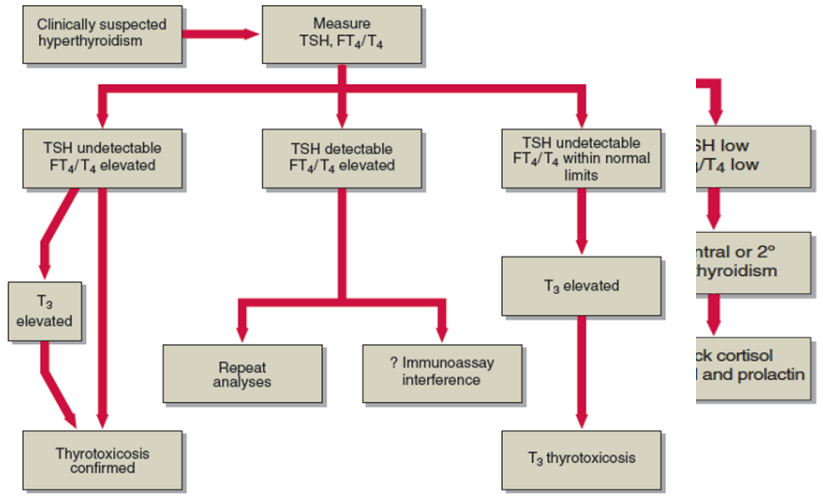


Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

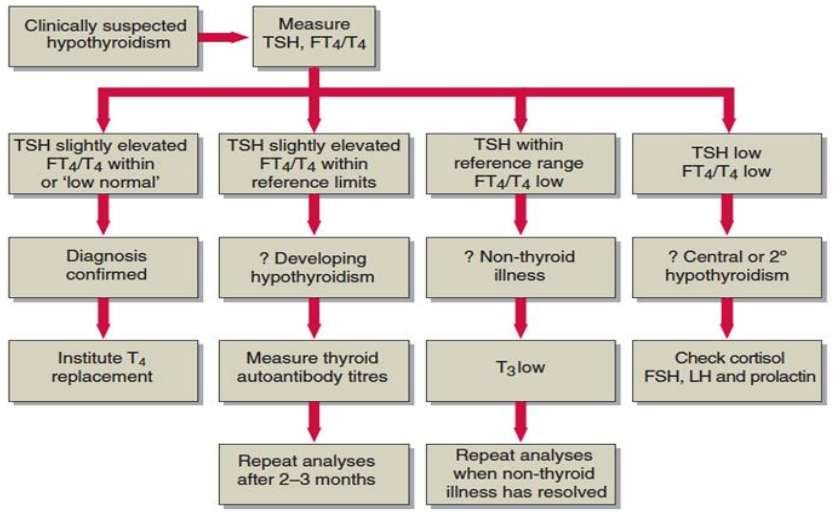
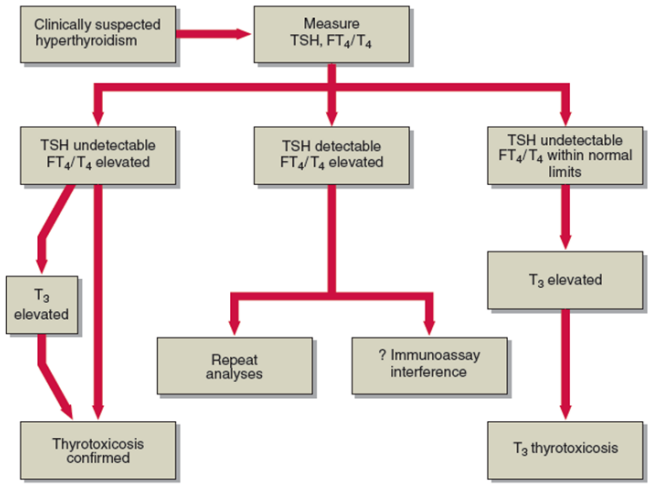
	Hypothyroidism	Hyperthyroidism
	↑TSH, ↓thyroid hormones ↓TSH, ↓thyroid hormones **Non-thyroidal illness**	**1-primary** ↓TSH, ↑T4 **2-Hyperstimulation** of thyroid gland by pituitary gland Tissues are exposed to high levels of thyroid hormones (thyrotoxicosis)
	Hashimoto's thyroiditis Surgical treatment of hyperthyroidism 3. Drug effects 4. TSH deficiency Severe iodine deficiency s in thyroid synthesis / thyroid resistance	1. `Graves' disease 2. Toxic multinodular goitre 3. Thyroid adenoma 4. Thyroiditis 5. Excessive intake of iodine / iodine drugs 6. Excessive intake of T4 and T3
Clinical features	Tiredness / cold intolerance / weight gain / dry skin	Palpitation & agitation, tremor & Heart intolerance & Weight gain
Lab diagnosis		
Treatment	**Replacement therapy** levothyroxine T4	1. **Antithyroid drugs:** carbimazole, propylthiouracil 2. **Radioiodine:** sodium 131I inhibits T4/T3 synthesis 3. **Surgery:** thyroidectomy

Fig 45.1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Summary

Thyroid hormones	T3&T4&rT3 " most active to least active"
Synthesis	tyroid gland
Transported in Blood	**1-bounded to :** TBP 70% Albumin 25% Pre-albumin 5% 2- free ''active form''
At peripheral tissue	de-iodinate T4 to T3 or rT3 by deiodinase enzymes
Function	1-maturation of all body tissues 2-thermogenesis 3-increase O2 concamtion &metabolic rate
Regulation	T3/T4exert negative feedback control on the hypothalamus and pituitary
Function test	**1-TSH :** thyroid function **2- Total T4 or free T4:** thyroid function&monitoring **3-Total T3 or free T3** :T3 Toxicosis & early detection thyrotoxicosis **4- Antibodies:**Hashimoto's thyroiditis & graves
Thermogenesis	Tightly controlled temperature homeostasis **1- obligatory :** heat production due to due to basal metabolic rate **2-Facultative :** On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle
Thyroid thermogenesis	Thyroid hormone regulates mitochondrial UCPs , These protons are released as heat **1-new ''central'' :** act on hypothalamus by activation of brown adipose tissue (UCP1) **2-classical ''pripheral '':** act on muscles and liver by activation of enzyme by unkown mechanism (UCP3)

QUIZ

Q1 : Which one of the following cases is associated with permanent brain damage?

A. Untreated congenital Hypothyroidism
B. Genetic Hypothyroidism in children
C. Hashimoto's thyroiditis
D. Goiter

Q2 : 78 year old patient known to have longstanding hypothyroidism came to your clinic one day, which of the following diseases do you expect him to have an increased risk of getting ?

A. Emphysema
B. Myocardial Infarction
C. Asthma
D. Irritable bowel syndrome

Q3 : Which one of the following is the most likely cause of hyperthyroidism ?

A. Thyroid adenoma
B. Graves' disease
C. Thyroiditis
D. Excessive intake of T_4 and T_3

Q4 : Which one of the following proteins is responsible for transportation of the largest amount of Thyroxine ?

A. Albumin
B. Selenium
C. Transthyretin
D. TBG

Q5 : Which one of the following is considered a first line test in TFT ?

A. TSH measurement
B. Total T4
C. Total T3
D. TRH measurement

Q6 : Which one of the following is the major cause of hypothyroidism?

A. Hashimoto's thyroiditis
B. Graves' disease
C. TSH deficiency
D. Severe iodine deficiency

QUIZ

Q7 : 9 year old boy came to your clinic with his mother. She says that she is worried about him because he is too hot when she touches his forehead and that he is much thinner than his fellow students at school. She also complains of his enlarged neck and how she has to tailor him a thobe with a wider collar.

A) List 3 diseases that may cause Hyperthyroidism.

Thyroiditis, Graves' disease, Toxic multinodular goiter, Thyroid adenoma, Excessive intake of iodine/ iodine drugs

B) List 3 other clinical features that are associated with hyperthyroidism.

1. Sweating
2. Fatigue
3. Palpitation
4. Diarrhea
5. Eyelid retraction

C) What is the possible treatment ? Explain why.

Anti-thyroidal drugs like: Carbimazole and propylthiouracil.

Because this patient is young.

D) Let's say this patient is 90 years old, Would the treatment be different ?

Yes, we would treat him with Radioiodine and we might consider subtotal thyroidectomy.

Suggestions and recommendations

1) A 2) B 3) B 4) D 5) A 6) A

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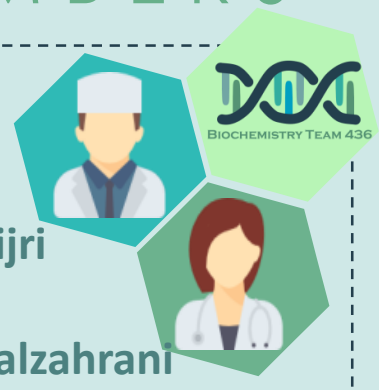
TEAM MEMBERS



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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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