جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Thyroid hormones and thermogenesis

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Endocrine block

MED437
KING SAUD UNIVERSITY

Objectives:

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

- Describe the types and biosynthesis, actions and 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

Types of Thyroid Hormones

- **Thyroxine T4**
- **Tri-iodothyronine T3**

Biosynthesis of Thyroid Hormones:

- Synthesized in the **Thyroid gland** by:
  - Iodination and coupling of two tyrosine molecules
  - Binding to thyroglobulin protein
- Thyroid gland mostly secretes T_4
- Peripheral tissues (liver, kidney, etc.) de-iodinate T_4 to T_3
- catalyzed by Deiodinase enzymes
- T_4 can be metabolized to rT_3 (inactive form)

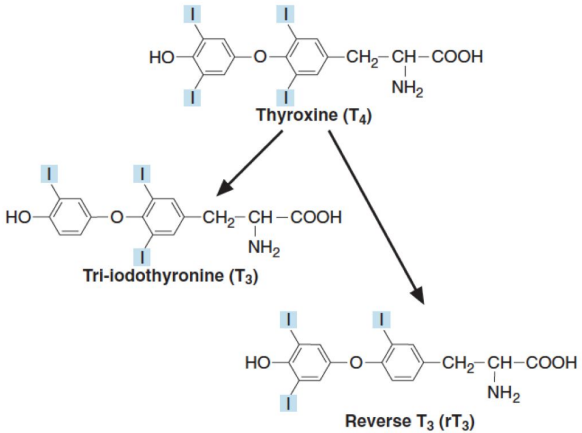


Fig 44.1 **The chemical structures of T_4, T_3 and rT_3.**

- T_3 is the most active form.
- Iodine binds to the Tyrosine molecules present on the Thyroglobulin with the help of **Thyroid Peroxidase** (TPO) enzyme
- rT_3 have an unknown function, but studies showed it have an protective function(regulation) which means whenever T_4 is raised in the body, it will get converted to rT_3 .

Biosynthesis of Thyroid Hormones

- T_3 is more biologically active form.
- Most of T_4 is transported in plasma as protein-bound:
  - Thyroxine Binding globulin (TBG)-bound (70%)
  - Albumin-bound (25%)
  - Transthyretin (pre-albumin)-bound (5%)
- The unbound (free) form of T_4 and T_3 are biologically active[1]

- Depending on the need of the body, the bound and unbound forms are reversible, so when the body needs more thyroid hormones more unbound form of thyroid hormones will be found in the blood, and vice versa.
- **1:** Bound form is inactive

Thyroid Hormone Actions

- 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.

*means it can affect the temperature by the production of heat.

Clinical evidence of the wide spectrum of thyroid hormone action:

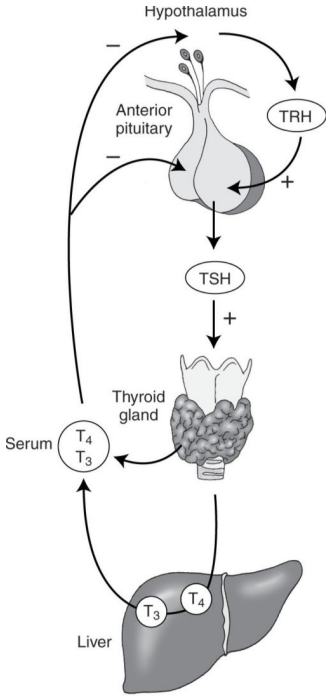
- Untreated congenital hypothyroidism → permanent brain damage[1]
- Hypothyroid children have:
  - Delayed skeletal maturation → short stature .
  - Delayed puberty.
- Hypothyroid patients have **high serum cholesterol** due to:
  - Down regulation of LDL receptors on liver cells.
  - Failure of sterol excretion via the gut[2]

1: If the Hypothyroidism not treated in the first 3 months after the child is born.
2: leading to impaired lipid profile

Regulation of Thyroid Hormone Secretion

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

1. The **hypothalamus** senses low levels of T3/T4 and **releases thyrotropin releasing hormone (TRH)**
2. **TRH** stimulates the **pituitary** to produce **thyroid stimulating hormone (TSH)**
3. **TSH** stimulates the thyroid to produce T3/T4 until levels return to **normal**
4. T3/T4 exert negative feedback control on the hypothalamus and pituitary
5. Controlling the release of both TRH and TSH



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

TSH levels can also be affected by the other hormones released from the hypothalamus and anterior pituitary, even if the person doesn't have a thyroid disorder

First line:TSH and free T4
1: It is more helpful to measure the free T4, because the bound hormone can be affected by the the binding protein, example in liver disease and pregnancy

Thyroid Function Tests

Dr osman said focus on thyroid function test.

Biochemistry437

TSH measurement:	Total T4 or free T4[1]:
1. Assessment of thyroid function 2. **Highly sensitive** test (detects very low conc.) Even Though it is not secreted from the thyroid, but it directly regulates thyroid function	1-Assessment of thyroid function 2-Monitors thyroid treatment (both anti--thyroid and thyroid replacement treatment) TSH may take up to 8 weeks to adjust to new level during treatment So during this time, we can monitor the treatment by T4
Total T3 or free T3	**Antibodies:**
Useful for assessing hyperthyroidism in which rise in T3 is independent of T4 T3 toxicosis: In some patients only T3 rises (T4 is normal) For earlier identification of thyrotoxicosis	1-Diagnosis and monitoring of autoimmune thyroid disease: • Hashimoto's thyroiditis (antibodies against TSH receptors that **suppress** thyroid secretion • Graves' disease (antibodies against TSH receptors that **stimulate** thyroid secretion) Others: IGg against TSH receptor or thyroid peroxidase enzyme "anti TPO"

Goitre, Hypo and Hyperthyroidism

Goitre: Enlarged thyroid gland[4]

Goitre may be **associated with**:

- Hypofunction
- Hyperfunction
- Normal thyroid hormone conc. (euthyroid)[1]

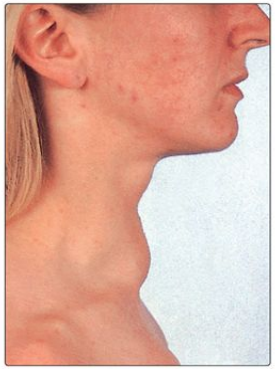


Fig 44.2 **A patient with a goitre.**

Causes of development of goiter:

Iodine, selenium deficiency[2] [3]	Hashimoto's thyroiditis	Graves' disease (hyperthyroidism)	Congenital hypothyroidism / thyroid cancer

1: Euthyroid means normal, for example if a patient had any thyroid illness and you put the patient on treatment and the thyroid hormone levels are maintained.
2: Iodine or selenium deficiency is the cause of goitre development in majority of the cases
3: Selenium is required for proper function of the peroxidase enzymes involved in synthesis of thyroid hormones. just like glutathione peroxidase enzyme which we took in GIT
4: Uninodular or multinodular or diffused, identified by radioactive iodine scans

Hypothyroidism

Hypothyroidism: Deficiency of thyroid hormones

Types	Primary hypothyroidism	Secondary hypothyroidism
	Failure of thyroid gland (the problem in the gland itself) **(Elevated TSH, deficiency of thyroid hormones)** (we don't have enough T3 & T4 so by feedback mechanism TSH will be elevated)	• Failure of the pituitary gland to secrete TSH (rare) • Failure of the hypothalamic-pituitary-thyroid axis
Causes	• Hashimoto's thyroiditis (majority of the cases) • Radioiodine or surgical treatment of hyperthyroidism (person had hyperthyroidism then underwent partial or complete surgery or given the radioactive iodine that destroys the cells, later on he could progress to hypothyroidism) • Drug effects (drugs against hyperthyroidism, prolonged treatment, high doses that is why it needs monitoring) • TSH deficiency (usually in hypothyroidism levels of TSH is high but if there is congenital deficiency of TSH or problem in pituitary its levels will be low, this is the only case of hypothyroidism where TSH is low) • Congenital defects in thyroid synthesis / thyroid resistance • Severe iodine deficiency	
Clinical features	Tiredness / cold intolerance / weight gain / dry skin	
Treatment	Replacement therapy with levothyroxine (T4) (hypothyroidism can be easily detected and treated with good outcome)	

Hypothyroidism

Non-thyroidal illness:

- In some diseases, the normal regulation of TSH, T_3 and T_4 secretion and metabolism is disturbed[1]
- Most of T_4 is converted to rT_3 (inactive) (reverse T3)[2]
- Causing thyroid hormone deficiency
- Secretion of T_4 and T_3 is decreased

1: When a person has chronic illness that is not related to the thyroid gland but it is affecting it ex:**infection**.
2: rT3 has no known role in the body, but it is proposed that it protect against thyrotoxicosis

Biochemical investigation of suspected Hypothyroidism

When clinically suspect hypothyroidism, first line of investigations is TSH & free T4

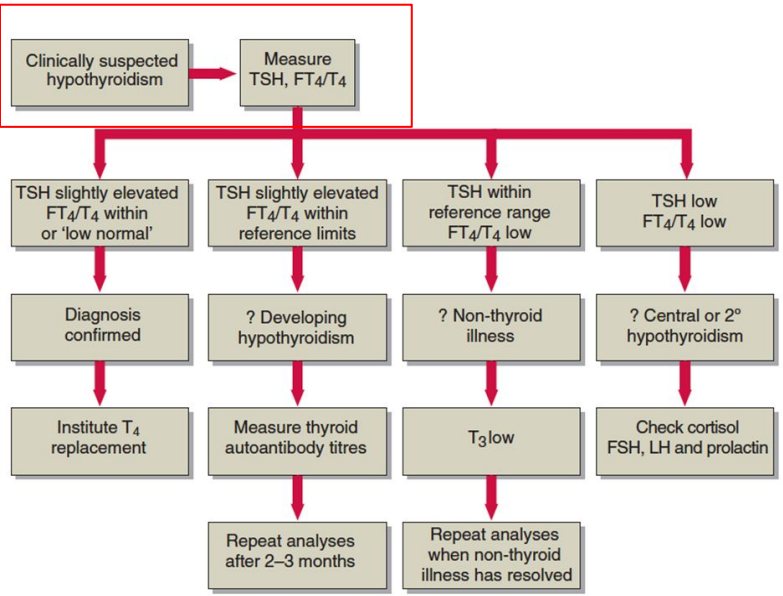


Fig 45.1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

Don't skip the table!

	1 (the typical picture)	2	3	4
TSH	**Elevated** This is the most important result	**Elevated**	**Within reference range**	**Low**
FT4 (free) \T4	**Within or low normal**	**Within reference limits**	**Low**	**Low**
diagnosis	**Confirmed hypothyroidism** (most of time in hypothyroid patients T4 levels are within normal range only TSH high)	**Developing hypothyroidism** (still in the process of developing hypothyroidism due to destruction)	**Non-thyroid illness** (temporary or transient condition when patient chronically ill or acute problem that lead to change in metabolism)	**2ry or central hypothyroidism** (due to a defect in the hypothalamus or the effect of other hormones)
Further	Institute T4 Replacement (treatment depending on symptoms)	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	Check cortisol FSH,LH and prolactin

Hyperthyroidism

- Hyperstimulation of thyroid gland by pituitary gland
- Hypersecretion of thyroid hormones
- Tissues are exposed to high levels of thyroid hormones (thyrotoxicosis) (hyperthyroidisim means high levels of T3 &T4 which in turn by feedback mechanism cause decrease in TSH)

Causes:

- Graves' disease
- Toxic multinodular goitre
- Thyroid adenoma (not in all cases only when adenoma is functional)
- Thyroiditis
- Excessive intake of iodine / iodine drugs
- Excessive intake of T_4 and T_3

Graves' disease

- 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 [agonists]
- Causing hypersecretion of thyroid hormone

Hyperthyroidism

Biochemistry437

Clinical features:

- Weight loss with normal appetite
- Sweating/ heat intolerance
- Fatigue
- Palpitation/ agitation, tremor
- Angina, heart failure
- Diarrhea
- Eyelid retraction and lid lag (Exophthalmos)
  Cause: the antibodies attack some of orbital muscles of the eye

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

Diagnosis

- Suppressed / undetectable TSH level.
- Raised thyroid hormones levels.
- Confirms primary hyperthyroidism.
- Free T_4 and TSH are first-line tests for diagnosis of thyroid dysfunction.

Problems in diagnosis

In pregnancy: ↑ estrogen → ↑ TBG → ↑ total T_4 but normal free T_4.

- 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 results.

Hyperthyroidism

Biochemistry437

Treatment:

- Antithyroid drugs: carbimazole, propylthiouracil. Suppress synthesis of thyroid hormone.
- Radioiodine: sodium ^{131}I (iodine), inhibits T_4/T_3 synthesis. And kills thyroid cells
- Surgery: thyroidectomy. Sometimes patients may develop hypothyroidism, and we give them supplement therapy.

	1	2	3
TSH	Undetectable	Detectable (not effected)	Undetectable
FT4\T4	Elevated	Elevated	Within normal limits
Further	T3 Levels (mostly will be elevated)	• Repeat analyses • Immunoassay interference	T3 Levels (must measure)
Diagnosis	Thyrotoxicosis conformed	-	If T3 elevated = T3 Thyrotoxicosis

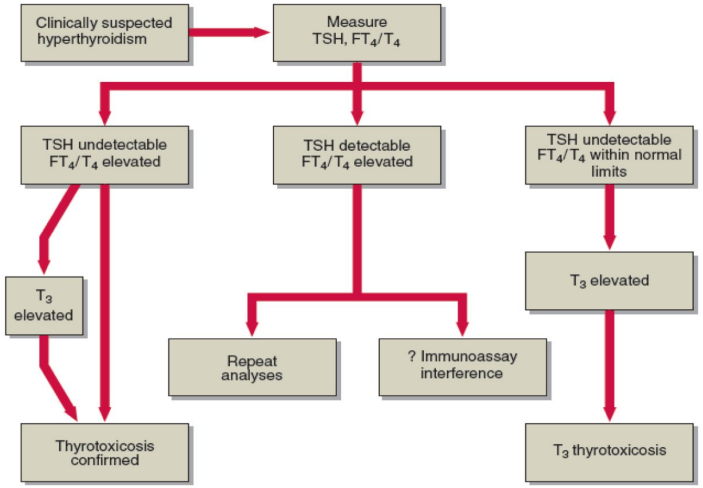


Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

Thermogenesis (Heat production)

Biochemistry437

- Humans are homeothermic (keep constant body temp.)
- Tightly controlled temperature homeostasis.
- Thermogenesis is of two types:

1- **Obligatory**[1] **:** Heat production due to basal metabolic rate.

2- **Facultative**[2]**:** on-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.

- Facultative thermogenesis in brown adipose tissue is stimulated by sympathetic nervous system.[3]

IMPORTANT !
Where does the heat produced?
From the ETC , there're channels called UCPs "uncoupling protiens"through which some of the protons are released as heat
(NO ATP GENERATION)

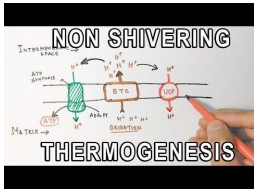
Thyroid Hormone & Thermogenesis

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

1: no activities just the basic physiological functions.
2: like in shivering , exercising.
3: In neonates the brown adipose tissue produce heat that is non shivering thermogenesis to protect them from cold.

Thyroid Thermogenesis

2 concepts



Amazing video

Biochemistry437

Thyroid hormone (T3)

Classical, peripheral

Affects body tissue cells (muscle, liver)[1]

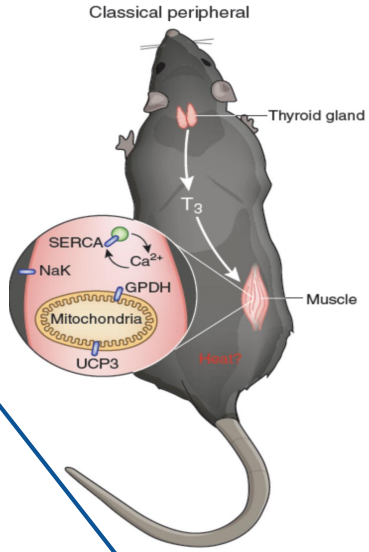
Activates certain enzymes by unknown mechanism

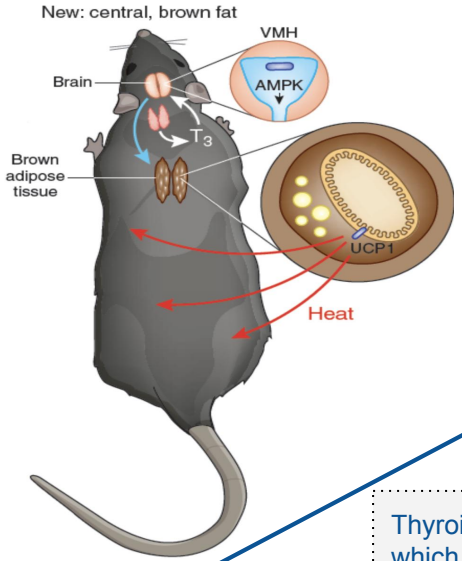
New: central brown fat

Hypothalamus

Activates brown adipose tissue

Increased body energy





THERMOGENESIS

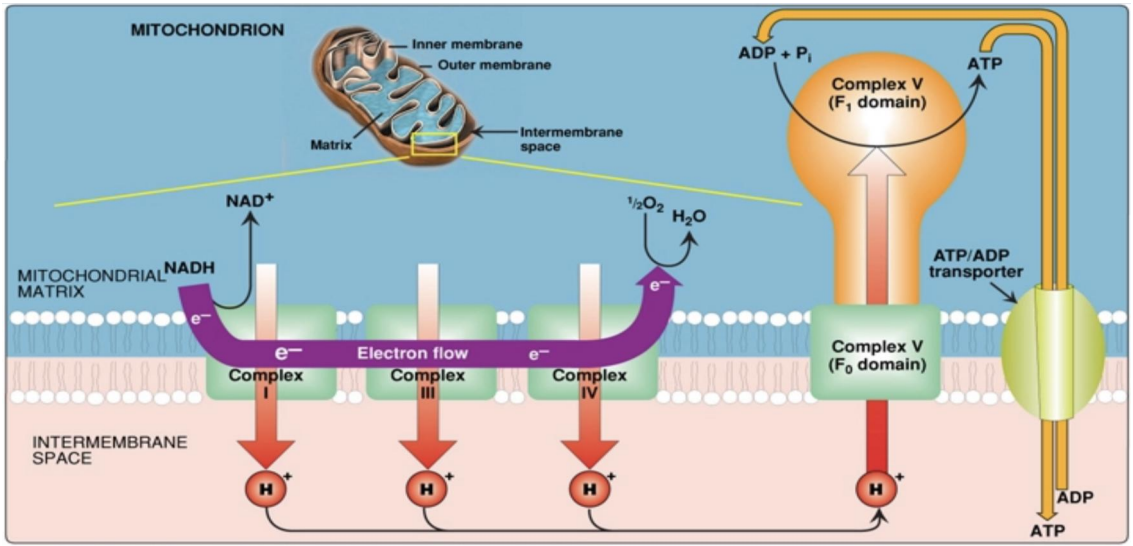
Which increase the metabolic rate by increasing: GPDH enzyme, increasing amount of UCP3, and activate the NA/K+ pump

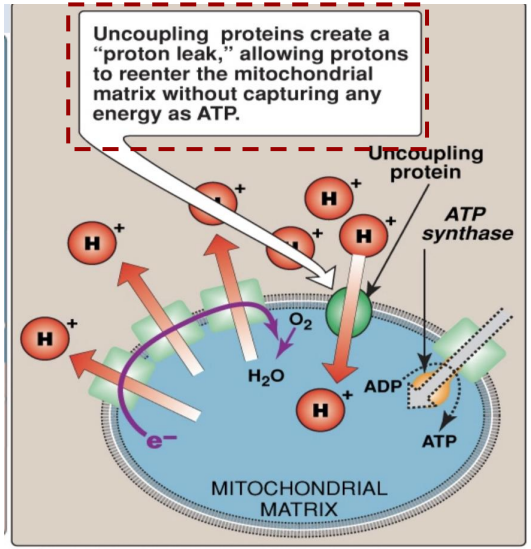
1.These are the tissues where the major metabolic activities happen

Thyroid hormone will affects the brain, which inactivates the enzyme AMPK “AMP kinase”, inactivation of this enzyme will activate brown adipose tissue by: activating UCP1, activating the sympathetic system.

Thyroid Thermogenesis

- In respiratory chain, some protons re-enter the mitochondrial matrix thru uncoupling proteins (UCPs) without ATP synthesis. These protons are released as heat.
- Thyroid hormone regulates mitochondrial UCPs. Examples : **UCP1** in brown adipose tissue , **UCP3** in muscle, other tissues





Summary

Types of thyroid hormones: **Thyroxine (T4), Tri-iodothyronine (T3) & Reverse T3 (rR3)**
• T3 is the more biologically active form
• Most of T4 is transported in plasma bound to Thyroxin Binding globulin.
• Thyroid Hormone essential for normal maturation and metabolism of all body tissues
• Regulation of Thyroid Hormone Secretion by thyrotropin releasing hormone (TRH) and Thyroid stimulating hormone(TSH)

Thyroid Function Tests (TFT):
• **TSH measurement**:
Indicates thyroid status and first-line test
• **Total T4 or free T4**:
Indicates thyroid status and Monitors thyroid treatment
• **Total T3 or free T3**:
T3 toxicosis and For earlier identification of thyrotoxicosis
• **Antibodies**:
Diagnosis and monitoring of autoimmune thyroid disease (Hashimoto's thyroiditis) Diagnosis of Grave's disease.

• **Goitre** :Enlarged thyroid gland
• **Hypothyroidism** Diagnosis Elevated TSH level confirms hypothyroidism
• **Hyperthyroidism** Diagnosis Suppressed TSH level, Raised thyroid hormone level, Confirms primary hyperthyroidism
• **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)

MCQs:

1. The Thyroid gland mostly secretes which one of the following?
A) T3
B) T4
C) T1
D) T2

2. Deiodination process is catalyzed by
A) hydrolase enzymes
B) deiodinase enzymes
C) oxidase enzymes
D) reductase enzymes

3.which form of Thyroid Hormones is more active?
A) Free T4
B) Free T3
C) T4-albumin bound
D) T4-(pre-albumin) bound

4.High thyroid hormone levels
A) suppress only TRH
B) suppress only TSH
C) suppress both TRH and TSH
D) do nothing regarding the regulation of Thyroid synthesis

5.which on of the following is not correct about Graves' disease?
A) Most common cause of hyperthyroidism
B) An autoimmune disease
C) The antibodies mimic the action of pituitary hormone
D) Due to antibodies against TRH receptors on thyroid gland

1- B
2- B
3- B
4- C
5- D

Biochemistry437

Girls team

- لمياء القويز
- غادة الحيدري
- لجين عبدالله
- نورة بن حسن
- روان المشعل
- شهد الجبرين
- اروى الجهني
- رزان الزهراني

Boys team

Team leaders

- رهام الحلبي
- معاذ الحمود

@biochemistry437

teambiochem437@gmail.com