SAWA UNIVERSITY

Clinical Endocrinology

Thyroid gland

Sawa University

College of health and medical techniques

Department of Medical Laboratories

جامعـــــة ســـــاوة الاهلية

كليـــة التقنيـــات الصحيـة والطبيـة

قسم تقنيات المختبرات الطبية

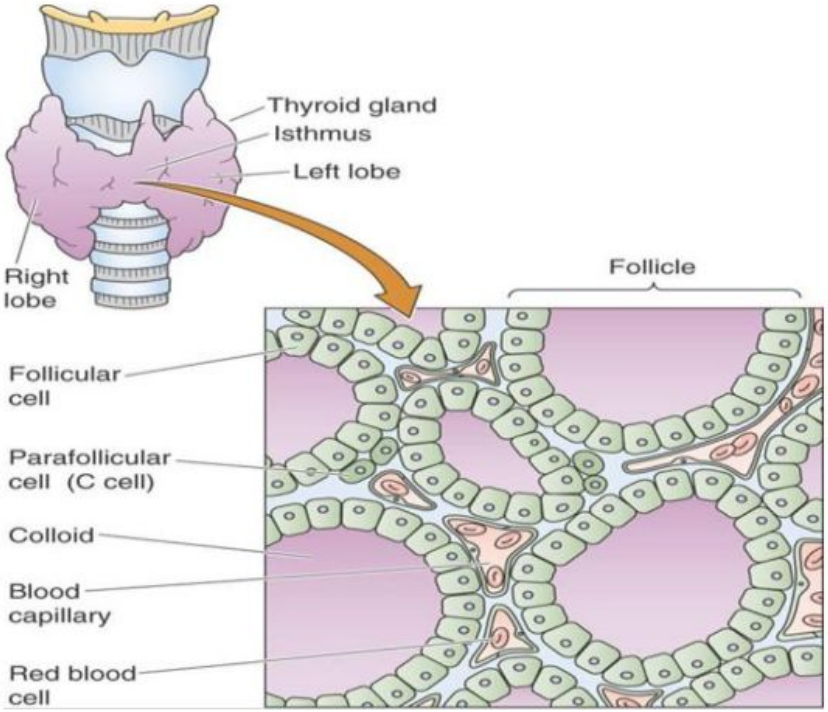
الجانب النظري محاضرة رقم 7,8

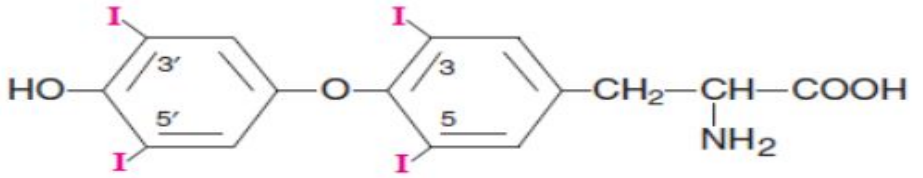
Theoretical Lecture No. 7,8

.Third . Stage المرحلـــــــــــة الثالـثة

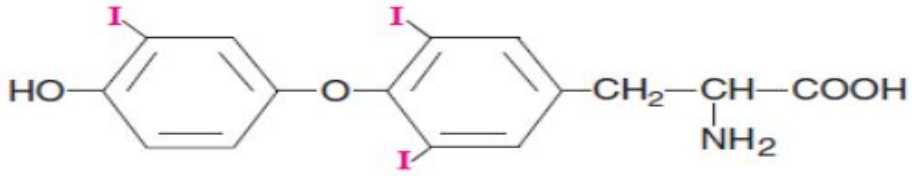
تدريسي المادة : م.م عـقيـل محمد رسـول

Thyroid gland (**weighs** about **30 g in adults**) is **located** **on either side of the trachea below the larynx**. **It produces**, **Thyroxine (T4), Tri-iodo thyronine (T3) and 'Reverse' T3** **by Follicular cells** which *regulate the metabolic rate of the body*. Thyroid gland also **secretes calcitonin by** **Parafollicular C-cells** a hormone concerned **with calcium homeostasis.**

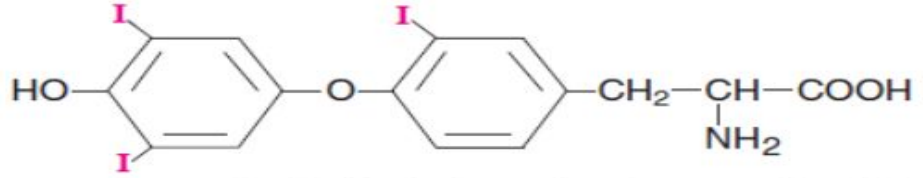




3, 5, 3′, 5′-Tetraiodothyronine (thyroxine, T_4)



3,5,3′-Triiodothyronine (T_3)

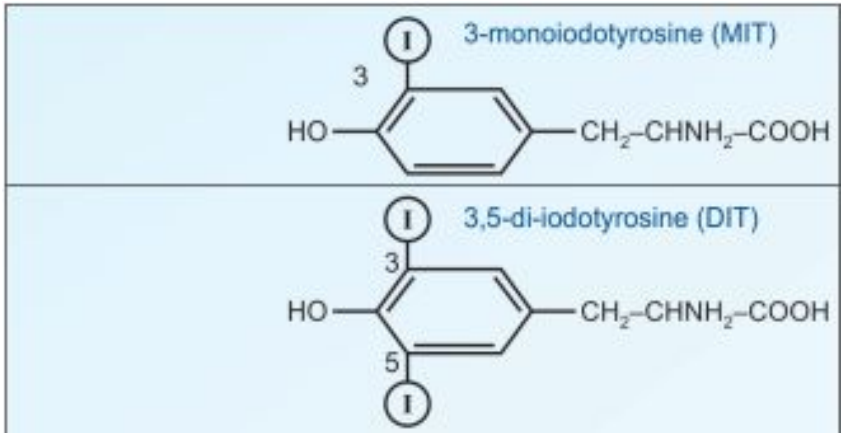


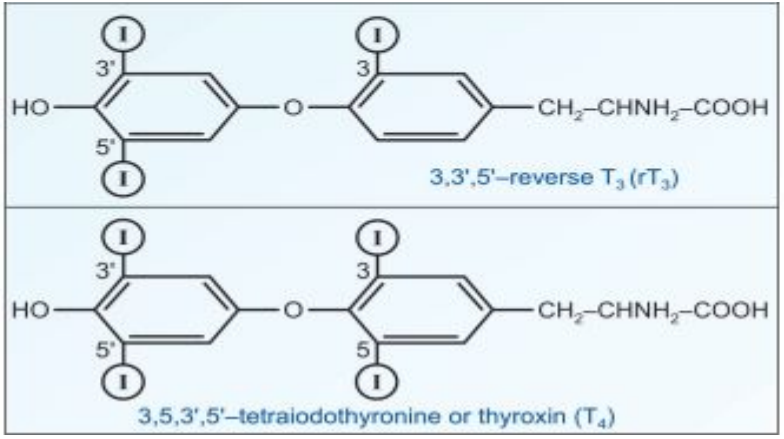
3, 3′, 5′-Triiodothyronine (reverse T_3, rT_3)

Biosynthesis Of Thyroid Hormones

Two raw materials (substrates) required by thyroid gland to synthesize the thyroid hormones are: **A. Thyroglobulin** **B. Iodine**

A. Thyroglobulin and synthesis of T3 and T4: Thyroglobulin is **a glycoprotein** and **precursor** for the **synthesis of T3 and T4**. Thyroglobulin contains about **140 tyrosine residues** which *can serve as substrates for iodine* for the *formation of thyroid hormones*. Tyrosine (of thyroglobulin) is first **iodinated** at **position 3** to form **monoiodotyrosine (MIT)** and then at **position 5 to form diiodotyrosine (DIT). Two molecules of DIT couple to form thyroxine (T4). One molecule of MIT, when coupled with one molecule of DIT, triiodothyronine (T3) is produced**





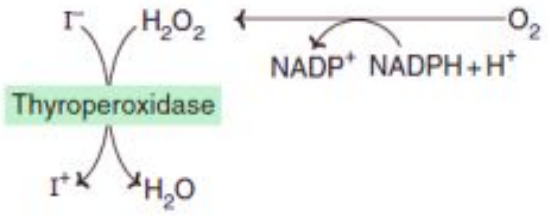
B. Iodine

Uptake of iodide: The uptake of iodide by the thyroid gland occurs against a concentration gradient (about 20: 1). It is an **energy requiring process** and is linked to the ATPase dependent Na+-K+ pump.

Iodide uptake is primarily **controlled by TSH**.

Antithyroid agents such as **thiocyanate and perchlorate inhibit iodide transport**.

Formation of active iodine: The **conversion of iodide (I–)** to **active iodine (I+)** is an **essential step** for its incorporation into thyroid hormones. **Thyroid is the only tissue that can oxidize I– to a higher valence state I+.** This reaction **requires H2O2** and **is catalyzed by the enzyme thyroperoxidase**. ***An NADPH*** *dependent system supplies H2O2*



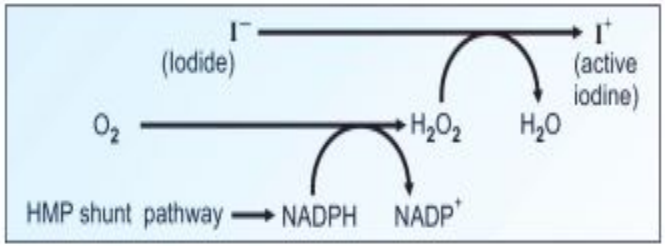


Fig. 53.2: Step 2 of thyroxine synthesis

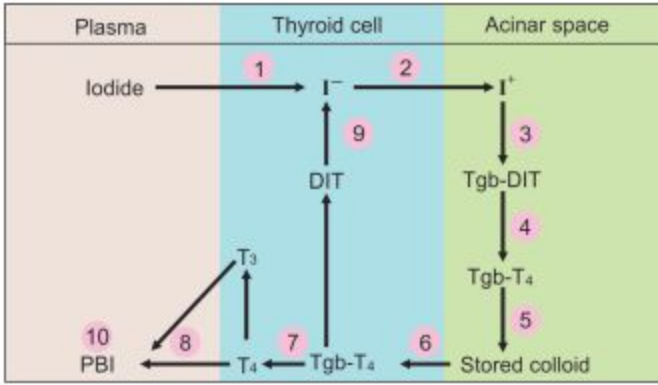
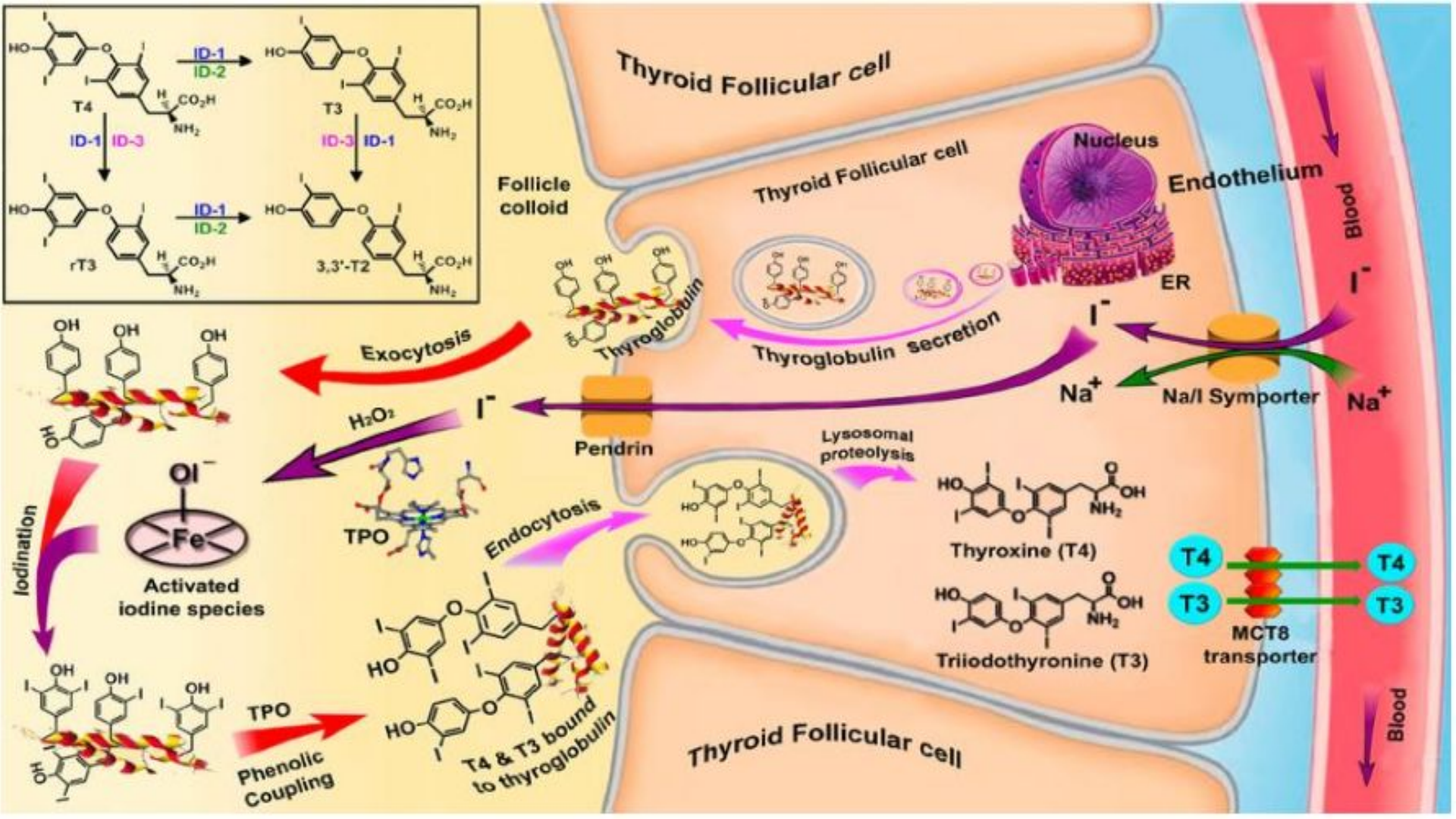


Fig. 53.1: Metabolism of thyroid hormones

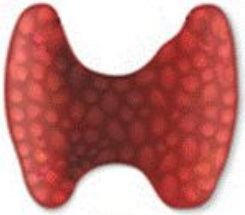
Storage and release of thyroid hormones: **Thyroglobulin containing T4 and T3 can be stored** for **several months in the thyroid gland**. It is estimated that the **stored thyroid** hormones can meet **the body requirement for 1-3 months**.
Thyroglobulin is digested by lysosomal proteolytic enzymes in the thyroid gland. The **free** hormones **thyroxine (90%) and triiodothyronine (10%) is released** into the blood, a process **stimulated by TSH**.
MIT and DIT produced in the thyroid gland **undergo deiodination** by the **enzyme deiodinase** and the **iodine thus liberated can be reutilized**.

Transport of T4 and T3: Two specific binding proteins**—thyroxine binding globulin (TBG) and thyroxine binding prealbumin (TBPA)—**are **responsible for the transport of thyroid hormones.**
Both **T4 and T3 are more predominantly bound to TBG**. A small fraction of free hormones is biologically active. **T4 has a half-life of 4-7 days while T3 has about one day.**


T4
T3
rT3
3,3'-T2
ID-1
ID-2
ID-3
Thyroid Follicular cell
Follicle colloid
Nucleus
Endothelium
Blood
ER
Thyroglobulin
Thyroglobulin secretion
Exocytosis
H_2O_2
I^-
Na^+
Na/I Symporter
Pendrin
Lysosomal proteolysis
Endocytosis
TPO
OI^-
Fe
Activated iodine species
Iodination
Thyroxine (T4)
Triiodothyronine (T3)
MCT8 transporter
T4 & T3 bound to thyroglobulin
Phenolic Coupling

للفهم والاطلاع

Thyroid Gland



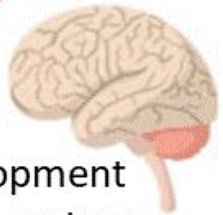
T3

T4

Calcitonin

Heart function

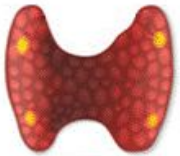
Digestion



Brain development and nervous system

Bone health

Muscle contractions



Parathyroid hormone production

Bone health

Kidney clearance rate

Biochemical functions of thyroid hormones

Triiodothyronine (T3) is about **four times more active** in its biological functions **than thyroxine (T4).** The following are **the biochemical functions** attributed to thyroid hormones (T3 and T4).

1. **Influence on the metabolic rate**: Thyroid hormones **stimulate** the metabolic activities and **increases the oxygen consumption** in most of the tissues of the body (**exception—brain, lungs, testes and retina).**

Na+-K+ ATP pump: This is an **energy dependent** process which **consumes a major** share of **cellular ATP**.

Na+-K+ ATPase activity is directly **correlated to thyroid hormones** and this, in turn, **with ATP utilization**. **Obesity** in some individuals is attributed to a **decreased energy utilization and heat production** *due to diminished Na+-K+ ATPase activity*.

2. Effect on protein synthesis: Thyroid hormones **act like steroid hormones** in promoting protein synthesis by acting at the transcriptional level (**activate DNA to produce RNA**). **Thyroid hormones**, thus, function as **anabolic hormones** and **cause positive nitrogen balance and promote growth and development.**

3. Influence on carbohydrate metabolism: Thyroid hormones **promote intestinal** absorption of glucose and its utilization. These hormones **increase gluconeogenesis and glycogenolysis**, with an overall effect of **enhancing blood glucose level** (**hyperglycemia**).

4. Effect on lipid metabolism: **Lipid turnover and utilization are stimulated by thyroid hormones. Hypothyroidism** is **associated with elevated plasma cholesterol** levels which **can be reversed by** thyroid hormone administration.

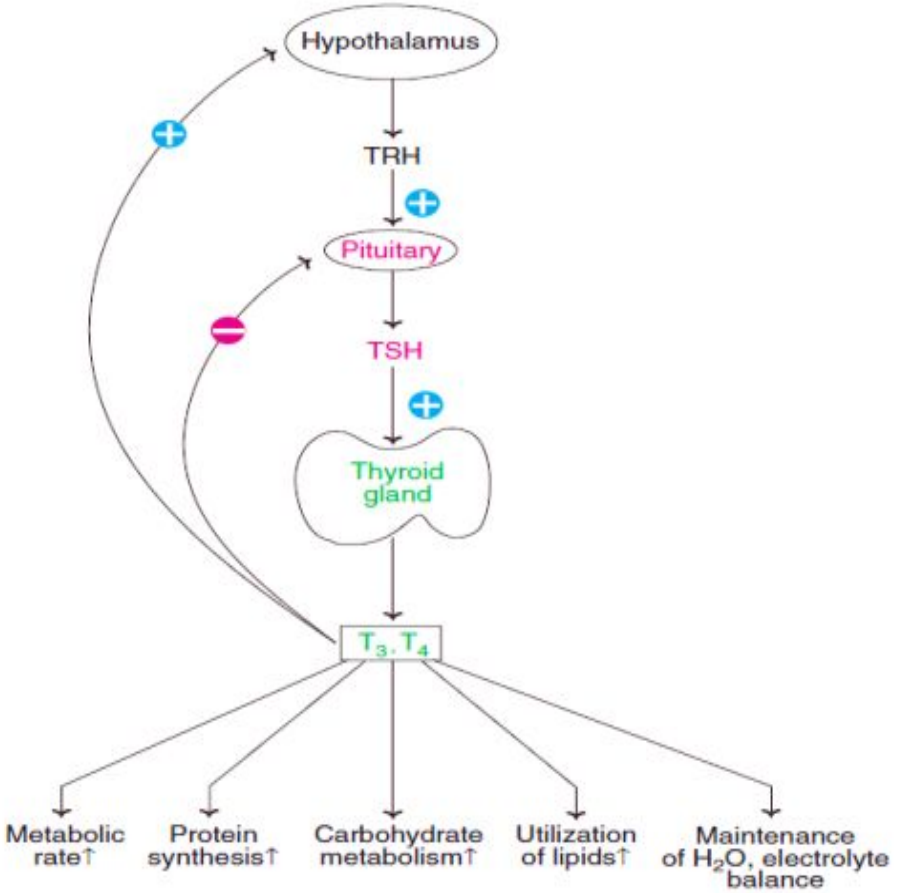
Regulation of T3 and T4 synthesis

The synthesis of thyroid hormones is **controlled by feedback regulation**. **T3 appears** to **be more actively involved than T4** in the regulation process. The production of **(TSH) by pituitary**, and (**TRH) by hypothalamus** are **inhibited by T3 and, to a lesser degree, by T4**.

The **increased synthesis of TSH and TRH occurs** in **response to decreased circulatory levels of T3 and T4**. As already discussed, the body has *sufficient stores of hormones to last for several weeks*. Hence it ***takes some months to observe thyroid functional deficiency***

Metabolic fate of T3 and T4

Thyroid hormones **undergo deiodination** in the **peripheral tissues**. The **iodine liberated may be reutilized by the thyroid**. **T3 and T4** may get conjugated with glucuronic acid or sulfate in the liver and excreted through bile. **Thyroid hormones** are also subjected to **deamination to** produce tetraiodothyroacetic acid (from T4) **and** triiodothyroacetic acid (from T3) which may then **undergo conjugation and excretion.**



Abnormalities of thyroid function

Among the endocrine glands, thyroid is the most susceptible for hypo- or hyperfunction. Three abnormalities associated with thyroid functions are known.

1) **Goiter**: Any **abnormal increase in the size** of the thyroid gland is **known as goiter.** Enlargement of thyroid gland is mostly to compensate the decreased synthesis of thyroid hormones and is **associated with elevated TSH**. **Goiter is primarily** *due to a failure in the autoregulation of T3 and T4 synthesis*. This may be **caused by deficiency or excess of iodide.**

2) Goitrogenic substances (goitrogens): These are the **substances that interfere with the production of thyroid hormones**. These include thiocyanates, nitrates and perchlorates and the drugs such as thiourea, thiouracil, thiocarbamide etc. Certain *plant foods—cabbage, cauliflower and turnip—contain goitrogenic factors (mostly thiocyanates).*

3) Simple endemic goiter: This is **due to iodine deficiency in the diet**. *It is mostly found in the geographical regions away from sea coast where the water and soil are* **low in iodine content**. **Consumption of iodized salt** is advocated **to overcome** the problem of endemic goiter. In certain cases, ***administration of thyroid hormone is also employed.***

Hyperthyroidism: This is also known as **thyrotoxicosis** and is associated with overproduction of thyroid hormones. Hyperthyroidism is characterized by increased metabolic rate (higher BMR) nervousness, irritability, anxiety, rapid heart rate, loss of weight despite increased appetite, weakness, diarrhea, sweating, sensitivity to heat and often protrusion of eyeballs (exophthalmos).

-Hyperthyroidism is **caused by** Grave's disease (particularly in the **developed countries**) or due to increased intake of thyroid hormones. Grave's disease is due **to elevated thyroid stimulating IgG** also known as **long-acting thyroid stimulator (LATS**) which **activates TSH** and, thereby, **increases thyroid hormonal production.**

-**Thyrotoxicosis** is diagnosed by *scanning and/or estimation of T3, T4 (both elevated) and TSH (decreased)* in plasma. The **treatment** includes administration of **antithyroid drugs**. In severe cases, **thyroid gland is surgically removed.**

Hypothyroidism: This is **due to** an impairment in the function of thyroid gland that often **causes decreased circulatory levels of T3 and T4**. Disorders of pituitary or hypothalamus also contribute to hypothyroidism. Women are more susceptible than men.

-Hypothyroidism is **characterized by reduced BMR**, slow heart rate, weight gain, sluggish behavior, constipation, sensitivity to cold, dry skin etc. ***Hypothyroidism in children*** *is associated with physical and mental retardation, collectively known as* ***cretinism*****.** -Early diagnosis and proper treatment are essential. **Hypothyroidism** in adult **causes myxoedema**, **characterized by** bagginess under the eyes, puffiness of face, slowness in physical and mental activities. Thyroid hormonal administration is employed to treat hypothyroidism.

Questions :

1. **How do thyroid hormones primarily influence metabolism?**
2. **What is the effect of hypothyroidism on cholesterol levels?**
3. **Which hormone primarily regulates the synthesis of TSH?**

Learning Resources for Hormone Mechanisms

Here are excellent sources to deepen your understanding of this topic:

Medical Textbooks:

"Harper's Illustrated Biochemistry" (Chapter on Hormones & Signal Transduction): Provides a detailed, yet clear, biochemical perspective on second messenger systems.

"Guyton and Hall Textbook of Medical Physiology" (Chapter 74: Introduction to Endocrinology): Excellent for understanding the physiological principles of hormone-receptor interactions and signaling.

"Greenspan's Basic & Clinical Endocrinology": A comprehensive resource that links basic mechanisms to clinical practice.

YouTube Channels:

Armando Hasudungan: His detailed drawings are fantastic for visualizing signal transduction pathways.

Dr. Najeeb Lectures: Provides extremely detailed lectures on the entire process.