



EGYPTIAN ACADEMIC JOURNAL OF
BIOLOGICAL SCIENCES
ZOOLOGY

B

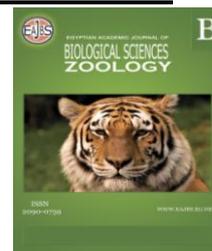


ISSN
2090-0759

WWW.EAJBS.EG.NET

Vol. 14 No. 1 (2022)

www.eajbs.eg.net



Thyroid Hormone Concentration and Receptor

Nagham Hasan Ali¹ and Amir A. Majeed²

1. College of Dentistry, Tikrit University

2. Dijalah University College/College of Dentistry

E.mail*: Naghaas@tu.edu.iq

REVIEW INFO

Review History

Received:29/2/2022

Accepted:14/4/2022

Available:17/4/2022

Keywords:

Thyroid gland, hormone, alpha receptors, beta receptors, nuclear receptors.

ABSTRACT

Hormones are hormones secreted by the thyroid gland and their primary function is to regulate the speed of metabolism in many tissues. The thyroid gland releases its hormones into the bloodstream in response to a regulating hormone released by the pituitary gland called thyroid-stimulating hormone. It is the only organ in the body that has the ability to synthesize iodine in large quantities for use in the synthesis of thyroid hormones. It consists of two lobes, joined together by the isthmus, located above the windpipe, just below the cartilage, which is the marker for its location. The weight of the thyroid glands in humans ranges from 15-to 20 grams and the blood supply changes depending on the functioning of the gland. There are lymphatic vessels, but their function in relation to endocrine function is uncertain.

INTRODUCTION

The thyroid gland is a small gland, about 5 cm in size, located under the skin under Adam's apple in the neck. In the center, in a region called the isthmus, the two parts of the gland join, which gives the thyroid gland the shape of a tight tie. It is normally difficult to see the thyroid gland and can barely be felt (Shibusawa *et al.*, 2003). As with a swollen goiter, it is convenient for doctors to feel, and it may appear as a prominent bulge at the bottom or sides of Adam's apple. The thyroid gland secretes thyroid hormones, which control the body's metabolic rate (Abdulbaqi *et al.*, 2018). an enzyme called thyroxine-binding globulin carries the bulk of T4 and T3 into the bloodstream. In the blood, only a limited volume of T4 and T3 are readily available. In fact, it is this free part of the hormone that is active. When the free hormone is used by the body, more of it is released by the thyroxine-bound globulin (Chiamolera *et al.*, 2012). The thyroid gland requires iodine, the ingredient present in food and water, to produce the two thyroid hormones. The gland of the thyroid stores and processes iodine in order to convert it into a thyroid hormone. With the use of thyroid hormones, some of the iodine in those hormones is released, then returns to the thyroid gland and is recycled to produce more thyroid hormones (Ferrara *et al.*, 2012). The strange thing is that the thyroid gland releases fewer thyroid hormones if it is exposed to high levels of iodine transported to it through the blood. There is, thus, a complex system that regulates the body's levels of thyroid hormones (Moran *et al.*, 2013). Next, right before the pituitary gland in the brain, the hypothalamus secretes the hormone thyrotropin, which allows the

pituitary gland to develop thyroid-stimulating hormone (TSH). TSH activates the thyroid gland, as its name implies, to produce thyroid hormones. Depending on if blood levels of thyroid hormones are too high or too low, the pituitary gland inhibits or speeds up the production of TSH. The thyroid gland also releases the hormone calcitonin, which, by helping to incorporate calcium into the bones, can increase bone strength. (Warnmark *et al.*, 2003).

Definition of Thyroid Hormones:

They are hormones secreted by the thyroid gland and their primary function is to regulate the speed of metabolism in many tissues. An increase or decrease in the thyroid gland's production of hormones can cause some diseases (Kaneshige *et al.*, 2001). The thyroid gland releases its hormones into the bloodstream in response to a regulating hormone released by the pituitary gland called thyroid stimulating hormone (Barry *et al.*, 2010). The thyroid gland is the only organ in the body that has the ability to synthesize iodine in large quantities for use in the synthesis of thyroid hormones (Oetting *et al.*, 2007). This gland arises from the endoderm layer of the front of the fetus's gastrointestinal tract. It appears as a cyst-like denta from the ventral surface of the pharynx (Ortiga-Carvalho *et al.*, 2005). Then the dimensional end of this diphtheria gradually expands and becomes dilobed. As for the end of the pharynx, it narrows, forming the thyroid-lingual duct, which then disappears. The thyroid lobe occupies an anterior position in relation to the trachea. The thyroid gland consists of two lobes, joined together by the isthmus. In mammals, the thyroid gland is located above the windpipe, just below the cartilage, which is the marker for the thyroid gland's location. The presence of remnants of the lingual thyroid duct near the isthmus is noted in the structure of the hierarchical lobe feature. The weight of the thyroid gland in humans ranges from 15-20 grams. The functional unit of the thyroid gland is the vesicle, which consists of a single layer of cubic epithelial cells surrounding a lumen containing a colloidal substance called colloid. The vesicle diameter may insist about 200 μm . There are variations in the diameters of the vesicles even within the gland itself. The vesicles are surrounded by a network of capillaries. When the gland is ineffective, the amount of colloid increases and the histological composition of the thyroid gland changes in most domestic animals (Dahham *et al.*, 2019). The vesicle cells synthesize thyrogobulin, which is released into the colloid-containing lumen. Thyroclobulin is important because it forms the basis for the thyroid gland's attachment process to the upper arteries that arise from the external carotid arteries, as well as the lower thyroid arteries that arise from the subclavian arteries. The blood supply changes depending on the functioning of the gland (Al-Tekreeti *et al.*, 2017). There are lymphatic vessels, but their function in relation to endocrine function is uncertain. Also, the thyroid gland in some mammals, including humans, is rich in sympathetic post-ganglionic nerve fibers whose function is vascular motility (El-Hilali *et al.*, 2016).. As well as its nerve connection with the cells of the vesicles (Sap *et al.*, 1987). The stimulation of these nerve fibers leads to the secretion of thyroid hormones, as these cells respond to the stimulating hormone of the thyroid gland by releasing histamine, serotonin and other substances. These released amines directly affect the follicular cells to initiate the release of thyroid hormones or to increase blood flow to the thyroid gland (Bander *et al.*, 2015). The thyroid gland is surrounded by two layers of connective tissue. The outer layer is attached to the cervical ligaments and the inner layer is attached to the surface of the gland. Thyroid cells are characterized by fine villi that extend into the colloid. The mammalian thyroid gland contains cells that are a source of the hormone calcitonin (Dheeb *et al.*, 2015).

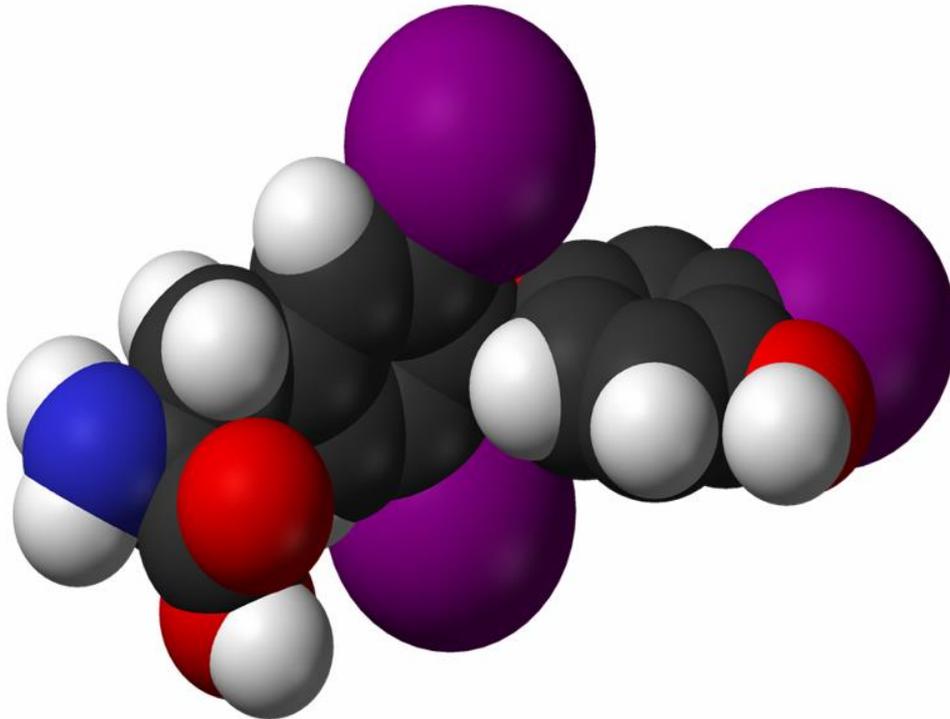


Fig. 1: Thyronine Triple Iodine T₃(Chiamolera *et al.*, 2009).

Functions Thyroid Hormone and Actions Axis Receptor:

Normal thyroid hormone function requires normal transport of thyroid hormone through the cell membrane, appropriate elimination of iodine, presence of nuclear thyroid hormone receptors, thyroid hormone response agents, co-steroids, co-inhibitors, and natural histone elastinosis (Phan *et al.*, 2010). The syndrome is a rare syndrome in which levels of thyroid hormones are elevated, while the level of thyroid-stimulating hormone (TSH) is not suppressed, or is not suppressed completely as expected. The first report of this case appeared in 1967 (Bochukova *et al.*, 2012).

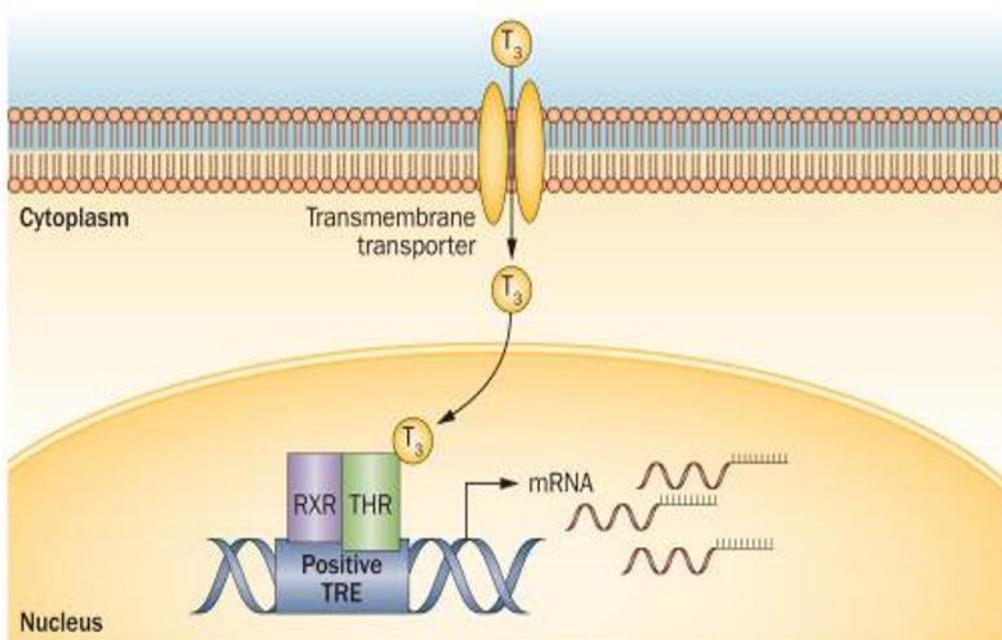


Fig. 2: Thyroid hormone action (Nikrodhanond *et al.*, 2006).

It is basically a decreased end-organ response to thyroid hormones. The biochemical properties are similar to that of TSH, binds to TSH receptors on the epithelial cells of the normal thyroid gland or to highly differentiated tumor tissue in the thyroid gland and stimulate iodine uptake, production and secretion of thyroglobulin, triiodothyronine, and thyroid hormone.

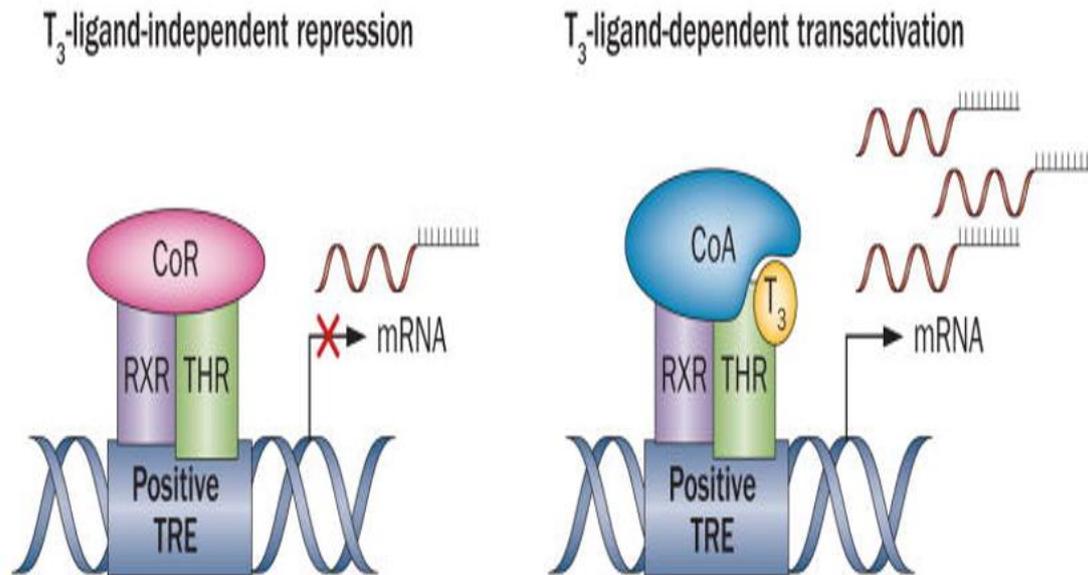


Fig.3: Gene regulation by thyroid hormones. (Brent *et al.*,2012).

Physiological Effects of Thyroid Hormones and Secretion of The Hormone:

Thyroid hormones affect most body functions as they directly affect a number of physiological processes, and they are necessary for the work of other hormones in these processes, for example, thyroid hormones must be present with somatotropin in early development. The deficiency of thyroid hormones in humans causes major disturbances in growth, development, reproduction, behavior and metabolism (van *et al.*, 2012). Thyroid hormones are unique in their effects that appear on almost every tissue of the body during a person's life. The thyroid hormone is necessary for the functioning of many body tissues. In a healthy person, the gland permanently secretes thyroxine (T₄), which is converted into thyroxine triiodine in other organs by the enzyme selenium-dependent (iodothyronine diiodinase). Tri-thyroxine binds to the thyroid hormone receptor in the cell nucleus, and there it works to stimulate the operation of certain genes to produce a group of proteins. In addition, the hormone binds to $\alpha\beta$, the $\alpha\beta$ cell envelope protein, stimulating the reverse transporter of sodium and hydrogen and performing a host of other functions such as angiogenesis and cell growth (Refetoff *et al.*, 2014). In the blood, most of the thyroid hormones (99.97%) are bound to transporter proteins such as thyroxine-binding globulin, only the hormone not bound to the transporter proteins is biologically active. Molecules of thyroglobulin. The process is controlled by the thyroid-stimulating hormone produced by the pituitary gland, an insufficient amount of iodine can cause a deficiency in the thyroid hormone (Kaneshige *et al.*, 2000). Both the hypothalamus and the pituitary and thyroid glands play an important role in maintaining the normal thyroid hormone, the production of TSH from the pituitary gland The anterior is stimulated by the releasing hormone thyrotropin produced by the hypothalamus, the production of both TSH and the thyrotropin-releasing hormone is reduced by negative thyroxine reflux, the insufficient amount of the releasing hormone thyrotropin, which, in a rare event leads to insufficient thyroid-stimulating

hormone and consequently a deficiency of thyroid hormone (Refetoff *et al.*, 2007). Hypothyroidism. The hypothalamus secretes a hormone called thyrotropin-releasing hormone (TRH), which in turn causes thyroid-stimulating hormone (TSH) to be released. TSH sends a signal to the thyroid gland to release the thyroid hormones: thyroxine (T4), and triiodothyronine (T3). Converting T4 to active T3 is carried out in peripheral tissues with the help of deiodinase enzymes. Thyronine triiodine has an adverse effect on the pituitary gland; This reduces the secretion of the thyroid-stimulating hormone. Triiodothyronine (T3): a hormone produced by the thyroid gland. This hormone affects many physiological processes in the human body, including growth and metabolism, as well as the regulation of body temperature and heart rate. TRH represents only 20% of thyroid hormones, while thyroxine accounts for the remainder (Dheeb *et al.*, 2015).

Thyroid system

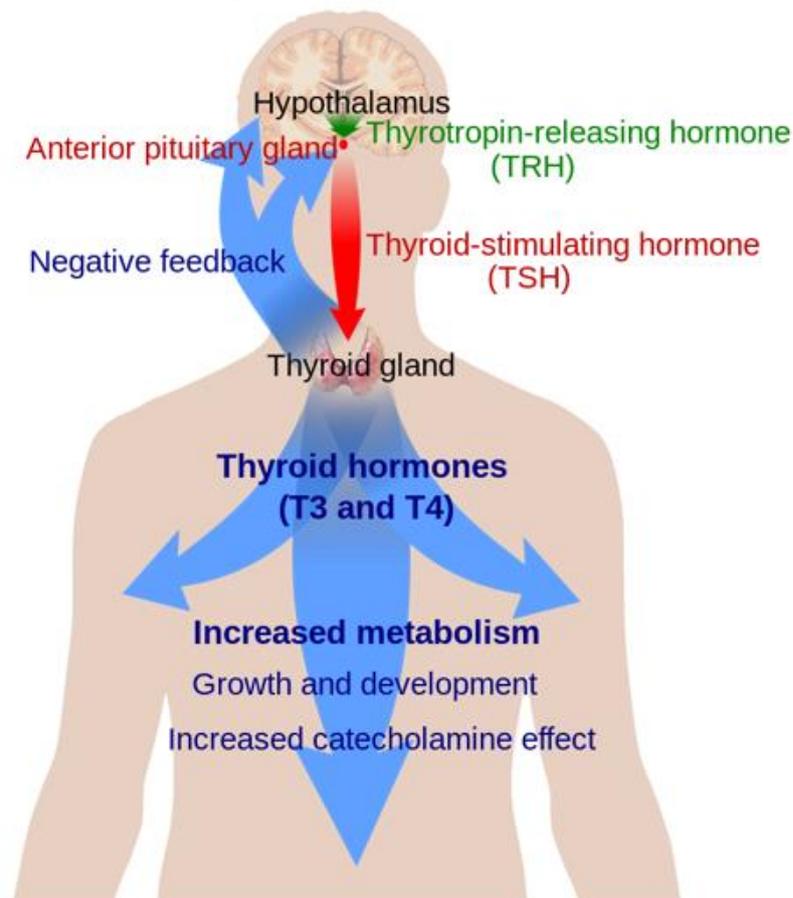


Fig.4: Regulating thyroid hormones (Bianco et al, 2011).

Despite this, TRH is four times as effective as thyroxine. The biological half-life of TRH is short, at only 2.5 days, compared to the biological half-life of T4 of 6.5 days.

Goiter:

Goiter, also known as hyperthyroidism, goiter, swollen thyroid gland, or parathyroid gland is one of the most common thyroid problems, and this condition is swelling in the neck area. Specifically, the anterior aspect of the windpipe is the result of an increase in the size of the thyroid gland, in fact, the occurrence of hypertrophy does not necessarily mean that there is a malfunction of the thyroid gland (Hussain *et al.*, 2018). Hormones, and it can be said that goiter may occur with the thyroid gland

continues to develop, in what is known as euthyroidism, regular levels of its hormones. Hyperthyroidism is the development of vast quantities from the gland. other symptoms may be described and Diagnosis of goiter This may include asking the patient to swallow during the physical examination, and after the hyperthyroidism is diagnosed, the affected doctor may undergo a series of tests and other tests to detect other thyroid disorders and the causes of the condition (Dheeb *et al.*, 2015).

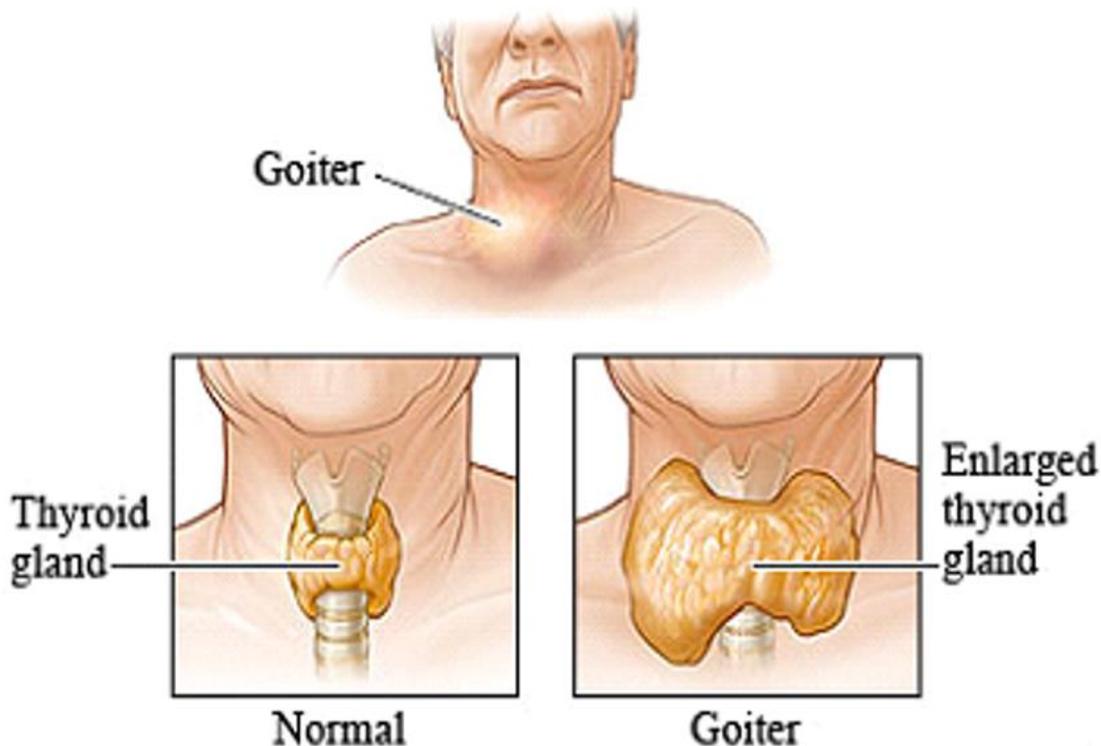


Fig. 5: normal and goiter thyroid gland (Cheng SY *et al.*, 2010)

This includes a thyroid function test, which contributes to the detection, and other tests may be required in certain cases, which can be shown as follows: Ultrasound scan: This contributes to a better examination of the thyroid gland, in addition to determining the size of the enlargement that occurred in it. Radioactive iodine scan: This includes injecting the patient with radioactive iodine, in order to obtain a detailed picture of the thyroid gland (Hussein *et al.*, 2019). Thyroid antibody tests: which can be requested by the doctor to help him diagnose and determine the appropriate treatment for goiter, specifically to distinguish thyroid disorders caused by autoimmune diseases from other thyroid diseases and disorders. Fine needle biopsy: Fine Needle Aspiration In some very rare cases, the nodule that appeared on the thyroid gland may be cancerous, as more than 95% of the thyroid nodules are benign and non-cancerous, and despite this, to ensure the health and safety of the patient, the doctor may request a biopsy of the thyroid nodule to be examined under a microscope and to confirm of their nature; Benign or precancerous (Nouri *et al.*, 2015).

Thyroid Cancer:

Among the cells of the thyroid gland, thyroid cancer develops-this a butterfly-shaped gland that lies at the base of your mouth. In order to control the heart rhythm, blood pressure, body temperature and weight, the thyroid gland secretes hormones. is due to modern technologies that have allowed them to find small cancers in the thyroid gland, which they could not detect in the past. Thyroid cancer occurs when cells in that gland undergo genetic changes (mutations). Mutations allow cells to grow and multiply

rapidly (Hussain *et al.*, 2017). These cells do not die as normal cells do. The accumulating thyroid cells form a tumor. The abnormal cells can invade nearby tissues. Papillary thyroid cancer occurs from cells that contain thyroid hormones and store them. It can occur at any age but is most common in individuals between 30 and 50 years of age as two different types of thyroid cancer. Follicular thyroid cancer. Follicular thyroid cancer affects the follicular cells of the thyroid gland. It most often affects people over the age of 50. Hurtle cell carcinoma is a rare and more aggressive condition than follicular thyroid cancer. anaplastic thyroid cancer. anaplastic thyroid cancer is a rare type of thyroid cancer that begins in the follicular cells. This cancer multiplies quickly.

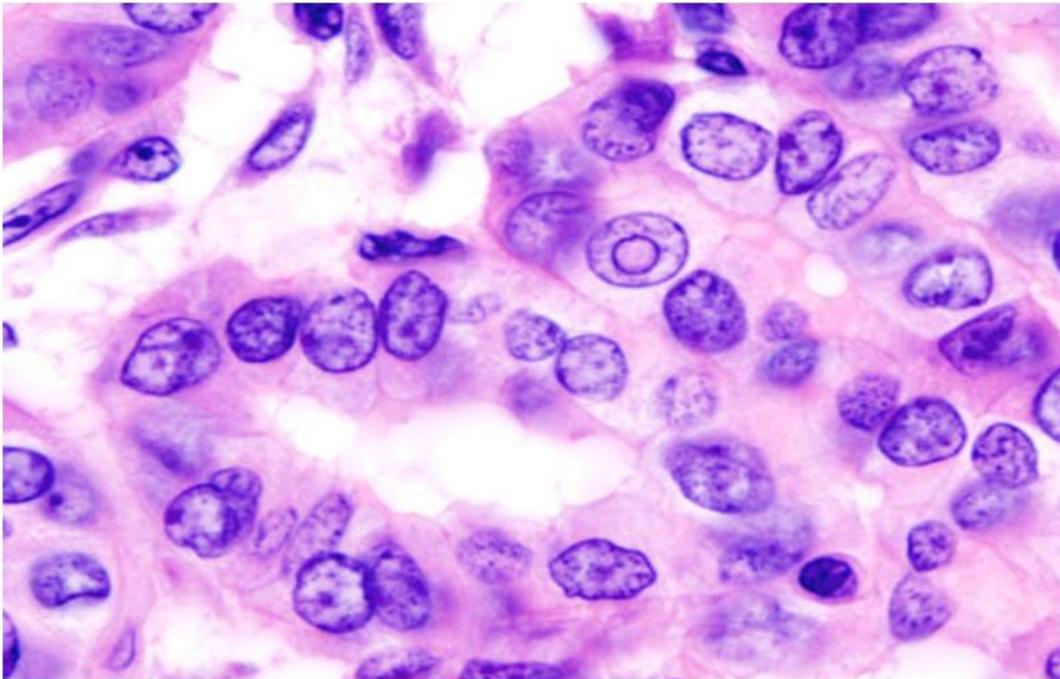


Fig. 6: Illustration of thyroid cancer (Azziz *et al.*, 2006).

Medullary thyroid cancer. Medullary thyroid cancer begins in cells known as C cells in the thyroid gland that is responsible for the production of the hormone. The occurrence of medullary thyroid cancer in its early stages can be demonstrated by an elevated blood calcitonin level (Dheeb *et al.*, 2014). The possibility is boosted by some genetic syndromes. In the thyroid gland, many other uncommon forms of cancer arise. Among the methods of cancer treatment for the thyroid gland removing the thyroid gland and the central neck area by means of surgery is the first step in treating thyroid cancer in most cases. Thyroid preservation can be applied in some cases, when the cancer is less aggressive (differentiated cancer, no evidence of lymph node proliferation, i.e., major genetic modifications, p53 mutations etc.) in patients under the age of 45 years (Hammadi *et al.*, 2019). An operation should be performed if the diagnosis is established to be differentiated thyroid cancer (such as papillary thyroid cancer) or if a needle biopsy is suspected, while a watchful wait strategy is not recommended in any evidence-based guidelines. Watchful waiting reduces overdiagnosis or unnecessary medical care for old thyroid cancer patients. Radioactive iodine-131 is used in patients with papillary or follicular thyroid cancer on thyroid tissue remaining after surgery and treatment for thyroid cancer. Patients with medullary thyroid carcinoma, anaplastic thyroid carcinoma, do not benefit from this treatment (Gereben *et al.*, 2008).

CONCLUSION

There is no question over a tiny goiter that does not trigger physical or aesthetic concerns. However, a large goiter can make breathing or chewing painful and can lead to coughing and hoarseness. a goiter that comes from other disorders, such as hypothyroidism or hyperthyroidism, may be linked with a variety of symptoms ranging from weakness and weight gain to unintended weight loss, irritability and trouble sleeping.

REFERENCES

- Abbott D.H., Dumesic D.A., Franks S. (2002). Developmental origin of polycystic ovary syndrome-a hypothesis. *Journal of Endocrinology*; 174:1–5.
- Abdulbaqi, N. J. and Dheeb, B. I. and Irshad, R. (2018): Expression of Biotransformation and Antioxidant Genes in the Liver of Albino Mice after Exposure to Aflatoxin B1 and an Antioxidant Sourced from Turmeric (*Curcuma longa*). *Jordan Journal of Biological Sciences*, 11(2) 89 – 93.
- Al-Tekreeti, A. R., Al-Halbosiy, M. M. F., Dheeb, B. I., Hashim, A. J. and Al-Zuhairi, A. F. H. (2017). Molecular identification of clinical *Candida* isolates by simple and randomly amplified polymorphic DNA-PCR. *Arabian Journal for Science and Engineering*, Vol. 43,163–170.DOI 10.1007/s13369-017-2762-1.
- Azziz R., Carmina E, Dewailly D., *et al.* (2006). Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess guideline. *Journal of Clinical Endocrinology & Metabolism*, 91:4237–4245.
- Bander, K. I., Mohammed, S. H., Thalij, K. M. and Dheeb, B.I. (2015). Survey Study of the Allergic Fungi in Kirkuk Area and Use Molecular Detection for Identification. *Basic and Applied Research (IJSBAR)*,19(1):383-397.
- Barry J.A., Kay A.R., Navaratnarajah R., Iqbal S., Bamfo J.E., David A.L., *et al.* (2010). Umbilical vein testosterone in female infants born to mothers with polycystic ovary syndrome is elevated to male levels. *Journal of Obstetrics and Gynaecology*,30:444 – 446.
- Bianco A.C. (2011). Minireview: cracking the metabolic code for thyroid hormone signaling. *Endocrinology*; 152:3306–3311.
- Bochukova E., *et al.* (2012). A mutation in the thyroid hormone receptor α gene. *New England Journal of Medicine*,366:243–249.
- Brent G.A. (2012). Mechanisms of thyroid hormone action. *Journal of Clinical Investigation*, 122:3035–3043.
- Cheng S.Y., Leonard J.L., Davis P.J. (2010). Molecular aspects of thyroid hormone actions. *Endocrine Reviews*,31:139–170.
- Chiamolera M.I, Wondisford F.E. (2009). Minireview: Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. *Endocrinology*; 150:1091–1096.
- Chiamolera M.I., *et al.* (2012). Fundamentally distinct roles of thyroid hormone receptor isoforms in a thyrotroph cell line are due to differential DNA binding. *Molecular Endocrinology*, 26:926–939.
- Dahham, M.T., Omar, A.F., Dheeb B.I. (2019). Synergistic effect of tea tree oil on fungi causing vaginal thrush in pregnant women. *Journal of Biotechnology Research Center*, 13 (2)35-44.
- Dheeb B.I., Al-dujayli S.M.A., Ibrahim I.M., Abbas Q.A. (2019). Study the Antifungal Activity of ZnS:Mn Nanoparticles Against Some Isolated Pathogenic Fungi. *Journal of Physics: Conference Series*, 1178, 46–52.
- Dheeb, B. I. (2014). Immunohistochemical study of Tumor Necrosis Factor - α

- (TNF- α) expression in lung, liver, and spleen during aspergillosis infection. *BMC genomics*, 15 (2), 71.
- Dheeb, B. I., Al-Mashhadani, I. I., Ismail, E. N., Majeed, S. M., and Majeed, D. M. (2014). A Study of the Expression of Aflatoxin B1 Regulatory Gene in Clinical and Environmental *Aspergillus flavus* using Real-time PCR. *Basic and Applied Research (IJSBAR)*, 17 (1), 417-427.
- Dheeb, B. I., Al-Mudallal, N. H., Salman, Z. A. and Ali, M. (2015). The Inhibitory Effects of Human, Camel and Cow's Milk against Some Pathogenic Fungi in Iraq. *Jordan Journal of Biological Sciences*, 8(2) 89 – 93.
- Dheeb, B.I. (2015). Antifungal Activity of Alkaloids and Phenols Compounds extracted from black pepper *Piper nigrum* against some pathogenic fungi. *Journal of Biotechnology Research Centre*, 9 (2), 46-54.
- El-Hilali, F., El-Hilali, H., Dheeb, B. I., Traore, B. M., Messouak, M., Mazouz, H., Moumni, M., Belgacem, F. B. M. and El-Mowafy, A. M. (2016). Blood Transfusion Utility During Cardiopulmonary Bypass and Correlation with Key-Biochemical Laboratory Findings: A New Approach to Identify Preventive and Risk Factors (1-Year Practice at University Hospital Hassan-II of Fez). *Biochemistry and Analytical Biochemistry*, 5:3 DOI: 10.4172/2161-1009.1000290.
- Ferrara A.M., *et al.* (2012). Homozygous thyroid hormone receptor β -gene mutations in resistance to thyroid hormone: three new cases and review of the literature. *Journal of Clinical Endocrinology & Metabolism*, 97:1328–1336.
- Gereben B., *et al.* (2008). Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocrine Reviews*, 29:898–938.
- Hammadi, S.Y. Hussein, A.S. Majeed, M. Dheeb, B.I. Ismail. E.N. (2019). RAPD and ISSR analyses of *Saccharomyces cerevisiae* isolates from different sources. *Brc Journal of Advances in Business*, 12 (2), 40-50.
- Hamood, A.H.M. Abood, J.N. Dheeb B.I. (2020). The synergistic effect of fungus filter *Aspergillus terreus* and aqueous extract of *Fucus vesiculosus* on some growth characteristics of the *Ocimum basilicum* and its content of active substances. *Eurasian Journal of Biosciences*. 14,161-166.
- Hussain A.F., Sulaiman G.M., Dheeb B.I., Hashim A.J. (2018). Histopathological changes and expression of transforming growth factor-beta (TGF- β 3) in mice exposed to gliotoxin. *Journal of KS U – Science*, 27, 193–197.12.
- Hussain, A. F., Sulaiman, G. M., Dheeb, B. I., Hashim, A. J. and Seddiq, S. H. (2017). Improving conditions for gliotoxin production by local isolates of *Aspergillus fumigatus*. *Journal of biotechnology research center*, 11(2):14-24.
- Hussein, H.S., Dheeb B.I., Hamada, T.A. (2019). Studying the candida resistance and sensitivity for some antifungals. *Journal of Biotechnology Research Center*, 13 (2)25-34.
- Ibrahim, I. M., Iftikhar, M., Ali, I. M., Dheeb, B. I., Abbas, Q. A., Ramizy, A., Eisa, M. H. and Aljameel, A. I. (2017). Antifungal activity of wide band gap Thioglycolic acid capped ZnS:Mn semiconductor nanoparticles against some pathogenic fungi. *Materials Science and Engineering C*, 73:665–669.
- Kaneshige M., *et al.* (2000). Mice with a targeted mutation in the thyroid hormone β receptor gene exhibit impaired growth and resistance to thyroid hormone. *The Proceedings of the National Academy of Sciences USA*; 97:13209–13214.
- Kaneshige M., *et al.* (2001). A targeted dominant-negative mutation of the thyroid hormone α 1 receptor causes increased mortality, infertility, and dwarfism in mice. *The Proceedings of the National Academy of Sciences USA*; 98:15095–

15100.

- Moran C., *et al.* (2013). An adult female with resistance to thyroid hormone-mediated by defective thyroid hormone receptor α . *Journal of Clinical Endocrinology & Metabolism*, 98:4254–4261.
- Nikrodhanond A.A., *et al.* (2006). The dominant role of thyrotropin-releasing hormone in the hypothalamic-pituitary-thyroid axis. *Journal of Biological Chemistry (JBC)*, 281:5000–5007.
- Nouri, M. A., Al-Halbosi, M. M. F., Dheeb, B. I. and Hashim, A. J. (2015). Cytotoxicity and genotoxicity of gliotoxin on human lymphocytes in vitro. *Journal of KS U – Science*, 27, 193–197.
- Oetting A., Yen P.M. (2007). New insights into thyroid hormone action. *Best Practice & Research Clinical Endocrinology & Metabolism*, 21:193–208.
- Ortiga-Carvalho T.M., *et al.* (2005). Negative regulation by thyroid hormone receptors requires an intact coactivator-binding surface. *Journal of Clinical Investigation*, 115:2517–2523.
- Phan T.Q., Jow M.M., Privalsky M.L. (2010). DNA recognition by thyroid hormone and retinoic acid receptors: 3, 4, 5 rule modified. *Molecular and Cellular Endocrinology*, 319:88–98.
- Rassin, N. K., Nemat J. A, Dheeb, B. I. (2015). Molecular Identification of *Aspergillus fumigatus* Using ISSR and RAPD Markers. *Iraqi Journal of Science*, 56 (4A), 2788-2797.
- Refetoff S., Dumitrescu A.M. (2007). Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. *Best Practice & Research Clinical Endocrinology & Metabolism*, 21:277–305.
- Refetoff S., *et al.* (2014). Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. *Thyroid*, 24:407–409.
- Sap J., *et al.* (1986). The c-erb-A protein is a high-affinity receptor for thyroid hormone. *Nature*. 324:635–640.
- Shibusawa N., *et al.* (2003). Thyroid hormone action in the absence of thyroid hormone receptor DNA-binding *in vivo*. *Journal of Clinical Investigation*, 112:588–597.
- van Mullem A., *et al.* (2012). Clinical phenotype and mutant TR α 1. *New England Journal of Medicine*, 366:1451–1453.
- Warnmark A., Treuter E., Wright A.P., Gustafsson J.A. (2003). Activation functions 1 and 2 of nuclear receptors: molecular strategies for transcriptional activation. *Molecular Endocrinology*, 17:1901–1909.