Annals of Thyroid Research

Open Access

Austin Publishing Group

Special Article - Thyroid Gland

The Thyroid Gland

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Received: February 11, 2019; **Accepted:** February 18, 2019; **Published:** February 25, 2019

Letter to Editor

The thyroid gland, the largest single gland in the human organism, is the first to form in the human embryo by about the twelfth week of life.

The gland develops as a diverticulum of the primitive pharynx between the first and the second branchial pouch. It starts to form during the third week of intrauterine life, developing as a duct with a bifurcated distal extremity, penetrating the mesoderm, following a caudal direction and accompanying migration of the aortic arch. It runs along the primordial hyoid bone and the pharynx in the direction of the neck, occupying its definitive position on the anterior surface of the trachea by about the seventh week [1].

This thyroid rudiment remains temporarily attached to the trachea through the thyroglossal duct, whose distal segment occasionally gives origin to the pyramidal lobe. The thyroglossal duct undergoes involution starting on the sixth week, being represented in adult life by the foramen caecum, located on the medial posterior base of the tongue [1].

By about the fifth week, epithelial proliferation of the third branchial pouch occurs, giving origin to the thymus and to the lower parathyroids. Budding of the dorsal region of the fourth branchial pouch will give origin to the upper parathyroid glands. Incorporation of ultimobranchial body cells into the thyroid lobes occurs by about the seventh week, giving origin to the calcitonin producing cells (C cells or parafollicular cells), identified by the twelfth week. Primitive thyroid follicles are identified by the eighth week. Specific thyroid transcription factors - TTF-1, TTF-2 and PAX-8 - participate in the differentiation of follicular cells, influencing the Thyroglobulin (Tg) gene and the Thyroperoxidase Gene (TPO). The ability to take up iodine, to organify it and to incorporate it into the Tg molecule starts between the tenth and eleventh week. After the first trimester of gestation, Thyroxine (T4) is detected in fetal serum [1].

The thyroid gland resembles the shape of a butterfly, but its name originates from the Greek word tiros, which means shield [1]. During adult life, the gland weighs 15 to 25 grams and has a marked capacity to increase its volume under the action of a continuous or temporary stimulus. It contains about 3 million follicles, spherical structures of varying size consisting of a single layer of epithelial (follicular) cells and a central lumen consisting of Tg-rich colloid which corresponds to about 70 to 80% of the entire protein content of the gland. Hormone synthesis occurs in the apical portion of follicular cells close to the colloidal surface [2].

Disorders of glandular morphogenesis produce anatomical and/or functional abnormalities that may cause agenesis or ectopia of the gland, with changes in the quality of human life. The benefits of the thyroid for the appropriate general physiology of human beings were first shown about a little more than one hundred years ago [2].

Stimulation of follicular cells initially occurs at the level of the protein receptor site of TSH. Iodine is actively transported from the basement membrane to the interior of the follicular cells, reaching an intracellular concentration about 20 to 50 times higher than in plasma. A low intracellular sodium concentration is maintained by means of an active process that utilizes the Sodium Iodide Symporter (NIS), acting as a iodine ion cotransporter pump together with two sodium ions and utilizing energy generated by Na/K+ATPase. NIS also transports other ions such as pertechnetate (TcO_4), Sulfocyanide (SCN^-), Perchlorate (ClO_4), and Nitrate (NO_3). Iodine transport by NIS is stimulated by TSH through a self-regulating mechanism that varies in an inverse manner in relation to intracellular iodine concentration [2].

Inside the follicular cells, iodine is transported to colloid, an action performed by the protein pendrin that acts as a iodine/chloride transporter. A pendrin defect causes a type of hypothyroidism associated with changes in the auditory system (Pendred syndrome) [3]. Iodine is then organified and rapidly incorporated into the tyrosine residues of the Tg molecule using hydrogen peroxide (H_2O_2) in this process, in a reaction catalyzed by the enzyme TPO.

The coupling of iodotyrosine molecules (moniodotyrosine - MIT- and diiodotyrosine - DIT) in the Tg forms T3 and T4 by the action of TPO, which utilizes the H_2O_2 produced by the peroxide generating protein NADPH-oxidase, the thyroid oxidases (ThOx1 and ThOx2), and 2 dual oxidases (DUAX1 and DUOX2).

Peroxidase activity is controlled by TSH. High *in vivo* iodine concentrations promote a rapid inhibition of iodide organification and T4 synthesis and inhibition of hormone secretion (Wolff-Chaikoff effect), a transitory effect due to the inhibition of Tg proteolysis and the occupation of two peroxidase oxidation sites, which can prevent tyrosyne oxidation and also inhibit H_2O_2 generation or reduce the intracellular generation of AMPc. Colloid endocytosis then follows, with Tg proteolysis and the release of iodothyronines (T3 and T4). MIT and DIT not used for hormone synthesis undergo intrathyroid deiodination by the enzyme dehalogenase (DEHAL 1). Part of the formed T4 undergoes intraglandular deiodination before being secreted, giving origin to T3, a fact that increases the amount of released T3, rendering hormone synthesis more efficient.

The total amount of T4 in plasma is 45 times higher than the T3 content and the major source of T3 is T4 deiodination by the enzyme deiodinase.

Citation: Alves MLDA. The Thyroid Gland. Annals Thyroid Res. 2019; 5(1): 185-187.

The formed and released Thyroid Hormones (TH) interact with specific high affinity receptors present in the nucleus of their responding cells. TH may also have some cellular effects due to mechanisms independent of their nuclear receptors-somatic actions.

The synthesis and secretory activity of the thyroid gland is basically stimulated or controlled by Thyrotropin (TSH), so that, in the absence of TSH, the gland becomes hypoactive and strongly reduces TH availability, causing an increased synthesis and secretion of TSH and its hypothalamic releaser, the Thyrotropin Releasing Hormone (TRH).

Circulating T4 is more important than plasma T3 for the regulation of TSH secretion due to the presence of the enzyme 5'-D II, an isoform of deiodinase present in the pituitary thyrotroph. The fall of plasma T4 reduces the supply of T3 and T4, releasing the expression of the genes that code for the TSH molecule, and a small increase in T4 completely blocks the synthesis of TSH.

Other factors stimulate the growth of follicular cells independently of TSH. An example is IGF.

Deficient iodine intake is the main avoidable cause of mental retardation. Several governmental agencies have instituted programs of iodine fortification of industrialized salt for domestic consumption, or of iodine addition to drinking water or to bread, or even a supply of iodized oil in order to prevent this damage.

Congenital hypothyroidism may be due to defective fetal hormone production caused by a glandular defect or by maternal iodine deficiency, with the occurrence of cretinism. Hormone or iodine replacement reverses the hypothyroidism but not the damage to the nervous system. The prevalence ranges from 1: 2400 to 1:5000 liveborns and the condition can be detected early by screening with the neonatal heel prick test [3].

Hypothyroidism may also arise in the presence of Hashimoto's thyroiditis, affecting 2 to 20% of the population, and being more prevalent in older women [4].

Chronic excessive iodine intake also causes thyroid dysfunction, causing increased ion uptake by the gland and increased TH production, with consequent hyperthyroidism (Jod-Basedow effect). It may also cause subclinical hyperthyroidism among older people, with an increased risk of cardiac arrhythmia. The prevalence of hyperthyroidism is 2 to 3 % of the population [5-7].

Amiodarone, with almost 38% of its weight consisting of iodine, may cause the Wolff-Chaikoff effect and the Jod Basedow effect, and may also be a cause of thyrotoxicosis due to injury to follicular cells followed by hypothyroidism, transitory or not [5].

The main cause of hyperthyroidism is Basedow Graves disease-autoimmune hyperthyroidism-with a 0.5 to 2% population prevalence, mainly affecting young women. Graves hyperthyroidism has a genetic component and is due to modifications of genes such as CTLA-4, PTPN 22 and TSHR [5-7].

Nodular or multinodular goiter is another cause of hyperthyroidism.

It may also be secondary to a destructive process with excessive TH release which occurs in the presence of amiodarone, interleukin or interferon, in postpartum thyroiditis, acute thyroiditis, actinic thyroiditis, or in the thyrotoxicosis phase of Hashimoto's thyroiditis. In areas of iodine sufficiency, Graves disease is responsible for 80% of the cases of hyperthyroidism [5-7].

The volume of the thyroid may increase in a diffuse or localized manner (nodules). Diffuse goiter may occur in hypothyroidism due to enzymatic defects of hormone synthesis or to inflammatory processes or due to deficient iodine intake, with progression to hypothyroidism [8].

Thyroid nodules are very frequent in the general population, occurring in 4 to 7% of the population investigated by palpation, in about 30% of the population investigated by ultrasound, and in about 60% of autopsy cases. Thus, it is a considerable challenge to determine which of these diagnosed nodules are malignant and require a specific conduct [8,9].

Malignant nodules are detected in 3 to 28% of excised nodules by ultrasonography (standard, Doppler, elastography), by evaluation with the TIRADS system, by thermography, Fine Needle Aspiration Biopsy (FNB), by the BETHESDA criteria, and by molecular examination [8-14].

Carcinomas are present in 5 to 7% of patients with a diagnosis of thyroid nodules. The differentiated ones originate from follicular cells and are classified as papilliferous carcinoma-the most frequent and least aggressive – and the more aggressive follicular carcinoma associated with genetic mutations (translocation giving origin to the gene of fusion between PAX 8- TIF 1- and PPAR gamma). Anaplastic carcinoma is undifferentiated and quite aggressive. It occurs in about 1% cases and is associated with the presence of various mutated genes, and courses with "freezing" of the cervical region. Medullary carcinoma originates in C or parafollicular cells, secretes calcitonin and is frequently associated with the multiple endocrinopathies MEN2A and MEN2B [15-18].

The thyroid may also be affected by sarcomas and lymphoma, whose prevalence is 5% among thyroid neoplasias that occur in older women with Hashimoto's thyroiditis [18,19]. The gland may also be the target of metastases, especially of renal carcinoma, bronchogenic carcinoma, mammary carcinoma, malignant melanoma, and neoplastic processes of the upper digestive tract [17-19]. Malignant neoplasias require specific treatment according to subtype, severity and presence of metastases [20,21].

Conclusion

The thyroid gland is of vital importance for the human organism and disturbance of its functioning has serious consequences for the physiological health of humans.

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Annals Thyroid Res - Volume 5 Issue 1 - 2019
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Citation: Alves MLDA. The Thyroid Gland. Annals Thyroid Res. 2019; 5(1): 185-187.