Original Article

Thyroid gland - Historical aspects, Embryology, Anatomy and Physiology

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Abstract

Thyroid gland is an important endocrine organ. Its hormone thyroxine is essential for life. The structure and function of thyroid gland were discovered during 17th to 20th centuries. Thyroid surgery is being done since early 19th century, perfected by Theodre Kocher in early 20th century. Thyroid is the first endocrine gland to develop in embryo and is endodermal origin. The surgically important anatomical relations of thyroid are recurrent laryngeal nerve, parathyroid glands and external laryngeal nerve with variations. Thyroid gland secretes thyroxine hormone which contains Iodine. Thyroxine has effects on all organs of body and its secretion is regulated by Pituitary. Present article throws light on some historical aspects, embryology, anatomy and physiology of thyroid gland based on relevant articles and textbooks.

Key words

Inferior thyroid artery, Iodine, Recurrent laryngeal nerve, Thyroid, Thyroid follicle, Thyroxine.

Introduction

Thyroid is an important endocrine organ in human body. Its enlargement or goiter has been observed by ancient Greeks [1]. The current understanding of its anatomy, function, and diseases are due to researchers of 17th to 20th centuries. The understanding of its anatomical relations and functional status are of paramount importance to thyroid surgeon. There has been rapid advancement in thyroid surgery of late, yet an understanding of its anatomy and physiology is a must for all medical personnel. Present article intends to meet this requirement by review of selected articles and chapters on thyroid gland in standard texts.

Historical background

The fullness or swelling of neck from thyroid enlargement was referred to by the Greeks, including Galen as bronchocele (hernia or swelling of the windpipe). Pliny and Juvenal introduced Latin term, tumid gutter (Swollen throat) which eventually became the French goiter, and later the English goiter, in America goiter [1]. Galen described some secreting glands adjacent to thyroid cartilage which were named laryngeal gland by Eustachius. Wharton in 1656 named them glandulae thyroidaeae (Thyroid glands) because of their anatomic proximity to thyroid cartilage. It was established during 1700s that goiter was a disease of the thyroid [1].

The relationship between thyroid and various body functions was studied by experimental thyroidectomy as early as 1827 and concept of an internal secretory function was formulated by King 9 years later. The Reverdins and Kocher in 1883 became aware of the similarity between myxedema and the clinical picture that developed after successful removal of the thyroid. The injection of a glycerine extract of thyroid to relieve myxedema and finally, the feeding of lightly cooked sheep thyroid with successful relief of disease completed the background for knowledge about thyroid function.

In 1896, Bauman discovered high iodine concentration within the gland. The work of Oswald with thyroglobulin gave a firm basis to a relation between iodine and the thyroid. Kendall’s crystallization of l-thyroxine from thyroid tissue in 1915 and elucidation of the chemical structure of thyroxine (T_4) by Harington and Barger in 1926 and 1927, the nature of thyroid hormone was established. Gross and Pitt-Rivers found Tri-iodothyronine (T_3), a more potent and more rapid in onset of action than T_4 and was clinically effective in myxedema.

Paracelsus in Salzburg described endemic cretinism. Faggie described sporadic cretinism in 1871, which paved the way for Gulls report of the disease in adult, which was named by W.M. Ord as “Myxedema”. Goiter prevention by iodized salt was advocated by David Marine in 1917 and was proven by him in 1920 in Akron, Ohio [2].

Thyrotoxicosis was first described in 1786 by C H Parry but was reported in 1825 [3]. R J Graves described exophthalmic goiter and the disease named after him [3]. Magnus-Levy described the characteristic elevation of basal metabolic rate in this disorder [1]. Plummer in 1913 distinguished toxic adenomatous goiter from exophthalmic goiter and so the disease was named after him [3].

Needle aspiration of the thyroid was pioneered in the 1930s by Martin, which is now the gold standard in the evaluation of thyroid nodule [4].

Paulus most likely performed the first thyroid surgery in 500AD [5]. Prior to 1850, approximately 70 thyroidectomies were performed with a reported mortality rate of 41 percent, infection and hemorrhage being the major factors in the mortality rate [6]. Theodor Billroth performed approximately 20 thyroidectomies with a mortality rate of 40%. Advance in thyroid surgery came from Theodore Kocher who recognized the need to preserve the parathyroids. He reported more than 5000 successful thyroidectomies by 1912 [5]. He is called “Father of thyroid surgery” [6]. He was the first surgeon to be awarded the Nobel Prize in 1909 for medicine and physiology for thyroid work [3]. Since then thyroid surgeons like William Halsted, George Crile and Frank Lahey had great influence on the development of thyroid surgery [3]. Plummer found out that the administration of iodine (preoperatively and post operatively) would prevent the crises causing death after surgical treatment of exophthalmic goiter. His work turned the most treacherous operation known to surgery into one of the safest [3].

Video-assisted neck surgery for endoscopic resection of thyroid tumours was proposed by Shimizia, et al. A modification of this procedure called video-assisted endoscopic thyroidectomy was proposed by Ta-Sen Yeh, et al. in 2000 [7].

Embryology of thyroid gland

The thyroid is the first endocrine gland to develop in the embryo. It begins to form about 24 days after fertilization from a median endodermal thickening in the floor of the primordial pharynx. This thickening soon forms a small out-pouching – 'the thyroid primordium'. As the embryo and tongue grow, the developing thyroid gland descends in the neck, passing ventral to the developing hyoid bone and laryngeal cartilages. For a short time the thyroid gland is connected to the tongue by a narrow tube, the thyroglossal duct. At first the thyroid primordium is hollow but it soon becomes solid and divides into right and left lobes connected by the isthmus of the thyroid gland which lies anterior to the developing 2^{nd} and 3^{rd} tracheal rings. By seven weeks the thyroid assumes its definitive shape and reaches its final site in the neck. The thyroglossal duct by this time has normally degenerated and disappeared. The proximal opening of the thyroglossal duct persists as a small pit in the tongue-'the foramen cecum'. A pyramidal lobe extends superiorly from the isthmus in about 50% of people. The pyramidal lobe may be attached to the hyoid bone by fibrous tissue and /or smooth muscle- 'the levator of thyroid gland'. A pyramidal lobe and the associated smooth muscle represent a persistent part of the distal end of the thyroglossal duct [8].

Histogenesis of the thyroid gland

The thyroid primordium consists of a solid mass of endodermal cells which breaks into a network of epithelial cords as it is invaded by the surrounding vascular mesenchyme. By 10^{th} week the cords have divided into small cellular groups. A lumen forms in each cell cluster and cells become arranged in a single layer around a lumen. During 11^{th} week colloid begins to appear in these structures-thyroid follicles – thereafter, iodine concentration and the synthesis of thyroid hormones can be demonstrated [8].

Anatomy of thyroid gland

The thyroid gland is situated low down at the front of neck weighing about 25 g. The gland has two lobes, each pear shaped hugging anterolateral aspects of cervical trachea from oblique line of thyroid cartilage to 5^{th} or 6^{th} tracheal ring. The right lobe is often larger than left and isthmus joins them anteriorly at the level of 2^{nd} and 3^{rd} tracheal rings. Isthmus is plastered quite firmly to the anterior surface of trachea. A small portion of gland substance, pyramidal lobe often projects upwards from isthmus, generally to the left of midline. The gland has its own capsule and is also enclosed by an envelope of pretracheal fascia which is thickened posteriorly and attached to the cricoid cartilage and upper tracheal rings (suspensory ligament of Berry). This fixation and investment of gland by pretracheal fascia are responsible for the gland moving up and down with larynx during swallowing [9].

Measurements:
Each lobe: Vertical – 5 cm, Anteroposterior – 2 cm, Transverse – 3 cm
Isthmus: Vertical and Transverse – 1.25 cm [10].

Vascular supply: The thyroid gland has rich blood supply. Each thyroid lobe is supplied by a superior and an inferior thyroid artery and drained by three veins [11].

The superior vascular pedicle: This contains superior thyroid artery, which is the 1^{st} branch of the external carotid, and its accompanying vein, which drains into the internal jugular vein. These enter upper pole of gland at its apex and branches to the front and back of the gland. These vessels are easily dealt with surgically, because the loose space between the two capsules is developed at the upper pole of the thyroid lobe and a ligature is placed close to the upper pole, to include both vessels and exclude the external laryngeal nerves.

The inferior thyroid artery: Arises from thyrocervical trunk, passes behind the carotid sheath and then runs transversly across the space between this and the thyroid gland to enter the deep surface of the gland as several separate branches close to tracheothyroid groove. These are close to recurrent laryngeal nerve and inferior parathyroid gland and hence inferior thyroid artery should be ligated in its transverse portion medial to the carotid sheath.

The inferior thyroid veins: These leave lower border of gland and pass through the loose fascial space to join the left brachiocephalic vein. They are fragile and require to be ligated singly.

The middle thyroid vein: It is short, thin walled vessel, leaving the middle of the gland and directly courses laterally to pass in front of or behind the carotid artery and enter the internal jugular vein. It is the 1st vessel encountered in thyroidectomy.

The thyroidea ima artery: Runs from brachiocephalic trunk in front of trachea and it is small and surgically irrelevant.

Blood supply of retrosternal extension comes from neck and hence its operative removal can always be conducted by cervical approach.

Innervation: The thyroid gland receives its innervation from the superior, middle and inferior cervical sympathetic ganglia. They are vasomotor in function [10].

Lymphatic drainage: Major: Middle and Lower jugular, Posterior triangle nodes. **Lesser**: Pretracheal and para tracheal, Superior mediastinal nodes. Because of wide distribution of nodes, standard radical neck dissection has been abandoned in favor of ‘regional’ node removal in cases of management of thyroid neoplasms [11, 12].

The important close surgical relations of the thyroid gland: These are the recurrent laryngeal nerves, the external laryngeal nerves and the parathyroid glands. These should be recognized and cared for during thyroid surgery [11].

The External laryngeal nerve: A branch of superior laryngeal nerve, descends on the fascia of the inferior pharyngeal constrictor is closely related to superior vascular pedicle of thyroid and leaves this at a variable height above the gland to travel medially to cricothyroid muscle. It is important for pitch of voice and its damage alters the voice.

The Recurrent laryngeal nerve: This innervates laryngeal musculature and provides sensory innervation to the glottic larynx. The RLN arises from the vagus at the level of subclavian artery on the right and at the level of aortic arch on the left. They are taken caudally during embryonal growth and thus run an upward course to reach vocal cords. They lie in TE groove and then bear a variable relationship to the branches of inferior thyroid artery before entering the larynx. In majority, the nerve is found easily in TE groove just below thyroid gland but its course may vary and it may be much more lateral. In 0.3% to 0.8% of cases, a non recurrent nerve has been reported, which arises from cervical portion of vagus at the level of larynx or thyroid gland. Vast majority of these occur on right side in conjunction with an anomalous retroesophageal subclavian artery Rare cases of left non recurrent laryngeal nerve have been reported [13].

Parathyroid glands: The parathyroid glands, most commonly 4 in number arise from 3rd branchial pouch (Inferior parathyroids) and 4th branchial pouch (Superior parathyroids). The superior parathyroids most consistently located (80%) within 1 cm superior to the intersection of the RLN and the ITA near the crico thyroid joint.

Inferior parathyroids are more variable in the location due to their longer migration with inferior thyroid and thymus. 45%-60% located inferior, lateral or posterior to inferior thyroid pole below the level of ITA. 26%-35% located immediately inferior to the inferior thyroid pole in association with cervical thymus. < 1% located in anterior mediastinum.

The blood supply to the parathyroids is predominantly by way of ITA. To preserve parathyroids along with blood supply, a medial to lateral dissection along the thyroid capsule plane is utilized. Parathyroids are small bean shaped structures with a yellow tan to caramel color [13].

Structure

The thyroid consists of large number of closed follicles (200-300 microm in diameter) lined by a single layer of epithelial cells. The follicles contain colloid. Colloid is made up of proteins, especially the iodinated glycoprotein, thyroglobulin, a 19S protein to which tyrosine residues is bound and in which thyroid hormone synthesis and storage takes place. The follicles are bound together in groups to form lobules each supplied by an end artery [14]. There are para follicular cells constituting < 2% of total cells which are scattered on outer aspects of the follicles and secrete calcitonin [9]. The thyroid gland is highly vascular and is the only endocrine gland to store its secretion outside the cells [9].

Physiology of thyroid gland

The principal hormones secreted by the thyroid are thyroxine (T_4) and triiodothyronine (T_3). T_3 is also formed in the peripheral tissues by deiodination of T_4. Both hormones are iodine containing amino acids. T_3 is more active. Naturally occurring forms are L–Isomers (levo isomers) [15]. The hormones are bound to thyroglobulin within the colloid. Synthesis in the thyroglobulin complex is controlled by several enzymes, in distinct steps.

- Tapping of inorganic iodide from the blood.
- Oxidation of iodide to iodine.
- Binding of iodine with tyrosine to from iodotyrosines.
- Coupling of mono-iodotyrosines and di-iodotyrosines to form T_3 and T_4

When hormones are required, the complex is resorbed into the cell and thyroglobulin is broken down. T_3 and T_4 are liberated and enter the blood, where they are bound to serum proteins: albumin, thyroxine binding globulin and thyroxine binding prealbumin. The small amount which remains free is biologically active. T_3 is the more important physiological hormone and is quick acting (within a few hours), where as T_4 acts slowly (4-14 days) [16].

Iodine metabolism: Iodine is a raw material essential for thyroid hormone synthesis. Minimum daily required intake to maintain normal thyroid function is 150 µg. Normal plasma Iodine level is 0.3 µg/dl. Normal diet contains about 500mcg Iodine [15].

Thyroid hormones

Normal levels: T_3 - 70-190ng/dl (1.1 – 2.9 nmol/L), T4 - 5-12 mcg/dl (64 –154 nmol/L) [17]
Normal daily secretion: T_3 - 4 µg (7 nmol), T_4 - 80 µg (103 nmol) [15]

Mechanism of action

Thyroid hormones enter cells and T_3 binds to thyroid receptors in the nucleus. T_4 can also bind, but not as avidly. The hormone-receptor complex then binds to DNA via Zinc fingers and alters the expression of a variety of different genes that code for enzymes which regulate cell function [15]. Physiologic effects of thyroid hormones are as per **Table – 1** [15].

Regulation of thyroid secretion [15]

Thyroid function is regulated primarily by variations in the circulating level of pituitary thyroid stimulating hormone (TSH). In addition to TSH receptors the thyroid cells contain receptors for IGF-1, EGF, gamma interferon and TNF-alfa, growth factors. IGF – 1 and EGF promote growth whereas gamma interferon and TNF-alfa inhibit growth.

Thyroid stimulating hormone: Glycoprotein secreted by anterior pituitary.

Table – 1: Physiologic effects of thyroid hormones [15]

Target tissue	Effect	Mechanism
Heart	Chronotropic, Inotropic	Increase number of beta-adrenergic receptors. Enhance response to circulating catecholamines. Increase proportion of a myosin heavy chain
Adipose tissue	Catabolic	Stimulate lipolysis
Muscle	Catabolic	Increase protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increase rate of carbohydrate absorption
Lipoprotein	Metabolic	Stimulate formation of LDL receptors
Other	Calorigenic	Stimulate oxygen consumption by metabolically active tissues (except testes, uterus, lymphnodes, spleen, anterior pituitary). Increase metabolic rate.

Normal level: 0.4-5.0 microIU/ml (0.4-5.0mu/L) [17], Normal daily secretion is 110 µg. Half life is 60 minutes.TSH secretion increased by TRH and by cold and decreased by increased free T_4 and T_3 and by stress and heat.

Effects of TSH on thyroid: Increases iodide binding**,** Increases synthesis T_3, T_4 and iodotyrosines**,** Increases secretion of thyroglobulin into colloid and also endocytosis of colloid, Blood flow increases, the cells hypertrophy and weight of gland increases.

The pituitary thyroid Axis

Secretion of TSH depends upon the level of circulating thyroid hormones and is modified in a classic negative feedback manner.

Conclusion

Thyroid is an important endocrine organ. The knowledge of embryology, anatomy especially relations to parathyroids and recurrent laryngeal nerve and their variations are important to thyroid surgeon. Iodine is needed for thyroxine synthesis which plays an important role in body metabolism.

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