PROFILE OF EUTHYROID GOITERS IN CHILDREN AND THE ROLE OF LEVOTHYROXINE

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CERTIFICATE

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DECLARATION

I declare that this dissertation entitled **"PROFILE OF EUTHYROID GOITERS IN CHILDREN AND THE ROLE OF LEVOTHYROXINE"** has been conducted by me at the Institute of Child Health and Hospital for Children, under the guidance and supervision of my unit chief **Prof. Dr. K. R. Ravindaran, M.D., DCH., Ph.D.,** and the head of the department of Endocrinology, **Prof. Dr. P. G. Sundararaman, M.D., DCH., D.M., (Endocrinology).** It is submitted in part of fulfillment of the award of the degree of M.D (Pediatrics) for the March 2007 examination to be held under the Tamil Nadu Dr. M. G. R. Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

(Dr. MOHAMED SAJJID)

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CONTENTS

INTRODUCTION

ANATOMY OF THE THYROID GLAND[1]

The Thyroid Gland (Glandula Thyreiodea; Thyroid Body) — the thyroid gland is a highly vascular organ, situated at the front and sides of the neck; it consists of right and left lobes connected across the middle line by a narrow portion, the isthmus. Its weight is somewhat variable, but is usually about 30 grams. It is slightly heavier in the female, in whom it becomes enlarged during menstruation and pregnancy

The lobes (lobuli gl. thyreoideæ) are conical in shape, the apex of each being directed upward and lateralward as far as the junction of the middle with the lower third of the thyroid cartilage; the base looks downward, and is on a level with the fifth or sixth tracheal ring. Each lobe is about 5 cm. long; its greatest width is about 3 cm. and its thickness about 2 cm. The lateral or superficial surface is convex, and covered by the skin, the superficial and deep fasciæ, the Sternocleidomastoideus, the superior belly of the Omohyoideus, the Sternohyoideus and Sternothyreoideus, and beneath the last muscle by the pretracheal layer of the deep fascia, which forms a capsule for the

gland. The deep or medial surface is moulded over the underlying structures, viz., the thyroid and cricoid cartilages, the trachea, the Constrictor pharyngis inferior and posterior part of the Cricothyreoideus, the esophagus (particularly on the left side of the neck), the superior and inferior thyroid arteries, and the recurrent nerves. The anterior border is thin, and inclines obliquely from above downward toward the middle line of the neck, while the posterior border is thick and overlaps the common carotid artery, and, as a rule, the parathyroids.

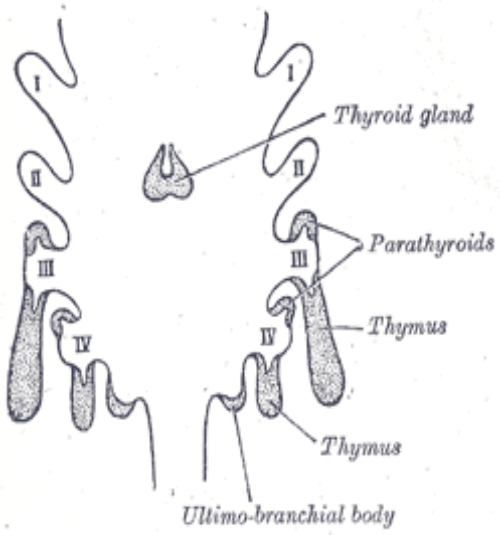
The isthmus (isthmus gl. thyreoidea) connects together the lower thirds of the lobes; it measures about 1.25 cm. in breadth, and the same in depth, and usually covers the second and third rings of the trachea. Its situation and size present, however, many variations. In the middle line of the neck it is covered by the skin and fascia, and close to the middle line, on either side, by the Sternothyreoideus. Across its upper border runs an anastomotic branch uniting the two superior thyroid arteries; at its lower border are the inferior thyroid veins. Sometimes the isthmus is altogether wanting.

A third lobe, of conical shape, called the pyramidal lobe, frequently arises from the upper part of the isthmus, or from the adjacent portion of either lobe, but most commonly the left, and ascends as far as

the hyoid bone. It is occasionally quite detached, or may be divided into two or more parts.

A fibrous or muscular band is sometimes found attached, above, to the body of the hyoid bone, and below to the isthmus of the gland, or its pyramidal lobe. When muscular, it is termed the Levator glandulæ thyreoideæ.

Small detached portions of thyroid tissue are sometimes found in the vicinity of the lateral lobes or above the isthmus; they are called accessory thyroid glands (glandulæ thyreoideæ accessoriæ).

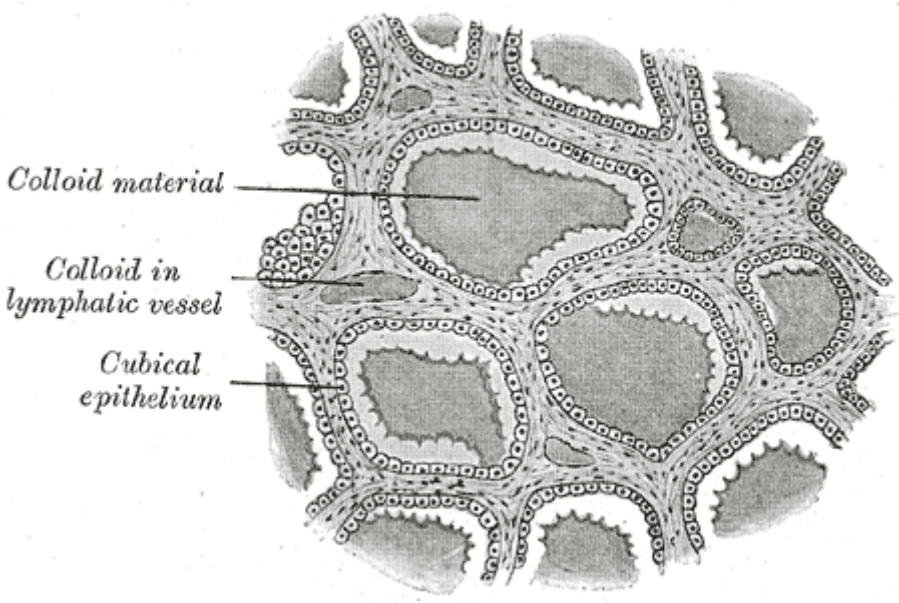


Scheme showing development of branchial epithelial bodies

I, II, III, IV. Branchial pouches

Development.—The thyroid gland is developed from a median diverticulum which appears about the fourth week on the summit of the tuberculum impar, but later is found in the furrow immediately behind the tuberculum. It grows downward and backward as a tubular duct, which bifurcates and subsequently subdivides into a series of cellular cords, from which the isthmus and lateral lobes of the thyroid gland are developed. The ultimo-branchial bodies from the fifth pharyngeal pouches are enveloped by the lateral lobes of the thyroid gland; they give rise to the calcitonin-producing cells—also called parafollicular cells—of the thyroid gland. The connection of the diverticulum with the pharynx is termed the thyroglossal duct; its continuity is subsequently interrupted, and it undergoes degeneration, its upper end being represented by the foramen cecum of the tongue, and its lower by the pyramidal lobe of the thyroid gland

Structure.—The thyroid gland is invested by a thin capsule of connective tissue, which projects into its substance and imperfectly divides it into masses of irregular form and size. When the organ is cut into, it is of a brownish-red color, and is seen to be made up of a number of closed vesicles, containing a yellow glairy fluid, and separated from each other by intermediate connective tissue



Section of thyroid gland of sheep. X 160.

The vesicles of the thyroid of the adult animal are generally closed spherical sacs; but in some young animals, e. g., young dogs, the vesicles are more or less tubular and branched. This appearance is supposed to be due to the mode of growth of the gland, and merely indicates that an increase in the number of vesicles is taking place. Each vesicle is lined by a single layer of cubical epithelium. There does not appear to be a basement membrane, so that the epithelial cells are in direct contact with the connective-tissue reticulum which supports the acini. The vesicles are of various sizes and shapes, and contain as a normal product a viscid, homogeneous, semifluid, slightly yellowish, colloid material; red corpuscles are found in it in various stages of

disintegration and decolorization, the yellow tinge being probably due to the hemoglobin, which is thus set free from the colored corpuscles. The colloid material contains an iodine compound, iodothyrin, and is readily stained by eosin. The thyroid gland prepares and secretes into the vascular channels the hormones thyroxine and triiodothyronine, formed under normal conditions in the outer pole of the cell and excreted from it directly without passing by the indirect route through the follicular cavity. In addition to this direct mode of secretion there is an indirect mode which consists in the condensation of the secretion into the form of droplets, having high content of solids, and the extension of these droplets into the follicular cavity. These droplets are formed in the same zone of the cell as that in which the primary or direct secretion is formed.

This internal secretion of the thyroid contains the hormones thyroxine and triiodothyronine which act as a chemical stimulus to other tissues, increasing their metabolism.

Vessels and Nerves.—The arteries supplying the thyroid gland are the superior and inferior thyroids and sometimes an additional branch (thyroidea ima) from the innominate artery or the arch of the aorta, which ascends upon the front of the trachea. The arteries are remarkable

for their large size and frequent anastomoses. The veins form a plexus on the surface of the gland and on the front of the trachea; from this plexus the superior, middle, and inferior thyroid veins arise; the superior and middle end in the internal jugular, the inferior in the innominate vein. The capillary blood vessels form a dense plexus in the connective tissue around the vesicles, between the epithelium of the vesicles and the endothelium of the lymphatics, which surround a greater or smaller part of the circumference of the vesicle. The lymphatic vessels run in the interlobular connective tissue, not uncommonly surrounding the arteries which they accompany, and communicate with a net-work in the capsule of the gland; they may contain colloid material. They end in the thoracic and right lymphatic trunks. The nerves are derived from the middle and inferior cervical ganglia of the sympathetic.

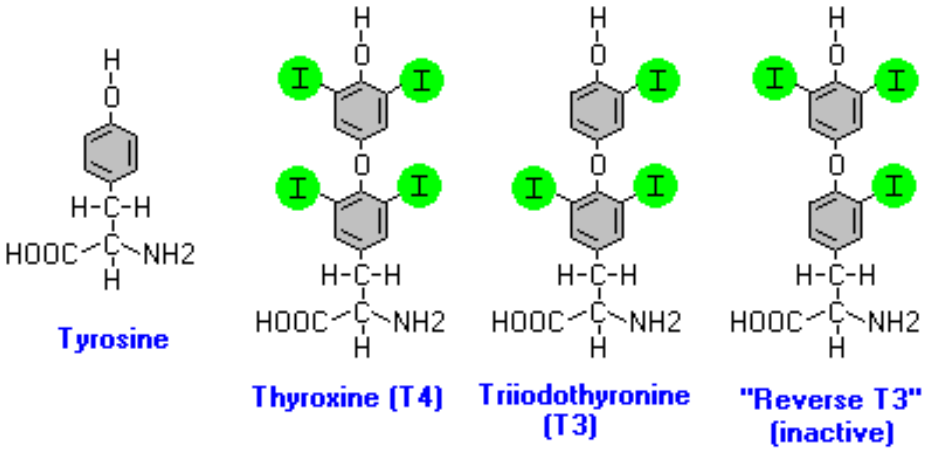
FUNCTION OF THE THYROID GLAND[2]

Chemistry of Thyroid Hormones

Thyroid hormones are derivatives of the the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:

- thyroxine (also known as T4 or L-3,5,3',5'-tetraiodothyronine)
- triiodotyronine (T3 or L-3,5,3'-triiodothyronine)

As shown in the following diagram, the thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or five positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3,3',5'-T3) is such an example.



Large majority of the thyroid hormone secreted from the thyroid gland is T4, but T3 is the considerably more active hormone. Although some T3 is also secreted, the bulk of the T3 is derived by deiodination of T4 in peripheral tissues, especially liver and kidney. Deiodination of T4 also yields reverse T3, a molecule with no known metabolic activity.

Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is thyroxine-binding globulin, a glycoprotein synthesized in the liver. Two other carriers of import are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.

Synthesis and Secretion of Thyroid Hormones

Thyroid hormones are synthesized by mechanisms fundamentally different from what is seen in other endocrine systems. Thyroid follicles serve as both factory and warehouse for production of thyroid hormones.

The entire synthetic process occurs in three major steps, which are, at least in some ways, analogous to those used in the manufacture of integrated circuits (ICs):

- Production and accumulation of the raw materials (in the case of ICs, a large wafer of doped silicon)
- Fabrication or synthesis of the hormones on a backbone or scaffold of precursor (etching several ICs on the silicon wafer)
- Release of the free hormones from the scaffold and secretion into blood (cutting individual ICs out of the larger wafer and distributing them)

The recipe for making thyroid hormones calls for two principle raw materials:

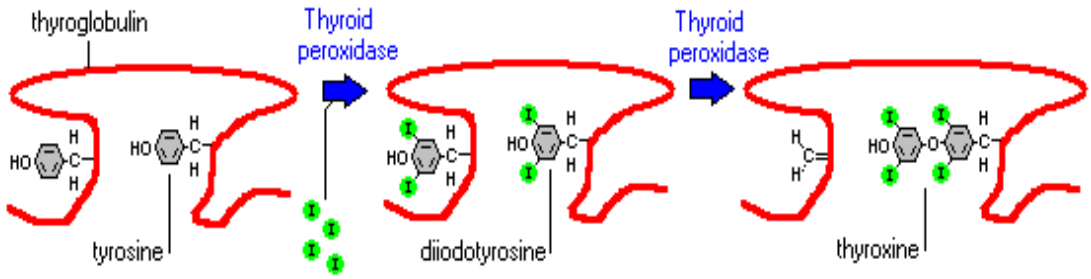
- Tyrosines are provided from a large glycoprotein scaffold called thyroglobulin, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.

- Iodine, or more accurately iodide (I^-), is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "iodine trap". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

1. Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").

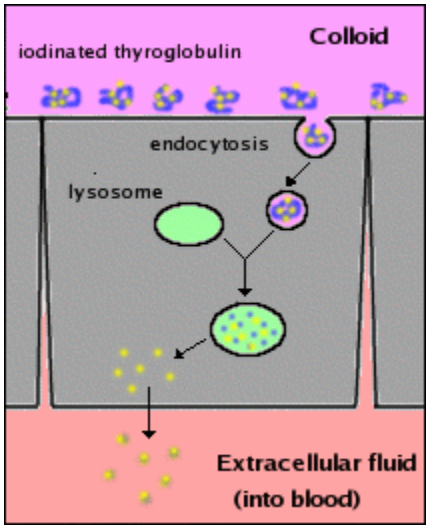
2. Synthesis of thyroxine or triiodothyronine from two iodotyrosines (also known as “coupling of iodotyrosines”)



Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.
- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobluin, thereby liberating free thyroid hormones.
- Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.



Control of Thyroid Hormone Synthesis and Secretion

Each of the processes described above appears to be stimulated by thyroid-stimulating hormone from the anterior pituitary gland. Binding of TSH to its receptors on thyroid epithelial cells stimulates synthesis of the iodine transporter, thyroid peroxidase and thyroglobulin.

The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

MECHANISM OF ACTION AND PHYSIOLOGIC EFFECTS OF THYROID HORMONES IN THE BODY

Thyroid Hormone Receptors and Mechanism of Action

Receptors for thyroid hormones are intracellular DNA-binding proteins that function as hormone-responsive transcription factors, very similar conceptually to the receptors for steroid hormones.

Thyroid hormones enter cells through membrane transporter proteins. A number of plasma membrane transporters have been identified, some of which require ATP hydrolysis; the relative importance of different carrier systems is not yet clear and may differ among tissues. Once inside the nucleus, the hormone binds its receptor, and the hormone-receptor complex interacts with specific sequences of DNA in the promoters of responsive genes. The effect of the hormone-receptor complex binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes.

For the purpose of illustration, consider one mechanism by which thyroid hormones increase the strength of contraction of the heart. Cardiac contractility depends, in part, on the relative ratio of different types of myosin proteins in cardiac muscle. Transcription of some

myosin genes is stimulated by thyroid hormones, while transcription of others in inhibited. The net effect is to alter the ratio toward increased contractility.

Physiologic Effects of Thyroid Hormones

It is likely that all cells in the body are targets for thyroid hormones. While not strictly necessary for life, thyroid hormones have profound effects on many "big time" physiologic processes, such as development, growth and metabolism. Many of the effects of thyroid hormone have been delineated by study of deficiency and excess states, as discussed briefly below.

Metabolism: Thyroid hormones stimulate diverse metabolic activities of most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is to increase body heat production, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis. By way of analogy, the action of thyroid hormones is akin to blowing on a smouldering fire. A few examples of specific metabolic effects of thyroid hormones include:

- Lipid metabolism: Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in

plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels - one diagnostic indiction of hypothyroidism is increased blood cholesterol concentration.

- Carbohydrate metabolism: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.

Growth: Thyroid hormones are clearly necessary for normal growth in children and young animals, as evidenced by the growth-retardation observed in thyroid deficiency. Not surprisingly, the growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indiction that complex physiologic processes like growth depend upon multiple endocrine controls.

Development: A classical experiment in endocrinology was the demonstration that tadpoles deprived of thyroid hormone failed to undergo metamorphosis into frogs. Of critical importance in mammals is the fact that normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.

Other Effects: As mentioned above, there do not seem to be organs and tissues that are not affected by thyroid hormones. A few additional, well-documented effects of thyroid hormones include:

- Cardiovascular system: Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs.
- Central nervous system: Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone, and the individual tends to feel mentally sluggish, while too much induces anxiety and nervousness.
- Reproductive system: Normal reproductive behavior and physiology is dependent on having essentially normal levels of thyroid hormone. Hypothyroidism in particular is commonly associated with infertility.

Thyroid Disease States

Disease is associated with both inadequate production and overproduction of thyroid hormones. Both types of disease are relatively common afflictions of man and animals.

Hypothyroidism is the result from any condition that results in thyroid hormone deficiency. Two well-known examples include:

- **Iodine deficiency**: Iodide is absolutely necessary for production of thyroid hormones; without adequate iodine intake, thyroid hormones cannot be synthesized. Historically, this problem was seen particularly in areas with iodine-deficient soils, and frank iodine deficiency has been virtually eliminated by iodine supplementation of salt.

- **Primary thyroid disease**: Inflammatory diseases of the thyroid that destroy parts of the gland are clearly an important cause of hypothyroidism.

Common symptoms of hypothyroidism arising after early childhood include lethargy, fatigue, cold-intolerance, weakness, hair loss and reproductive failure. If these signs are severe, the clinical condition is called myxedema. In the case of iodide deficiency, the thyroid becomes inordinantly large and is called a goiter.

The most severe and devastating form of hypothyroidism is seen in young children with congenital thyroid deficiency. If that condition is not corrected by supplemental therapy soon after birth, the child will

suffer from cretinism, a form of irreversible growth and mental retardation.

Most cases of hypothyroidism are readily treated by oral administration of synthetic thyroid hormone. In times past, consumption of dessicated animal thyroid gland was used for the same purpose.

Hyperthyroidism results from secretion of thyroid hormones. In most species, this condition is less common than hypothyroidism. In humans the most common form of hyperthyroidism is Graves disease, an immune disease in which autoantibodies bind to and activate the thyroid-stimulating hormone receptor, leading to continual stimulation of thyroid hormone synthesis. Another interesting, but rare cause of hyperthyroidism is so-called hamburger thyrotoxicosis.

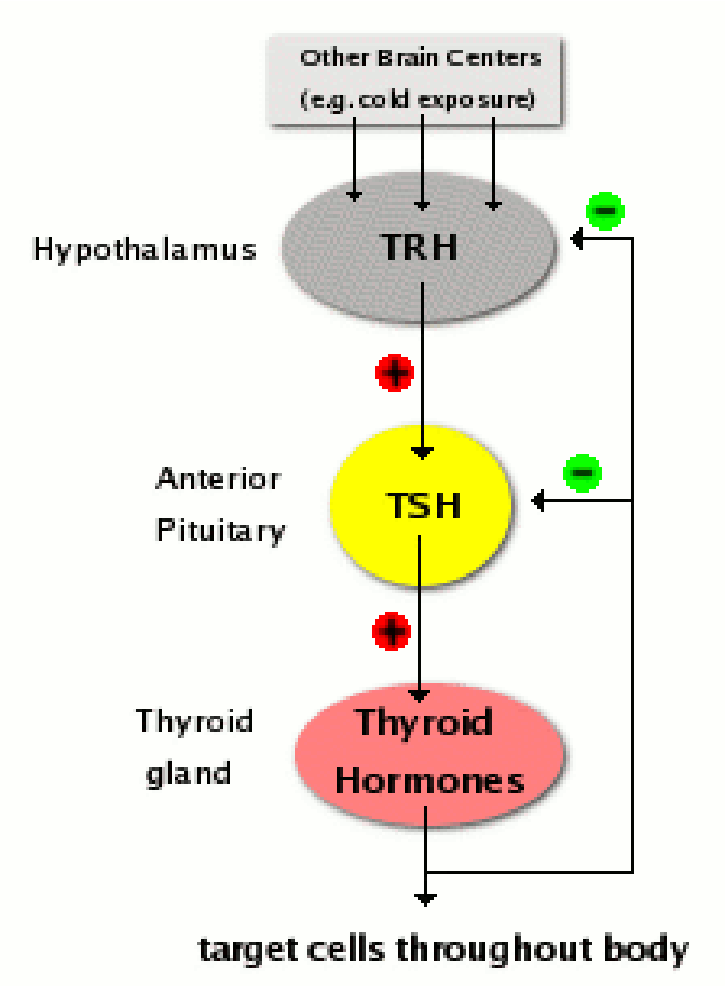
Common signs of hyperthyroidism are basically the opposite of those seen in hypothyroidism, and include nervousness, insomnia, high heart rate, eye disease and anxiety. Graves disease is commonly treated with anti-thyroid drugs (e.g. propylthiourea, methimazole), which suppress synthesis of thyroid hormones primarily by interfering with iodination of thyroglobulin by thyroid peroxidase.

The chief stimulator of thyroid hormone synthesis is thyroid-stimulating hormone from the anterior pituitary. Binding of TSH to receptors on thyroid epithelial cells seems to enhance all of the processes necessary for synthesis of thyroid hormones, including synthesis of the iodide transporter, thyroid peroxidase and thyroglobulin.

The magnitude of the TSH signal also sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis, and hence, thyroid hormone release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

The thyroid gland is part of the hypothalamic-pituitary-thyroid axis, and control of thyroid hormone secretion is exerted by classical negative feedback, as depicted in the diagram. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates TSH from the pituitary, which stimulates thyroid hormone release. As blood concentrations of thyroid hormones increase, they inhibit both TSH and TRH, leading to "shutdown" of thyroid epithelial cells. Later, when blood levels of thyroid hormone have decayed, the negative feedback signal fades, and the system wakes up again.

A number of other factors have been shown to influence thyroid hormone secretion. In rodents and young children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release. This makes sense considering the known ability of thyroid hormones to spark body heat production.



The hypothalamic-pituitary-thyroid axis

GOITER[3]

A swollen thyroid is called a goiter. Most goiters are caused by not enough iodine in the diet. Iodine is a substance found in shellfish and iodized salt.

Goiter is defined as an enlargement of the THYROID GLAND that may increase from about 20 grams to hundreds of grams in human adults. Goiter is observed in individuals with normal thyroid function (EUTHYROIDISM), thyroid deficiency (HYPOTHYROIDISM), or hormone overproduction (HYPERTHYROIDISM). Goiter may be congenital or acquired, sporadic or endemic (GOITER, ENDEMIC).

Abnormally enlarged thyroid gland; can result from under-production or over-production of hormone or from a deficiency of iodine in the diet

A goitre (or goiter) (Latin struma), also called a bronchocele, is a swelling in the neck (just below adam's apple or larynx) due to an enlarged thyroid gland. They are classified in different ways:

A "diffuse goitre" is a goitre that has spread through all of the thyroid (and is contrasted with a "simple goitre", "single thyroid nodule" and "multinodular goitre").

"Toxic goitre" refers to goitre with hyperthyroidism. These are derived from inflammation, neoplasm, and some kinds of activating autoimmune disease (Grave's disease). "Nontoxic goitre" (associated with normal or low thyroid levels) refers to all other types (such as that caused by lithium or certain other autoimmune diseases).

Following is a list of underlying conditions that could possibly cause Goiter includes:

Iodine deficiency

Hypothyroidism

Hyperthyroidism - goiters can arise from both increased and reduced thyroid hormones.

Autoimmune thyroid disease

Graves' disease

Hashimoto's thyroiditis

Other Thyroiditis

Thyroid cyst

Thyroid cancer

Puberty - can cause simple goiter

Pregnancy - can cause simple goiter

Inborn errors of metabolism causing defects in biosynthesis of thyroid hormones

Exposure to radiation

Deposition diseases

Thyroid hormone resistance

Goitrogenic foods - e.g. turnips

Medications - e.g. lithium

Some of the symptoms of Goiter include:

Swollen front of the neck

Physical symptoms due to goiter

Protruding eyes

Treatments for Goiter include:

Iodine in diet - if goiter is caused by iodine deficiency

Thyroid replacement therapy

Thyroxine

Thyroidectomy - mainly for nodular goiter

Antithyroid drugs – in Graves' disease

EUTHYROID GOITER[4, 5]

Euthyroid goiter which is also known as Simple goiter, Nontoxic diffuse or nodular goiter occurs due to an enlargement of the thyroid gland but without clinical or laboratory evidence of thyroid dysfunction.[4, 5]

Endemic goiter is defined as thyroid enlargement that occurs in more than 10% of a population, and sporadic goiter is a result of environmental or genetic factors that do not affect the general population.

A simple goiter occurs when the thyroid gland is unable to meet the metabolic demands of the body through sufficient hormone production. The thyroid gland compensates by enlarging, which usually overcomes mild deficiencies of thyroid hormone.

Pathophysiology

The histopathology varies with etiology and age of the goiter. Initially, uniform follicular epithelial hyperplasia (diffuse goiter) is present with an increase in thyroid mass. As the disorder persists, the thyroid architecture loses uniformity, with the development of areas of involution and fibrosis interspersed with areas of focal hyperplasia. This

process results in multiple nodules (multinodular goiter). On nuclear scintigraphy, some nodules are hot, with high isotope uptake (autonomous) or cold, with low isotope uptake, compared with the normal thyroid tissue. The development of nodules correlates with the development of functional autonomy and reduction in thyroid-stimulating hormone (TSH) levels. Clinically, the natural history of a nontoxic goiter is growth, nodule production, and functional autonomy resulting in thyrotoxicosis in a minority of patients.

Race

No convincing epidemiological studies suggest that race plays an important role in the development of nontoxic goiter. Generally, the lower socioeconomic conditions in nonindustrialized countries resulting in iodine deficiency have a more important role than race in the development of a goiter.

Sex

Diffuse and nodular goiter is more common in women than in men. According to the best estimate, 1.2-4.3 women have goiter for every man who has goiter.

Age

Sporadic goiter from dyshormonogenesis, a genetic error in proteins that are necessary for thyroid hormone synthesis, occurs during childhood. Endemic goiter due to iodine deficiency occurs during childhood and continues to increase in size with age. Other causes of sporadic goiter rarely occur before puberty and do not have a peak age of occurrence. Thyroid nodules increase in incidence with age.

Causes

Most common worldwide cause of endemic nontoxic goiter is iodine deficiency. However, in patients with sporadic goiter, the cause is usually unknown. Nontoxic goiters have many etiologies, including the following:

- Iodine deficiency: Goiter formation occurs with moderately deficient iodine intake of less than 50 mcg/d. Severe iodine deficiency associated with intake of less than 25 mcg/d is associated with hypothyroidism and cretinism.
- Iodine excess: Goiter formation due to iodine excess is rare and usually occurs in the setting of preexisting autoimmune thyroid disease.

- Goitrogens
    - Drugs - Propylthiouracil, lithium, phenylbutazone, aminoglutethimide, iodine-containing expectorants
    - Environmental agents - Phenolic and phthalate ester derivatives and resorcinol found downstream of coal and shale mines
    - Foods - Vegetables of the genus Brassica (eg, cabbage, turnips, brussels sprouts, rutabagas), seaweed, millet, cassava, and goitrin in grass and weeds
- Dyshormonogenesis: A defect in the thyroid hormone biosynthetic pathway is inherited.
- Childhood head and neck radiation: Radiation exposure during childhood results in benign and malignant nodules.

WHO GRADING OF GOITERS [6, 7]

Grade 0:

No goiter

Grade Ia:

Goiter detectable only by palpation and not visible when neck fully extended.

Grade Ib:

Goiter visible when neck fully extended and palpable.

Grade II:

Goiter visible when neck in natural position

Grade III:

Very large goiter visible from a considerable distance.

Grade IV:

Monstrous goiter.

WHO GRADING OF IODINE NUTRITION[8]

Epidemiological criteria for assessing iodine nutrition based on median Urinary Iodine (UI) concentrations in school-age children		
Median UI(µg/l)	Iodine intake	Iodine nutrition
<20	insufficient	Severe iodine deficiency
20-49	insufficient	Moderate iodine deficiency
50-99	insufficient	Mild iodine deficiency
100-199	Adequate	Optimal iodine nutrition
200-299	More than adequate	Risk of iodine-induced hyperthyroidism within 5 - 10 years following introduction of iodized salt in susceptible groups
=300	Excessive	Risk of adverse health consequences (iodine induced hyperthyroidism, auto-immune thyroid diseases)

REVIEW OF LITERATURE

1. Suppressive therapy with levothyroxine for euthyroid diffuse and nodular goiter[9]

Gullu S, Gurses MA, Baskal N, Uysal AR, Kamel AN, Erdogan G.

Department of Endocrinology and Metabolic Diseases, Ankara University Medical School, Turkey.

Endocr J. 1999 Feb;46(1):221-6.

In this study, 35 patients with euthyroid diffuse goiter and 35 patients with euthyroid nodular goiter were treated with Levothyroxine (L-T4) for six months. The mean decrease of thyroid volume at six months was about 20% (20.4 +/- 8.8 ml vs. 16 +/- 7.9 ml, P<0.001) in patients with diffuse goiter. A reduction of 50% or more in volume was detected in 31% (11/35) of the nodular goiter patients. 54% of the patients (19/35) showed a 10-49% decrease in nodule volume. Five of the patients were found to be insensitive to the therapy. Free T4 and free T3 levels increased and TSH levels decreased with L-T4 treatment in all patient groups. Patients with higher TSH levels (within normal limits) showed more volume reduction in the diffuse goiter group.

CONCLUSION: Suppressive thyroxine treatment is effective in reducing the size of the goiter, and nodules.

2. Efficacy of L-thyroxine (L-T4) therapy on the volume of the thyroid gland and nodules in patients with euthyroid nodular goiter[10]

Diacinti D, Salabe GB, Olivieri A, D'Erasmo E, Tomei E,

Lotz-Salabe H, De Martinis C.

Istituto di Clinica Medica II, Universita di Roma, La Sapienza.

Minerva Med. 1992 Nov;83(11):745-51.

The efficacy of treatment with TSH suppressive doses of L-thyroxine was evaluated by echography in 35 patients with euthyroid nodular goiter. Patients have been subdivided in two groups comparable for sex age and size of the goiter. Sixteen patients were treated for nine months with suppressive doses of thyroxine and nineteen were followed without therapy as control. Patients in treatment were then followed up for additional 9 months without therapy. The mean decrease of thyroid volume at nine months was 25% (27 +/- 10 ml vs 20 +/- 8 ml; $p < 0.01$). After discontinuation of treatment thyroid volume increased and had returned to base line values after nine months of follow up. In the control group mean thyroid volume had increased by 17.7% at nine months (28 +/- 17 vs 33 +/- 19 ml; $p < 0.001$). Thyroid nodules in

response to thyroid hormone treatment showed a variable behaviour: 30.7% (4/13) of the nodules responded to the therapy with a reduction > to 25% at the ninth month; the remaining nodules were insensitive to the therapy.

CONCLUSION: Suppressive thyroxine treatment is effective in reducing the goiter, nodules instead are only in part sensitive to the treatment. Thyroxine therapy of euthyroid nodular goiter must be followed for long term since upon thyroxine discontinuation there is a prompt reappearance of the goiter.

3. Ultrasound scanning assessment of L-thyroxine treatment effectiveness in a group of children with diffuse goiter[11]

Regalbuto C, Belfiore A, Giuffrida D, Ippolito A, Motta RM, Sava L.

Cattedra di Endocrinologia, University of Catania, Ospedale Garibaldi, Italy.

J Endocrinol Invest. 1991 Sep;14(8):675-8

In this prospectic study the effectiveness of one-year L-thyroxine treatment in a group of children with nontoxic diffuse goiter coming from an area with low iodine intake was evaluated by measuring the thyroid volume by ultrasound as ultrasound scanning is an accurate and objective method to assess thyroid volume and therefore useful to evaluate the effectiveness of L-thyroxine treatment in reducing goiter size, especially in children where clinical evaluation is inaccurate. 11 children (7 females, 4 males), age range 9-14 years were examined. At clinical examination, 6 patients had a goiter classified Ia (according to WHO criteria), 4 had a class Ib and only 1 had a class II goiter. In order to achieve an accurate goiter evaluation, the thyroid volume was determined by ultrasonic scanning with a 5 MHz linear probe before and after treatment. Patients were given a dose of L-thyroxine (1.5-2.0 micrograms/kg/day) in order to significantly reduce serum TSH levels

(from 1.8 +/- 0.6 to 0.8 +/- 0.5 mU/l, mean +/- SD). Patients were reexamined at 12 months of therapy and again at 10 months after therapy withdrawal. A significant reduction of the goiter volume (greater than 20%) was obtained in 6/11 (54%) patients, although serum TSH levels were fully suppressed only in one. The mean goiter size reduction in "responders" was -31.2 +/- 9.3% (m +/- SE). After therapy withdrawal goiter size increased in the majority of cases (in 4/11, greater than 20%).

CONCLUSION: L-thyroxine treatment is effective in reducing goiter size in the majority of children with a diffuse goiter.

4. Levothyroxine suppressive therapy in the medical management of nontoxic benign multinodular goiter[12]

Celani MF

Department of Medicine, Castelfranco Emilia Hospital, Modena, Italy.

Exp Clin Endocrinol. 1993;101(5):326-32.

The aim of this investigation was to evaluate the efficacy of levothyroxine suppressive therapy in the medical management of nontoxic benign multinodular goiter. 104 patients with multiple (2 to 5, mean = 2.5 +/- 0.7), solid (96%) or predominantly solid (4%), nonfunctional (68%) or hypofunctional (32%) thyroid nodules were studied. The benign (colloid) nature of 94% of the nodules was confirmed by fine-needle aspiration biopsy. All the patients received suppressive (2.2 micrograms per Kg body weight) daily oral doses of levothyroxine for 6 months. To confirm the effectiveness of the suppressive therapy, TSH levels were measured by an ultrasensitive immunometric assay at 3 and 6 month of treatment. For each patient, the volume of each nodule before and after levothyroxine therapy was evaluated by high-resolution ultrasonography. After 3 and 6 months of treatment, TSH levels were suppressed (lower than 0.1 mIU/l) in 75

patients and detectable in 29. At the end of the study, the volume of all the nodules was decreased by 50% or more (responder group) in 20/75 (27%) of the patients with suppressed TSH levels, and in 3/29 (10%) of those with detectable TSH values. In the latter group the proportion of patients in which one or more nodule(s) showed an increase in volume (48%) was significantly higher ($p < 0.0005$) than in patients with suppressed TSH (29%).

CONCLUSION: An effective TSH suppressive therapy is an useful tool in the treatment of nontoxic benign multinodular goiter.

5. The effect of treatment with levothyroxine or iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients[13]

Wilders-Truschnig MM, Warnkross H, Leb G, Langsteger W, Eber O, Tiran A, Dobnig H, Passath A, Lanzer G, Drexhage HA.

Department of Medicine, Karl Franzens University, Graz, Austria.

Clin Endocrinol (Oxf). 1993 Sep;39(3):281-6.

The effect of levothyroxine or iodine on thyroid size and on thyroid growth stimulating immunoglobulins in endemic goitre patients was assessed in thirty seven euthyroid patients. Levothyroxine or iodine was given orally in an open randomized prospective study (100 and 200 micrograms respectively). Thyroid size, thyroid growth stimulating immunoglobulins (mitosis arrest assay), basal TSH, free T3, free T4, thyroid anti-microsomal antibodies, antithyroglobulin antibodies, anti-TSH receptor antibodies and urinary iodine excretion were measured. Thyroid size decreased significantly in both groups, in the levothyroxine group more than in the iodine treated group. Thyroid growth stimulating immunoglobulins levels also decreased significantly in both groups. Between groups there was no statistically significant difference. A statistically significant correlation between thyroid growth stimulating

immunoglobulins reduction profiles and goitre size reduction could not be established. TSH levels became suppressed in the levothyroxine group while the T4 values rose; in the iodine treated group TSH levels stayed constant as did T4. None of the patients developed thyroid microsomal or thyroglobulin auto-antibodies and/or hyperthyroidism during the treatment.

CONCLUSION: Levothyroxine as well as iodine was effective in reducing thyroid size as well as thyroid growth stimulating immunoglobulins levels in endemic goitre patients. Since in both groups TSH levels were not related to thyroid size reduction, other factors than TSH suppression must be responsible for the observed thyroid size reduction. Iodine itself by virtue of its antiproliferative action on thyrocytes may have had a direct action on the goitre reduction during iodine treatment; however, the levothyroxine dose, containing less iodine, had a similar effect.

6. Treatment of juvenile goiter with levothyroxine, iodide or a combination of both: the value of ultrasound grey-scale analysis[14]

Einenkel D, Bauch KH, Benker G.

Department of Pediatrics, Hospital Erlabrunn, Germany.

Acta Endocrinol (Copenh). 1992 Oct;127(4):301-6

The effects of oral iodide, levothyroxine and of iodide and levothyroxine in combination were studied in three groups of 30 children, age 13-15 years, with euthyroid goitre. As endpoints of this study, we used thyroid volume reduction, thyroid hormones, thyrotropin and thyroid grey-scale histograms by computerized analysis. The three groups were well matched with respect to mean age, body weight and pretreatment thyroid volumes and thyroid hormones. Mean urinary iodide excretion before treatment was in the range of 30 micrograms/g creatinine, since the study was conducted in an iodine-deficient area. All three treatment regimens led to significant reductions in thyroid volume within one month. After six months on 100 micrograms of levothyroxine, thyroid volume had decreased from 14.1 +/- 4.2 ml to 8.3 +/- 2.6 ml (mean +/- SD); on 150 micrograms of iodide, from 18.5 +/- 6.2 ml to 8.8 +/- 2.7 ml; and on 100 micrograms of iodide plus 50 micrograms of levothyroxine, from 17.2 +/- 3.1 ml to 8.3 +/- 2.0 ml.

When treatment was discontinued for three months, or the dosage reduced, thyroid volume increased again in the levothyroxine (to 11.3 +/- 2.5 ml) but not in the iodide group. Grey-scale values (by ultrasound, computer-aided estimation) after nine months were significantly different between the three treatment groups; no change was observed with levothyroxine, but after 150 micrograms of iodide as well as after combined treatment with levothyroxine and iodide there were marked decreases of grey-scale values; this is interpreted as reflecting a decrease in follicle size and colloid content of the thyroid which takes place after iodide supplementation.

CONCLUSION: Iodide is the treatment of choice for iodine deficiency euthyroid goiters.

JUSTIFICATION OF THE STUDY

- The efficacy of levothyroxine suppressive therapy in the treatment of euthyroid goiters is controversial

- The literature contains conflicting reports, **for and against levothyroxine**, regarding the treatment of euthyroid goiters

For:

- According to one school of thought mild thyroid failure and subtle sub clinical hypothyroidism may be present in Euthyroid goiters as evidenced by high TSH levels. Without treatment, mild thyroid failure may develop into overt hypothyroidism at a rate of 5-26% per year. Hence treatment with thyroxine therapy is a must.[15]

- It is also said that 60% or more of the Euthyroid goiters respond to suppressive doses of levothyroxine by significant reduction in goiter size as revealed by USG.[15]

Against:

- According to another school of thought levothyroxine has little role to play in the management of Euthyroid goiters as the single

most prevalent cause of these goiters is iodine deficiency. Hence iodide supplementation should be the mainstay of treatment. Prophylactic thyroxine is not superior to mere follow up care of euthyroid patients with autoimmune thyroiditis. Possible life long therapy and risk of thyrotoxicosis make thyroxine an unattractive option for treatment of nodular goiters. Thyroxine has no role for goitrogen induced thyromegaly and its role in dyshormonogenesis is under study.[15]

- It is also said that the clinical observation of a "shrinking goiter" during thyroxine therapy is now well established by ultrasound investigations as a decrease in goiter volume of maximal 30 to 40%, only within the first few months of treatment, but after that no further significant reduction in goiter size has been demonstrated so far and abrupt withdrawal of thyroxine therapy results in a rebound increase of goiter volume within a few weeks.[15]

- To resolve these issues a well conducted study focusing on the above aspects becomes necessary. Hence the present study was undertaken.

AIMS AND OBJECTIVES OF THE STUDY

1. To study the complete **clinical and biochemical profile** of the children with Euthyroid goiters.

2. To evaluate **the effect of thyrotropin (TSH) suppressive therapy with levothyroxine** on the size of diffuse, multinodular and solitary nodular Euthyroid goiters in the pediatric population.

3. To study the side-effect profile of levothroxine therapy, if any.

4. To ascertain the existence of iodine deficiency in our pediatric population as it is the most important cause of Euthyroid goiters.

5. To study different pathologies of euthyroid goiters as evidenced by FNAC.

6. To evaluate the incidence of euthyroid goiters at the pediatric endocrinology department of Institute of Child Health and Hospital for Children

7. To compare this study with other similar kinds of studies.

SUBJECTS AND METHODS

METHODOLOGY

Study Design: Prospective randomized controlled trial comparing pediatric cases with Euthyroid goiter treated with levothyroxine as **Study Group** and a matched group with untreated Euthyroid goiter as **Control Group**.

Place of study: Endocrinology department of Institute of Child Health and Hospital for Children.

Period of study: October 2005 to September 2006.

Subjects: Pediatric patients with Euthyroid goiter attending the endocrine OPD of Institute of Child Health and Hospital for Children.

Sample size: For a confidence level of 95% with a confidence interval of +/- 5%, 37 cases and 37 controls were taken into the study.

Sampling technique: Random sampling.

Inclusion criteria: All children with Euthyroid goiters.

Exclusion criteria: Children with goiters due to hypothyroidism or hyperthyroidism.

MANOEUVRE

Patients were selected by random sampling based on the above set of criteria

Patients were subdivided into two groups (study and control) comparable for sex, age and size of the goiter.

Patients in the age group of 6 to 12, having grade 2 and above goiters with T3, T4 and TSH, measured by standard **Radioimmunoassay (RIA) technique,** in the normal range i.e. having Euthyroid goiters were admitted to the study.

The volume of the thyroid gland was measured at commencement of study by USG using 7.5MHZ high frequency probe.[16, 17]

The pathology of the euthyroid goiter was determined by **FNAC**.

Urinary iodine is a good biochemical marker for control of iodine deficiency disorders.[18]Most of the popular methods for urinary iodine determination are based on the **Sandell–Kolthoff reaction**.[19]The chloric acid digestion is the most commonly used but is hazardous.[20]Hence a simple, rapid, and quantitative method based on the **Sandell–Kolthoff reaction,** which uses the safer ammonium persulfate digestion,

incorporating both the reaction and the digestion process into a microplate format was adopted.[21]

Spot Urinary iodine levels were measured to determine the iodine status by **Simple Microplate Method**[22] for determination of Urinary Iodine, utilizing the principle of **Wet ashing.**[18]

Using a specially designed sealing cassette to prevent loss of vapor and cross-contamination among wells, ammonium persulfate digestion was performed in a microplate in an oven at 110 °C for 60 min. After the digestion mixture was transferred to a transparent microplate and the Sandell–Kolthoff reaction was performed at 25 °C for 30 min, urinary iodine was measured by a microplate reader at 405 nm.

Experimental procedure

APDM method[22]

1. Calibrators and urine samples (50 µL each) were pipetted into the wells of a polypropylene (PP) plate, followed by the addition of 100 µL of **ammonium persulfate solution** (final concentration, 0.87 mol/L).

2. The PP plate was set in a cassette.

3. The cassette was tightly closed and was kept for 60 min in an oven adjusted to 110 °C.

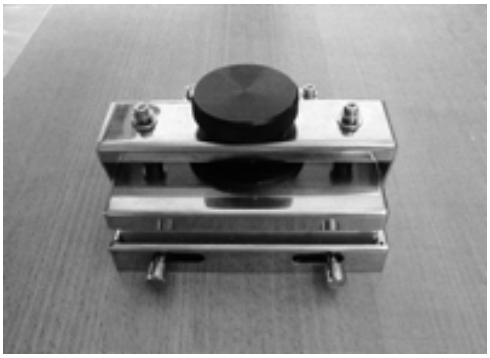
4. After digestion, the bottom of the cassette was cooled to room temperature with tap water to avoid condensation of vapor on the top of wells and to stop the digestion.

5. The cassette was opened, and 50-µL aliquots of the resulting digests were transferred to the corresponding wells of a polystyrene 96-well microtiter plate (MicroWell; Nalge Nunc International).

6. **Arsenious acid solution** (100 µL) was added to the wells and mixed.

7. 50 µL of **ceric ammonium sulfate solution** was then added quickly (within 1 min), using a multichannel pipette (Finnpipette Varichannel; Labsystems).

8. The reaction mixture was allowed to sit for 30 min at 25 °C, and the absorbance was measured at 405 nm with a microplate reader.



Sealing cassette used for digestion after a microplate is placed inside

The children in the study group were administered levothyroxine at a suppressive dose of 2μ/kg/day.[11, 12]

At the end of six months, thyroid function tests and ultrasound examinations were repeated in both the study and control groups.

STATISTICAL ANALYSIS

Standard statistical methods were applied to arrive at the p value, correlation coefficient and other statistical parameters with the help of statistician on computer and the results tabulated.

OBSERVATIONS

The p value of the various variables studied in the study

Study group

Parameter mean	At commencement	After 6 months	P value
Thyroid volume (CC)	5.26	3.86	0.000
T3 (ng/dl)	138.73	150.39	0.013
T4 (µg/dl)	7.83	11.1	0.000
TSH (µIU/ml)	2.57	0.76	0.000

Control group

Parameter mean	At commencement	After 6 months	P value
Thyroid volume (CC)	5.84	5.78	0.521
T3 (ng/dl)	149.57	141.26	0.000
T4 (µg/dl)	8.06	7.02	0.000
TSH (µIU/ml)	3.24	4.52	0.000

Iodine status

Iodine deficiency	Study group		Control group		P value
	N	%	N	%	
None	3	8.1	3	8.1	1.000
Mild	25	67.6	32	86.5	0.3538
Moderate	8	21.6	2	5.4	0.0578
Severe	1	2.7	0	0	0.998

Histology

Type	Study group		Control group		P value
	N	%	N	%	
Colloid Goiter	30	81.1	35	94.6	0.5351
Hashimoto's Thyroiditis	6	16.2	2	5.4	0.1573
Sub acute Granulomatous Thyroiditis	1	2.7	0	0	0.998

Gender distribution

Gender	Study group		Control group		P value
	N	%	N	%	
Girls	28	75.7	32	86.5	0.6056
Boys	9	24.3	5	13.5	0.2850

Age distribution

Ages	Study group	Control group	P value
6-12	34	34	1.000

The above tables show that in the **study group, all** parameters showed **significant change** ($p < 0.05$) due to levothyroxine therapy where as in the **control group,** thyroid volume **did not show any significant change** ($p > 0.05$). Other tables show that the **variations of variables** in the **study and control groups** are not significant ($p > 0.05$) and hence they are matched for all practical purposes.

Change in the mean volume of thyroid <u>at Commencement</u> and <u>after 6 months</u> in Study and Control groups

Study Group

Volume of Thyroid (CC)	Mean	SD
At Commencement	5.26	2.61
After 6 months	3.86	1.61

Decrement in the mean volume of thyroid is **27%**

P value is **0.000 (< 0.01, statistically significant at **)**

Control Group

Volume of Thyroid (CC)	Mean	SD
At Commencement	5.84	2.00
After 6 months	5.78	2.13

Decrement in the mean volume of thyroid is **1%**

P value is **0.521 (> 0.05, statistically not significant)**

<u>Inference:</u> All patients show response to levothyroxine therapy. Levothyroxine at suppressive dose causes decrement in the thyroid volume at the end of six months which is **statistically significant.**

Percentage of children showing none (>100mcg/L), mild (50-99mcg/L), moderate (20-49mcg/L) or severe (<20mcg/L) Iodine deficiency

	None	Mild	Moderate	Severe
Study Group	3	25	8	1
Control Group	3	32	2	
Total	6	57	10	1
Percentage	8.1	77	13.5	1.4

Inference: **77%, 13.5% and 1.4%** of the total children studied have **mild, moderate and severe** iodine deficiency respectively. On the whole **91.9%** of the total euthyroid goiter patients in this study have some kind of iodine deficiency.

Percentage of children in the study group showing <u>factitious (sub clinical) hyperthyroidism</u> i.e. elevation of T3 and/or T4 or suppression of TSH due to levothyroxine suppressive therapy

T3 (ng/dl)	Number of children having normal T3	Number of children having abnormal T3 (elevated)	Percentage of children having abnormal T3
At Commencement	37	0	0
After 6 months	35	2	5.4

T4 (μg/dl)	Number of children having normal T4	Number of children having abnormal T4 (elevated)	Percentage of children having abnormal T4
At Commencement	37	0	0
After 6 months	18	19	51.4

TSH (μIU/ml)	Number of children having normal TSH	Number of children having abnormal TSH (suppressed)	Percentage of children having abnormal TSH
At Commencement	37	0	0
After 6 months	14	23	62.2

<u>Inference:</u> Percentage of children showing factitious (sub clinical) hyper thyroidism i.e. elevation of T3 and/or T4 or suppression of TSH is **62.2%.** Among the 6 patients with Hashimoto's in the levothyroxine group 3 showed suppression of TSH < 0. 3 with levothyroxine therapy and 3 did not.

Histology wise distribution of Euthyroid goiters based on FNAC

	Colloid Goiter		Hashimoto's Thyroiditis		Sub acute Granulomatous Thyroiditis	
	N	%	N	%	N	%
Study Group	30	81.1	6	16.2	1	2.7
Control Group	35	94.6	2	5.4		
Total	65	87.8	8	10.8	1	1.4

Inference: Most of the Euthyroid goiters are **simple colloid goiters (87.8%).**

Mean decrement in volume of thyroid due to levothyroxine in different types of goiters in the Study group

Type of goiter	Mean volume of thyroid at commencement	Mean volume of thyroid after 6 months	Percentage decrement
Colloid Goiter	4.98	3.90	22
Hashimoto Thyroiditis	7.17	3.97	45
Sub acute Granulomatous Throiditis	2.20	2	10

Inference: Hashimoto's thyroiditis shows the maximum response to levothyroxine suppressive therapy with a mean decrement of **45%.**

Gender distribution of Euthyroid goiter patients

Variable	Study group	Control group	Total
Girls	28	32	60
Percentage of girls	75.7	86.5	81.1
Boys	9	5	14
Percentage of boys	24.3	13.5	18.9

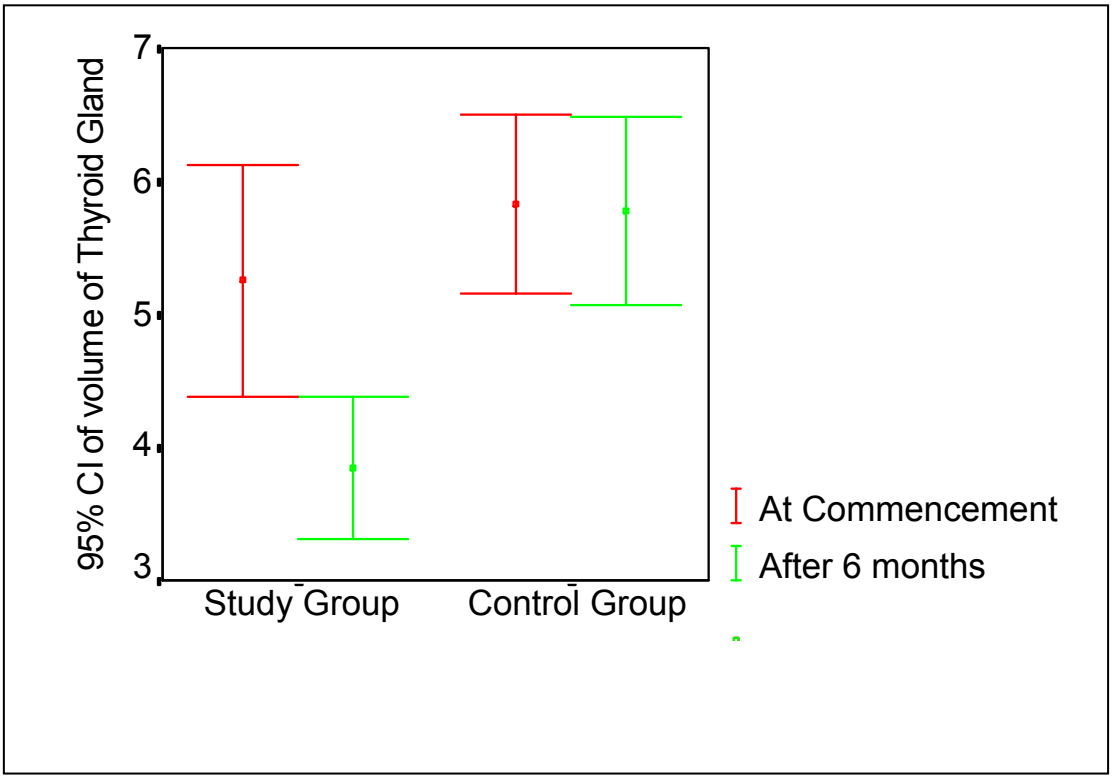
Inference: 81.1% of the Euthyroid goiter patients studied were girls and and 18.9% were boys.

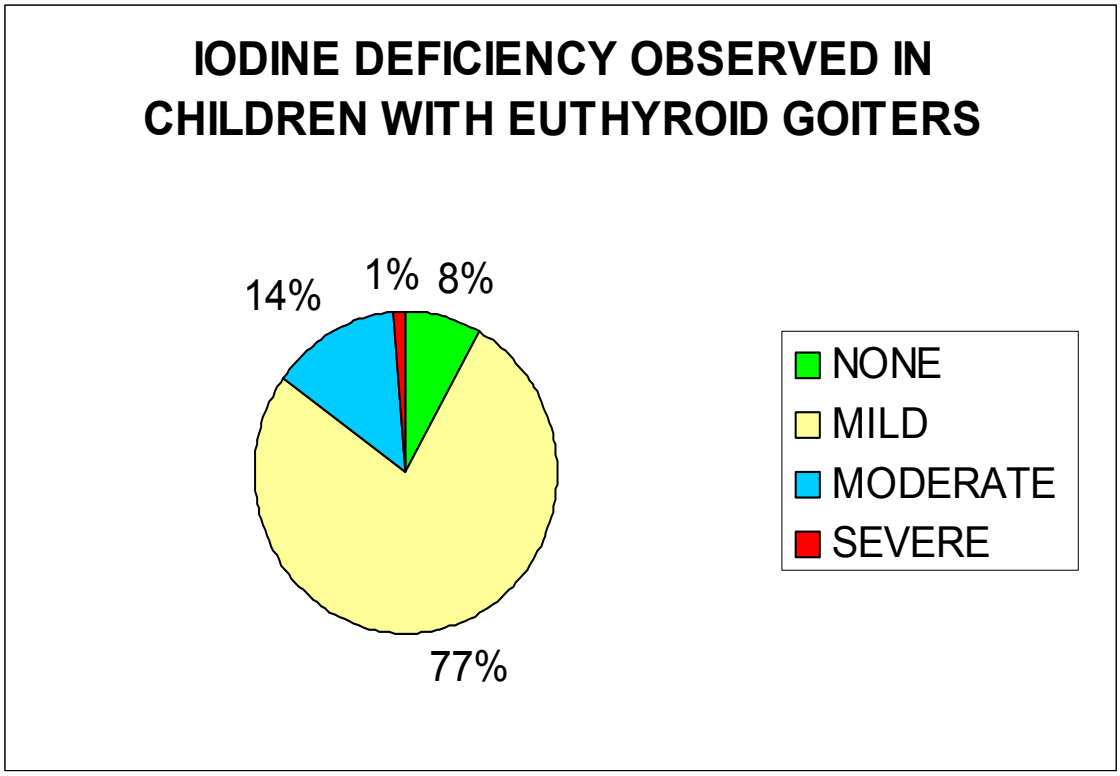
In our study **70** were **diffuse goiters** and **4** were **multi nodular goiters**, 2 each in study and control groups. The overall behavior of nodular goiters with or without levothyroxine therapy was similar to that of the colloid goiters.

All the goiters studied were **grade II goiters.**

None of the patients had any actual **side-effects.**

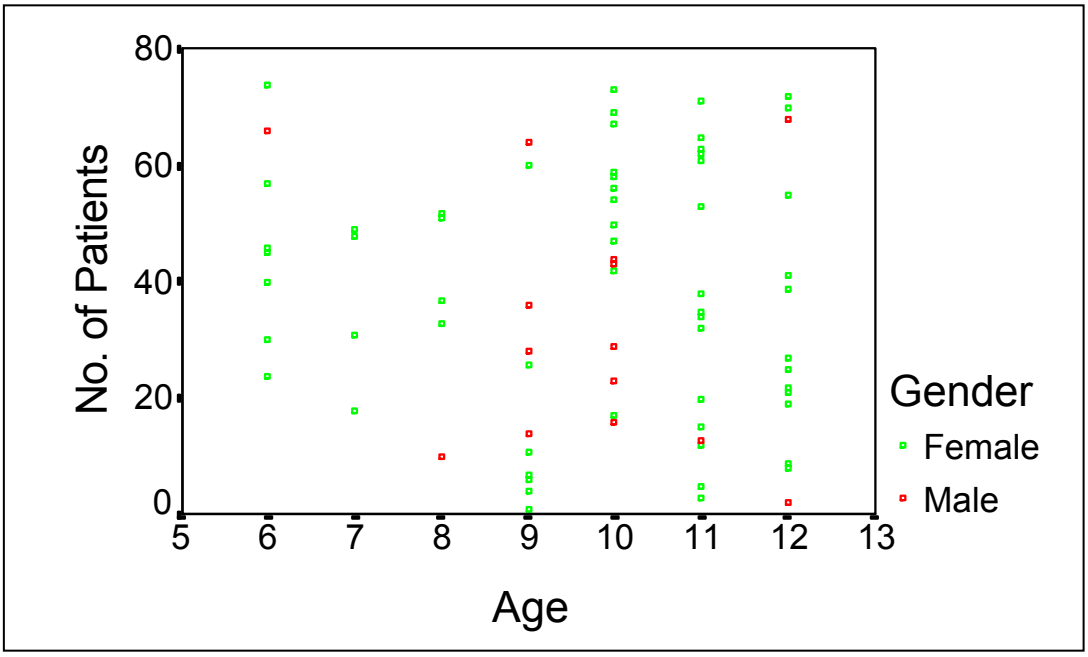
MEAN THYROID VOLUME IN THE STUDY AND CONTROL GROUP AT COMMENCEMENT AND AFTER SIX MONTHS




IODINE DEFICIENCY OBSERVED IN CHILDREN WITH EUTHYROID GOITERS
14%
1%
8%
77%
NONE
MILD
MODERATE
SEVERE

GENDER DISTRIBUTION OF EUTHYROID GOITER

PATIENTS FOR DIFFERENT AGES



SOME OF OUR EUTHYROID GOITER PATIENTS

DISCUSSION

The present study depicts that the incidence of grade II euthyroid goiters is 1.5% in the pediatric population aged 6 to 12 in the endocrinology department of Institute of Child Health and Hospital for Children. This could only be tip of the ice berg as this is hospital based and not community based study. The occurrence of euthyroid goiter depends on the endemicity of the area. The incidence is more in the endemic zones when compared to non endemic areas. This could be because of the difference in the iodine content of the soil in different places. Generally higher altitude areas which are above the sea level are endemic zones of euthyroid goiters as the iodine content of the soil and hence that of the vegetables and fruits grown in that soil is generally deficient. Also sea food is a rich source of iodine which is not available at high altitudes.[4, 5]

In the present study we found that the most common cause of euthyroid goiter in pediatric population aged 6 to 12 is probably iodine deficiency as 91.9% of the children studied had iodine deficiency with mild iodine deficiency being most common at 77%. World over the most common cause of euthyroid endemic goiters is iodine deficiency. This is again substantiated in our study. This shows that even in a non

endemic zone like ours at least mild iodine deficiency does exist in children with euthyroid goiters. This could be because of the cultural practices. Traditionally and culturally in many families rock salt is still being widely used instead of iodized salt. Due to this iodine deficiency disorders like euthyroid goiter exist even in non endemic zones like the one where the present study was conducted.[4, 5]

The mean percentage decrease in the size of the goiter after six months of levothyroxine therapy in the study group is **27%** in our study. Others have found out similar kind of decrement. Thyroid gland volume was static in the control group. In the study by Gullu S, et al[9] on 35 patients with euthyroid diffuse goiter and 35 patients with euthyroid nodular goiter, the mean decrease of thyroid volume at six months was about 20% for diffuse euthyroid goiters. Nodular goiters showed variable response with a reduction in size by 50% or more or nil decrement in size. Diacinti D, et al[10] in their study on 35 patients with euthyroid nodular goiters observed 25% mean decrease of thyroid volume after nine months of levothyroxine therapy in the study group. Nodules instead were found to be only in part sensitive to the treatment. Thyroid volume was static with no decrement or rather increased in the control group. They found goiter reappeared on discontinuation of levothyroxine therapy. Regalbuto C, et al[11] in their study on diffuse

goiters in children observed significant decline of more than 20% in children with euthyroid goiter on levothyroxine suppressive therapy for 12 months. They found the goiter size to increase on discontinuation of therapy. Celani MF[12] in his study with multinodular goiters found nodules behaving variably with a decrease by 50% or more or nil on levothyroxine suppressive therapy. Wilders-Truschnig MM, et al[13] in their study on 37 euthyroid patients concluded that levothyroxine as well as iodine was effective in reducing the thyroid size. Einenkel D, et al[14] in there study on treatment of juvenile goiter with three groups of 30 each with levothyroxine, iodide or a combination of both found a decrement of 41%, 52% and 52% respectively. When the treatment was discontinued for three months, thyroid volume increased again in the levothyroxine group but not in the iodide group.

From the above discussion it is evident that levothyroxine therapy in suppressive doses does result in a significant decrement in the size of euthyroid goiters. In our study also we found a statistically significant decline in thyroid volume in levothyroxine group in 6 months at a suppressive dose of 2mcg/kg/day.[11,12] Other studies have shown that this reduction in goiter size does not sustain if levothyroxine therapy is withdrawn. This aspect needs to be further elucidated.

Again a few of the above mentioned studies have shown that with iodine treatment for euthyroid goiters the reduction in goiter size was significant and moreover was sustained even after its withdrawal. In our study also we found at least mild iodine deficiency to be rampant in children with euthyroid goiters. Perhaps this is a pointer that euthyroid goiters can be better managed with iodine supplementation in the face of iodine deficiency. This aspect of our study needs to be further elucidated.

Most of the children in the study group showed a rise in T3, T4 and a significant decline of TSH level after six months. More the decline more was the volume reduction. 62.2% of children in the study group developed sub clinical hyperthyroidism in the study group on levothyroxine with TSH falling < 0.3μIU/ml. Other studies have also documented the suppression of TSH. Gullu S, et al found TSH levels decreased with levothyroxine therapy in all patient groups.[9] Regalbuto C, et al also found TSH levels to significantly reduce and was fully suppressed in one patient.[11] Celani MF found TSH to fall below 0.1μIU/ml in 75 patients, which is 72%, of the total 104 patients studied.[12] Wilders-Truschnig MM, et al found that TSH levels became suppressed while T4 values rose in the levothyroxine treated group; in the iodine treated group TSH levels remained constant as did T4.[13]

None of the authors have reported any side effects due to levothyroxine treatment in a suppressive dosage.[9, 10, 11, 12, 13, 14] This holds good for our study too where none of the patients had any actual side effects due to suppressive levothyroxine therapy.

87.8% of children in our study had simple colloid Euthyroid goiters as shown by FNAC which confirms the most common pathology of these goiters as established world over. Celani MF also in his study on euthyroid goiters found 94% of the 104 goiter patients studied to be having benign colloid goiter by FNAC.[12]

The greatest decrement of thyroid volume after levothyroxine therapy was found to be in Euthyroid goiter patients with Hashimoto's thyroiditis at 45%. Among the 6 patients with Hashimoto's in the levothyroxine group 3 showed suppression of TSH with levothyroxine therapy and 3 did not. Hence follow up care of euthyroid patients with autoimmune thyroiditis needs to be considered initially.

SUMMARY

- Iodine deficiency is the most common cause of Euthyroid goiters.
- Levothyroxine at a suppressive dose of 2μ/kg/day for 6 months causes a significant decline in the size of the thyroid gland as measured by USG.
- Children on levothyroxine suppressive therapy are likely to develop sub clinical hyperthyroidism which may be reversible after discontinuation of the therapy.
- Most of the Euthyroid goiters are colloid goiters as proved by FNAC.
- Greatest decrement in size observed in Euthyroid goiter patients due to Hashimoto's thyroiditis after levothyroxine suppressive therapy, shows that this type of goiter responds best to levothyroxine therapy.

CONCLUSION

- The cosmetic misery of Euthyroid goiters in children was focused in the present study.

- Deficiency of iodine necessary for hormonogenesis and prevention of goiters is the most common cause resulting in Euthyroid goiters which is well substantiated in our study.

- Suppressive levothyroxine therapy for a destined period of 6 months resulted in appreciable decline in the size of the goiter both clinically and when viewed through sonologically, thus comforting the patients.

- This study thus proves the usefulness of levothyroxine therapy in these subjects. The usage of iodine will further prove to be helpful in reducing the goiter size, more so with Hashimoto's thyroiditis along with levothyroxine therapy.

- Reversible iatrogenic sub clinical hyperthyroidism is observed in quite a number of patients in this study.

- This study is the first institution based amongst South Indian children which unravels the usefulness of measuring urinary

iodine in all Euthyroid goiters which will give an insight into management protocol and highlights the usefulness of levothyroxine suppressive therapy.

- Though the study is done in fewer sample size, future studies in larger numbers will be more useful and meaningful to substantiate our findings.

ANNEXURE 1 – PROFORMA

PROFORMA

Name:

Date of inclusion:Age:Sex:

Postal address:Telephone number:Father's name:

Mother's name:

Endocrine OPD number:

Anthropometrics:

Clinical examination:

Clinical grade of the goiter:

Thyroid function tests:

1. **T3**
2. **T4**
3. **TSH**

FNAC of the goiter:

Size of the goiter by USG:

Urinary iodine level:

Follow up:

ANNEXURE 2 – BIBLIOGRAPHY

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