

ABSTRACT

AIMS AND OBJECTIVES:

1. TO STUDY THE CLINICAL PROFILE OF HYPERTHYROIDISM
AT STANLEY HOSPITAL

2. TO STUDY ECHOCARDIOGRAPHIC FINDINGS IN THESE
PATIENTS

MATERIALS AND METHODS

PLACE OF STUDY:

DEPARTMENT OF GENERAL MEDICINE, ENDOCRINOLOGY OPD,
MEDICAL OPD, MEDICAL WARDS, STANLEY MEDICAL COLLEGE AND
HOSPITAL, CHENNAI.

DURATION:

NOV 2013 TO NOV 2014.

SAMPLE SIZE: 60

STUDY DESIGN:

PROSPECTIVE OBSERVATIONAL STUDY

PATIENT SELECTION:

ANY PATIENT COMING WITH SYMPTOMS SUGGESTIVE OF
HYPERTHYROID TO ENDOCRINOLOGY OPD, MEDICAL OPD
MEDICAL WARDS.

EXCLUSION CRITERIA:

PATIENTS WITH KNOWN HEART DISEASE.

METHODOLOGY:

Patients coming with symptoms suggestive of hyperthyroidism to OPDs from November 2013 to November 2014 are included in the study. Patients will be subjected to symptom analysis , clinical examination , laboratory investigations and Echocardiogram. The final analysis will be made at the end of the study to achieve the forementioned goals.

CONCLUSION

- Hyperthyroidism is more common in females of younger age group commonly in third decade of life.
- Hyperthyroid patients mostly presents with neck swelling and palpitation and menstrual irregularities forms the significant complaint in my study.
- Hyperthyroid has significant effect on cardiac activity. It is a high output state. Causing systolic and diastolic dysfunction , pulmonary hypertension, left ventricle chamber enlargement , heart failure.
- Hyperthyroidism-related cardiac changes was largely asymptomatic and reversible after restoration to an euthyroid state. So hyperthyroidism should be considered as the reversible cause in cardiac morbidity.
- As a non-invasive method, echocardiography can play a vital role in recognizing the cardiac pathology in hyperthyroidism as well as to follow up the response to therapy.

Keywords: Hyperthyroid, Echocardiogram, Grave's disease.

INTRODUCTION

Hyperthyroidism is a condition where thyroid gland produces excessive amount of thyroid hormone.

Most common causes are Grave's disease, toxic multinodular goiter, toxic adenoma, subacute thyroiditis, drugs, secondary hyperthyroidism

Clinical features were palpitation, neck swelling, nervousness, increased appetite & loss of weight, hair loss, heat intolerance, menstrual irregularities, loose stools and easy fatigability. On examining, patient may have goiter, tremors, eye signs, gynecomastia.

Lab investigation will reveal low TSH and high T3 and T4. Thyroid imaging, radioactive iodine uptake study, Thyroid biopsy, Thyroid autoantibodies were other tests to find out the etiology of the disease.

Main stay of treatment include antithyroid drugs, radioactive ablation, surgery.

Cardiovascular manifestations of hyperthyroidism were tachycardia, atrial fibrillation, increased cardiac output, systolic and diastolic dysfunction, worsening of heart failure, systolic murmur.

REVIEW OF LITERATURE

The thyroid gland is the largest organ specialized for endocrine function in the human body. The major function of the thyroid follicular cells is to secrete a sufficient amount of thyroid hormones, primarily 3,5,3',5'-l-tetraiodothyronine (T₄), and a lesser quantity of 3,5,3'-l-triiodothyronine (T₃). Thyroid hormones promote normal growth and development and regulate a number of homeostatic functions, including energy and heat production. In addition, the parafollicular cells of the human thyroid gland secrete calcitonin, which is important in calcium homeostasis.

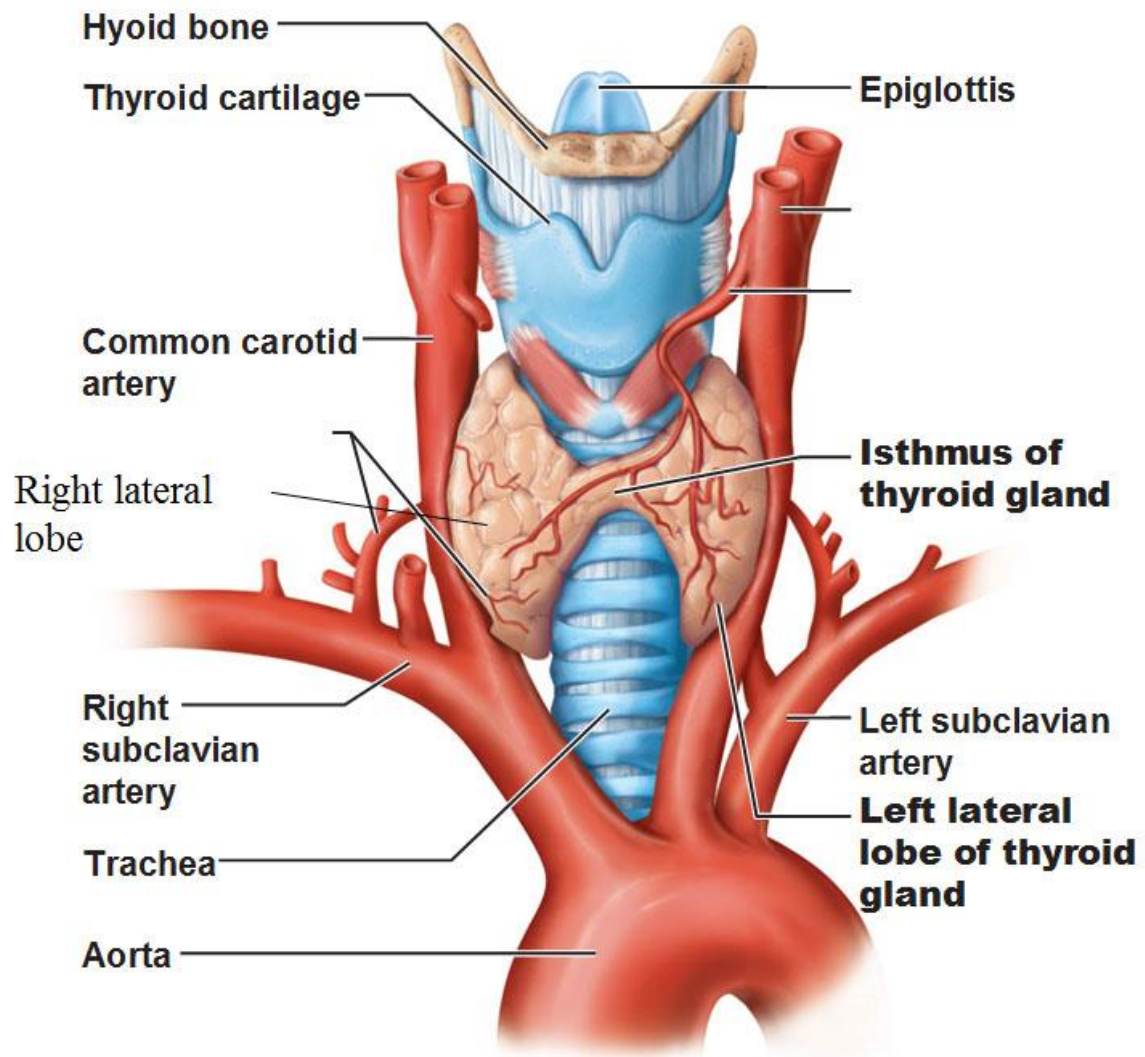
ANATOMY & HISTOLOGY

The thyroid gland originates as an outpouching in the floor of the pharynx, which grows downward anterior to the trachea, bifurcates, and forms a series of cellular cords. The lateral lobes of the thyroid connected by a thin isthmus formed from those tiny balls or follicles. The origin of the gland at the base of the tongue is evident as the foramen cecum. The course of its downward migration is marked by the thyroglossal duct, remnants of which may persist in adult life as thyroglossal duct cysts. These are mucus-filled cysts, lined with squamous epithelium, and are usually found in the anterior neck between the thyroid cartilage and the base of the tongue. A remnant of the caudal end of the thyroglossal duct is found in the pyramidal lobe, attached to the isthmus of the gland.

The isthmus of the thyroid gland is located just below the cricoid cartilage, midway between the apex of the thyroid cartilage (“Adam's apple”) and the suprasternal notch. Each lobe is pear-shaped and measures about 2.5–4 cm in length, 1.5–2 cm in width, and 1–1.5 cm in thickness. The weight of the gland in the normal individual, as determined by ultrasonic examination, varies depending on dietary iodine intake, age, and body weight but in adults is

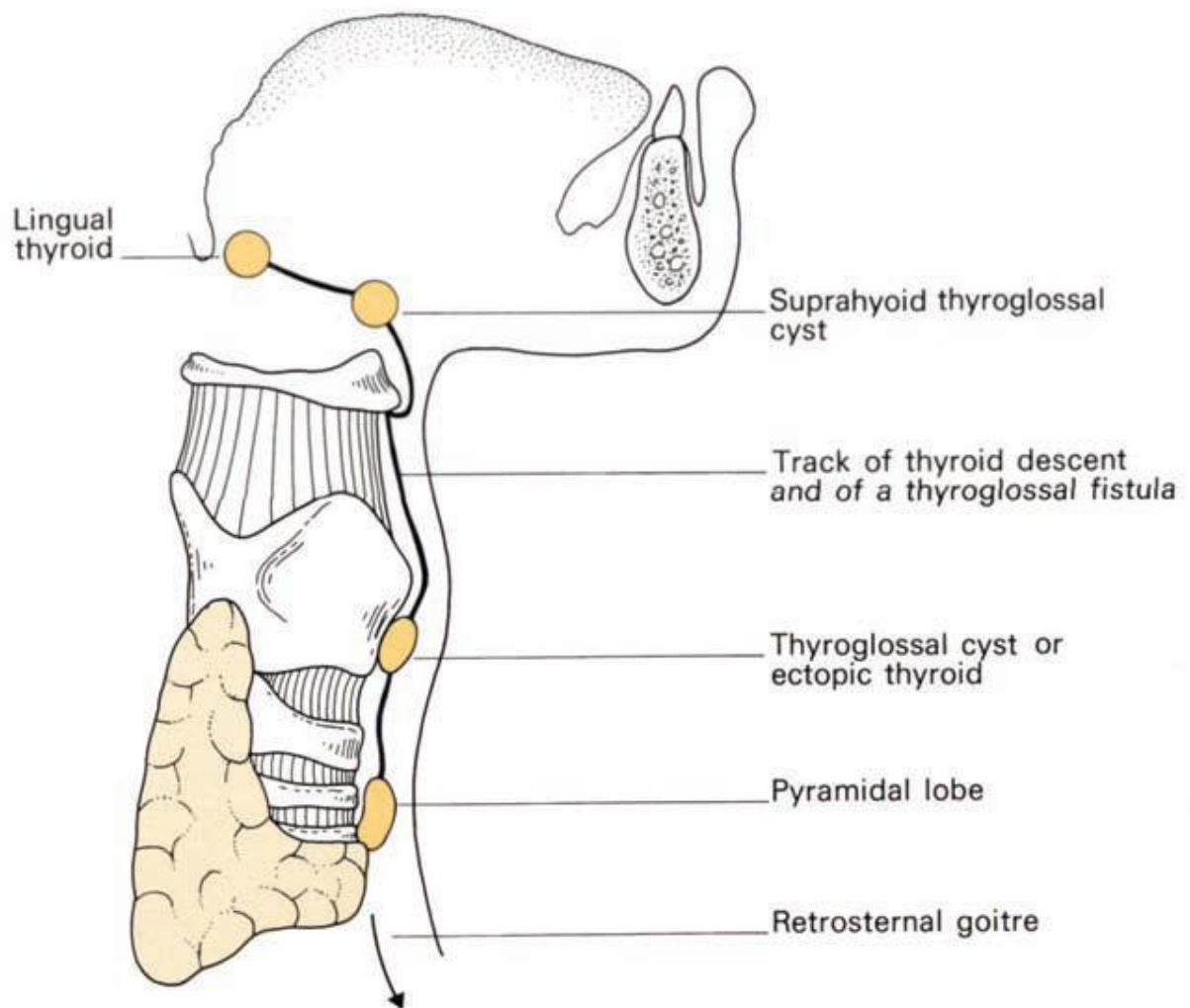
approximately 10–20 g. Upward growth of the thyroid gland is limited by the attachment of the sternothyroid muscle to the thyroid cartilage; however,

The Thyroid Gland



Gross anatomy of the thyroid gland, anterior view

posterior and downward growth is unhampered, so that thyroid enlargement, or goiter, will frequently extend posteriorly and inferiorly or even substernally.

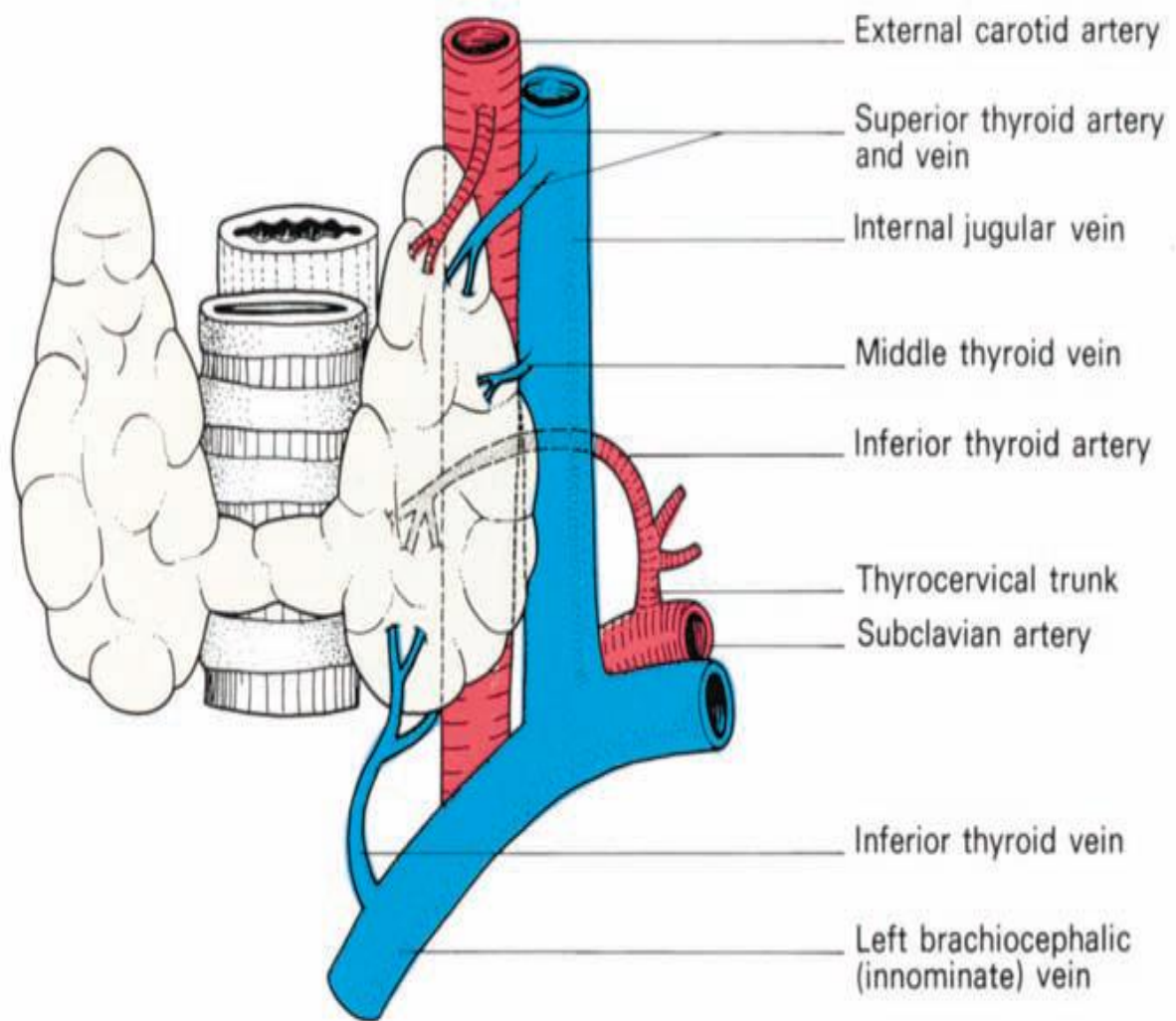


DEVELOPMENT OF THYROID GLAND

BLOOD SUPPLY OF THYROID

The thyroid gland is highly vascular organ . External carotid artery gives rise to superior thyroid artery , Thyrocervical trunk gives to inferior thyroid artery.and third and rare branch thyroid ima artery from brachiocephalic artery.

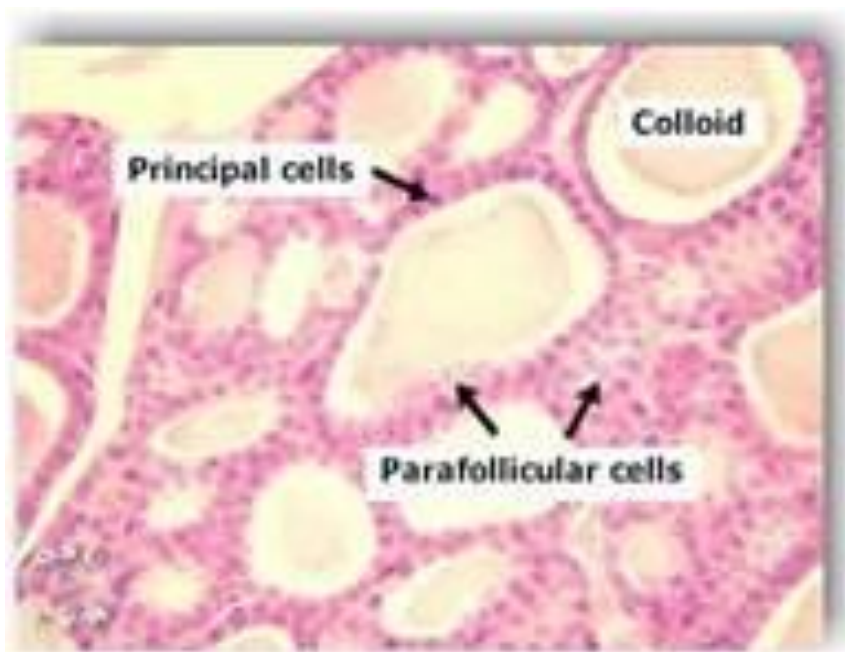
Superior,middle and inferior thyroid veins are formed from venous plexus on thyroid gland surface and on front of trachea. Superior and middle drains in internal jugular and inferior in innominate vein..; in hyperthyroidism, the blood flow to the gland is markedly increased, and a whistling sound, or bruit, may be heard over the lower poles of the gland and may even be felt in the same areas as a vibration, or thrill. Other important anatomic considerations include the two pairs of parathyroid glands that usually lie behind the upper and middle thyroid lobes and the recurrent laryngeal nerves, which course along the trachea behind the thyroid gland.



BLOOD SUPPLY OF THYROID GLAND

HISTOLOGY

On microscopic examination, the thyroid gland is found to consist of a series of follicles of varying sizes. The follicles contain a pink-staining material (with hematoxylin-eosin stain) called “colloid” and is enclosed by thyroid epithelium. Tissue culture studies suggest that each follicle may represent an individual clone of cells. These cells become columnar when stimulated by TSH and flattened when resting . The follicle cells synthesize thyroglobulin, which is extruded into the lumen of the follicle. The biosynthesis of T_4 and T_3 occurs within thyroglobulin at the cell-colloid interface. Surface of follicle gives rise to many microvilli.; these are involved in endocytosis of thyroglobulin, which is then hydrolyzed in the cell to release thyroid hormones



HISTOLOGY OF THYROID GLAND

PHYSIOLOGY

STRUCTURE OF THYROID HORMONES

Thyroid hormones are unique in that they contain 59–65% of the trace element iodine. The iodinated thyronines are derived from iodination of the phenolic rings of tyrosine residues in thyroglobulin to form mono- or diiodotyrosine, which are coupled to form T_3 or T_4 .

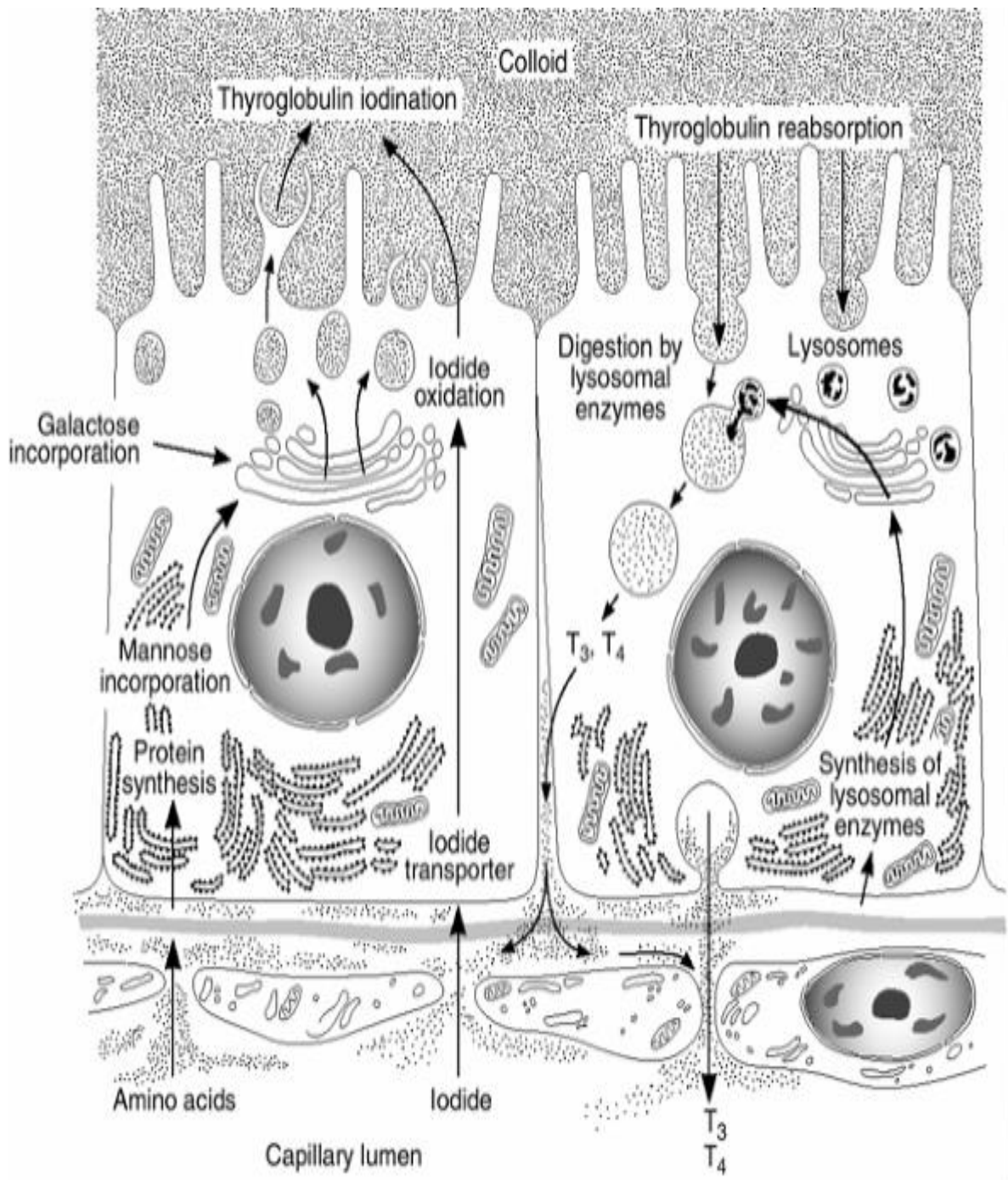
IODINE METABOLISM

Iodine enters the body in food or water in the form of iodide or iodate ion, the iodate ion being converted to iodide in the stomach. In the course of millennia, iodine was extracted from the soil and washed down into the oceans, so that in mountainous and inland areas the supply of iodine may be quite limited, whereas the element is plentiful in coastal areas. The thyroid gland concentrates and traps iodide and synthesizes and stores thyroid hormones in thyroglobulin, which compensates for the scarcity of iodine

The recommendations of the World Health Organization for optimal daily iodide intake are as follows: for adults, 150 μg ; during pregnancy and lactation, 200 μg ; for the first year of life, 50 μg ; for ages 1–6, 90 μg ; and for ages 7–12, 120 μg . If iodide intake is below 50 $\mu\text{g}/\text{d}$, the gland is unable to maintain adequate hormonal secretion, and thyroid hypertrophy (goiter) and hypothyroidism result. In the United States, the average daily iodide intake

increased from a range of 100–200 $\mu\text{g}/\text{d}$ in the 1960s to 240–740 $\mu\text{g}/\text{d}$ in the 1980s. This was largely due to the introduction of iodate as a dough conditioner, though other sources of dietary iodine included iodized salt, vitamin and mineral preparations, iodine-containing medications, and iodinated contrast media. In the 1990s, bromine salts replaced iodine in the baking industry, and iodine intake has fallen considerably, indicating the need for continued monitoring. Iodide is rapidly absorbed from the alimentary tract and distributed in extracellular fluids as well as in salivary, gastric, and breast secretions. Although the concentration of inorganic iodide in the extracellular fluid pool will vary directly with iodide intake, extracellular fluid I^- is usually quite low because of the rapid clearance of iodide from extracellular fluid by thyroidal uptake and renal clearance. In the example shown, the basal I^- concentration in extracellular fluid is only 0.6 $\mu\text{g}/\text{dl}$, or a sum of 150 μg of I^- in an extracellular pool of 25 L despite a daily oral intake of 500 μg I^- . In the thyroid gland there is active transport of I^- from the serum across the basement membrane of the thyroid cell. The thyroid gland takes up about 115 μg of I^- per 24 hours, or, in this example, about 18% of the available I^- . About 75 μg of I^- is utilized for hormone synthesis and stored in thyroglobulin; the remaining iodide goes to extracellular fluid. The thyroid pool of organified iodine is very large, averaging 8–10 mg, and represents a store of hormone and iodinated tyrosines, protecting the organism against a period of iodine lack. From this storage pool, about 75 μg of hormonal iodide is released into the circulation daily. This hormonal

iodide is mostly bound to serum thyroxine-binding proteins, forming a circulating pool of about 600 μg of hormonal I^- (as T_3 and T_4). From this pool, about 75 μg of I^- as T_3 and T_4 is taken up and metabolized by tissues. About 60 μg of I^- is returned to the iodide pool and about 15 μg of hormonal I^- is conjugated with glucuronide or sulfate in the liver and excreted into the stool.. In the USA, the 24-hour thyroidal radioiodine uptake has decreased from about 40–50% in the 1960s to about 8–30% in the 1990s because of increased dietary iodide intake.



Processes of synthesis and iodination of thyroglobulin and its reabsorption and digestion

THYROID HORMONE SYNTHESIS AND SECRETION

The production of thyroid hormone by the thyroid gland involves six major steps: (1) active carriage of iodide to the basement membrane into the thyroid cell (iodide trapping); (2) iodide oxidation & thyroglobulin iodination by tyrosyl residues; (3) T₃ and T₄ formation by coupling of iodotyrosine in thyroglobulin; (4) release of free iodothyronines and iodotyrosines by proteolysis; (5) iodotyrosines in the thyroid cell will be deiodonised and remanant iodide will be reused; and (6) intrathyroidal 5'-deiodination of T₄ to T₃.

Thyroid hormone synthesis involves a unique glycoprotein, thyroglobulin, and an essential enzyme, thyroperoxidase (TPO).

THYROGLOBULIN

Thyroglobulin is a large glycoprotein molecule containing 5496 amino acids, with a molecular weight of about 660,000 and a sedimentation coefficient of 19S. It contains about 140 tyrosyl residues and about 10% carbohydrate in the form of mannose, N-acetylglucosamine, galactose, fucose, sialic acid, and chondroitin sulfate. The 19S thyroglobulin compound is a dimer of two identical 12S subunits, but small amounts of the 12S monomer and a 27S tetramer are often present. The iodine content of the molecule can vary from 0.1% to 1% by weight. In thyroglobulin containing 0.5% iodine (26 atoms of iodine per 660-kDa molecule), there would be 5 molecules of monoiodotyrosine (MIT), 4.5 molecules of diiodotyrosine (DIT), 2.5 molecules of thyroxine (T₄),

and 0.7 molecules of triiodothyronine (T_3). About 75% of the thyroglobulin monomer consists of repetitive domains with no hormonogenic sites. There are four tyrosyl sites for hormonogenesis on the thyroglobulin molecule: One site is located at the amino terminal end of the molecule, and the other three are located in a sequence of 600 amino acids at the carboxyl terminal end. There is a surprising homology between this area of the thyroglobulin molecule and the structure of acetylcholinesterase, suggesting conservation in the evolution of these proteins.

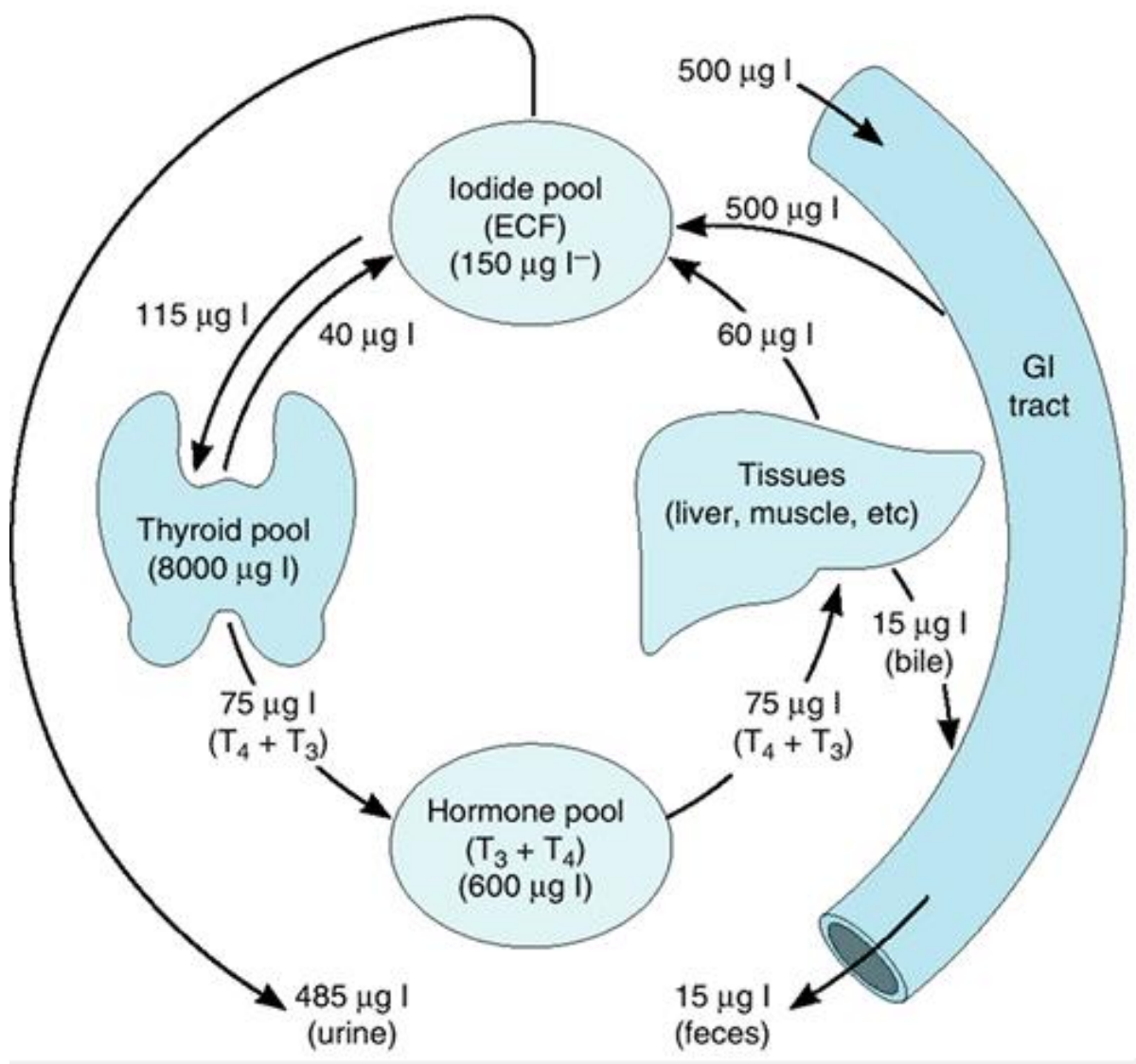
THYROIDAL PEROXIDASE

Thyroidal peroxidase is a membrane-bound glycoprotein with a molecular weight of about 102,000 and a heme compound as the prosthetic group of the enzyme. This enzyme mediates both the oxidation of iodide ions and the incorporation of iodine into tyrosine residues of thyroglobulin.

Thyroidal peroxidase is synthesized in the rough endoplasmic reticulum (RER). After insertion into the membrane of RER cisternae, it is transferred to the apical cell surface through Golgi elements and exocytic vesicles. Here, at the cell colloid interface, it is available for iodination and hormonogenesis in thyroglobulin. Thyroidal peroxidase biosynthesis is stimulated by TSH

IODIDE TRANSPORT (THE IODIDE TRAP)

I⁻ is transported across the basement membrane of the thyroid cell by an intrinsic membrane protein called the Na⁺/I⁻ symporter (NIS). At the apical border, a second I⁻ transport protein called pendrin moves iodine into the colloid where it is involved in hormonogenesis. The NIS derives its energy from Na⁺-K⁺ ATPase, which drives the transport process. This active transport system allows the human thyroid gland to maintain a concentration of free iodide 30–40 times that in plasma. The NIS is stimulated by TSH and by the TSH receptor-stimulating antibody found in Graves' disease. It is saturable with large amounts of iodide and inhibited by ions such as ClO₄⁻, SCN⁻, NO₃⁻, and TcO₄⁻. Some of these ions have clinical utility. Sodium perchlorate will discharge nonorganified iodide from the NIS and has been used to diagnose organification defects and in the treatment of iodide-induced hyperthyroidism. Sodium pertechnetate Tc99m, which has a 6-hour half-life and a 140-keV gamma emission, is used for rapid visualization of the thyroid gland for size and functioning nodules. Pendrin, encoded by the Pendred syndrome gene (PDS), is a transporter of chloride and iodide. Mutations in the PDS gene have been found in patients with goiter and congenital deafness (Pendred's syndrome). Although iodide is concentrated by salivary, gastric, and breast tissue, these tissues do not organify or store I⁻ and are not stimulated by TSH.



IODINE METABOLISM

IODINATION OF TYROSYL IN THYROGLOBULIN

Within the thyroid cell, at the cell-colloid interface, iodide is rapidly oxidized by H_2O_2 , catalyzed by thyroperoxidase, and converted to an active intermediate which is incorporated into tyrosyl residues in thyroglobulin. H_2O_2 is probably generated by a dihydronicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the presence of Ca^{2+} ; this process is stimulated by TSH. The iodinating intermediate may be iodinium ion (I^+), hypoiodate, or an iodine-free radical. The site of iodination at the apical (colloid) border of the thyroid cell can be demonstrated by autoradiography. Thyroidal peroxidase will catalyze iodination of tyrosyl molecules in proteins other than thyroglobulin, such as albumin or thyroglobulin fragments. However, no thyroactive hormones are formed in these proteins. The metabolically inactive protein may be released into the circulation, draining thyroidal iodide reserves.

COUPLING OF IODOTYROSYL RESIDUES IN THYROGLOBULIN

The coupling of iodotyrosyl residues in thyroglobulin is also catalyzed by thyroperoxidase. It is thought that this is an intramolecular mechanism involving three processes: (1) iodotyrosyl residues is oxidized to an activated form by thyroperoxidase; (2) in thyroglobulin, coupling of iodotyrosyl residues to form a quinol ether intermediate; and (3) iodothyronine is formed by division of quinol ether. For this process to occur, the dimeric structure of thyroglobulin is essential: Within the thyroglobulin molecule T4 is

formed by combining of two DIT molecules, and T₃ by combining an MIT & DIT. Thiocarbamide drugs—particularly propylthiouracil, methimazole, and carbimazole—are potent inhibitors of thyroperoxidase and will block thyroid hormone synthesis . These drugs are clinically useful in the management of hyperthyroidism.

PROTEOLYSIS OF THYROGLOBULIN & THYROID HORMONE

SECRETION

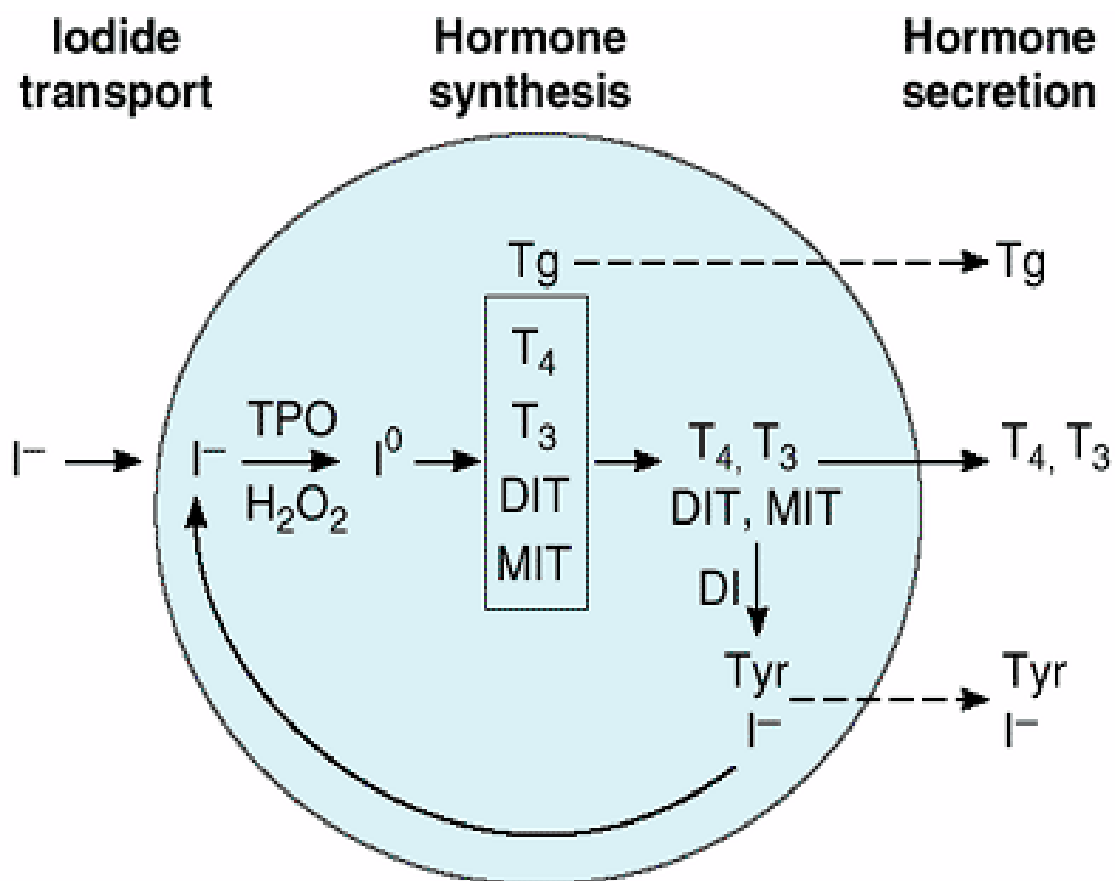
Rough endoplasmic reticulum secretes lysosomes and golgi apparatus packs it. These structures, surrounded by membrane, have an acidic interior and are filled with proteolytic enzymes, including proteases, endopeptidases, glycoside hydrolyases, phosphatases, and other enzymes. At the cell-colloid interface, colloid is engulfed into a colloid vesicle by a process of macropinocytosis or micropinocytosis and is absorbed into the thyroid cell. The lysosomes then fuse with the colloid vesicle and thyroglobulin gets hydrolysed and it releases MIT, DIT, T₃, T₄ , peptide fragments, and amino acids. T₃ and T₄ are released into the circulation, while DIT and MIT are deiodinated and the I⁻ is conserved. Thyroglobulin with a low iodine content is hydrolyzed more rapidly than thyroglobulin with a high iodine content, which may be beneficial in geographic areas where natural iodine intake is low. The mechanism of transport of T₃ and T₄ through the thyroid cell is not known, but it may involve a specific hormone carrier. TSH stimulates secretion of thyroid hormone by

activating adenylyl cyclase and by the cAMP , suggesting that it is cAMP-dependent.

Large amount of iodide restricts thyroglobulin proteolysis like lithium , which, as lithium carbonate, is used for the treatment of bipolar disorders. A little quantity of thyroglobulin which is not hydrolysed is secreted from the thyroid cell; this is markedly elevated in certain situations such as subacute thyroiditis, hyperthyroidism, or TSH-induced goiter . Thyroglobulin (perhaps modified) may also be synthesized and released by certain thyroid malignancies such as papillary or follicular thyroid cancer and may be useful as a marker for metastatic disease.

INTRATHYROIDAL DEIODINATION

MIT and DIT formed during the synthesis of thyroid hormone are deiodinated by intrathyroidal deiodinase . This enzyme is an NADPH-dependent flavoprotein found in mitochondria and microsomes. It targets only MIT and DIT but not on T_3 and T_4 . The iodide released is reutilized for hormone synthesis. The 5'-deiodinase that converts T_4 to T_3 in peripheral tissues is also found in the thyroid gland. In situations of iodide deficiency, the activity of this enzyme may increase the amount of T_3 secreted by the thyroid gland, increasing the metabolic efficiency of hormone synthesis.

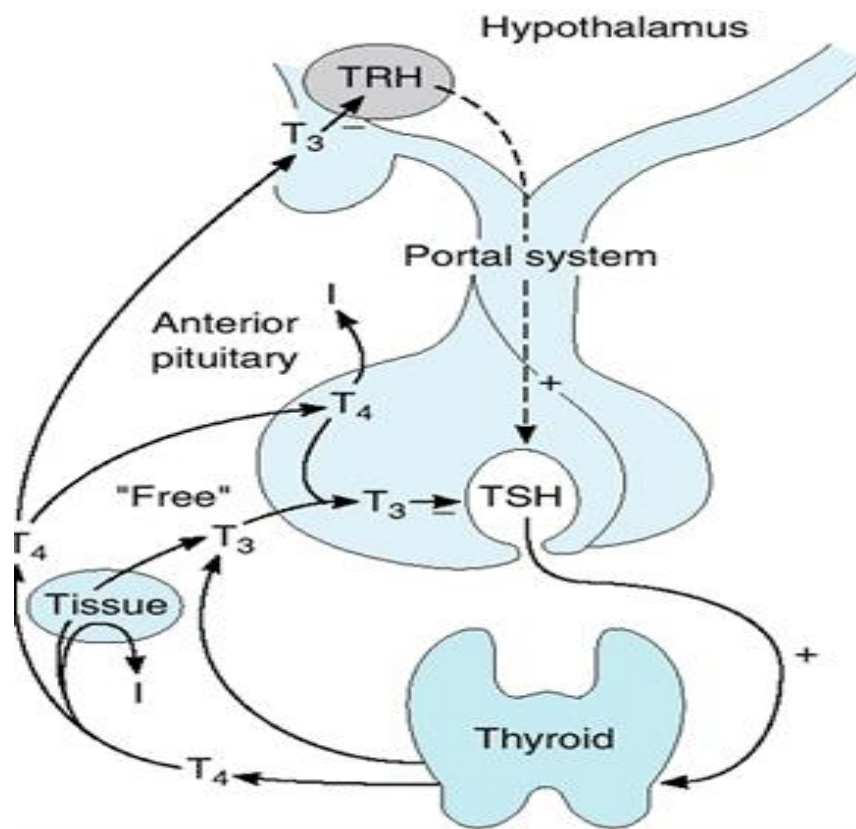


I^- : Iodide ion
 TPO: Thyroidal peroxidase
 I^0 : Active I
 Tg: Thyroglobulin
 Tyr: Tyrosine
 T_4 : Thyroxine
 T_3 : Triiodothyronine
 DIT: Diiodotyrosine
 MIT: Monoiodotyrosine
 DI: Deiodinase

THYROID HORMONE SYNTHESIS IN A THYROID FOLLICLE

CONTROL OF THYROID FUNCTION

The thyroid gland development and function and thyroid hormones effects are managed by four mechanisms : (i) TSH , thyroid stimulating hormone synthesized by thyrotropic releasing hormone called as hypothalamic pituitary thyroid axis. Thyroid gland is then stimulated by TSH for its growth; (2)T3 & T4 actions are controlled by peripheral and pituitary deiodinases ; (3)thyroid gland has its own autoregulation for iodine demand;(4)Thyroid function is controlled by TSH receptor autoantibodies. In addition, the effects of T₃ may be modified by the status of the T₃ receptor (repressor or activation) and potentially by nonthyroidal T₃ receptor agonists or antagonists.



THE HYPOTHALAMIC-HYPOPHYSIAL-THYROIDAL AXIS

THYROTROPIN-RELEASING HORMONE

Thyrotropin-releasing hormone (TRH) is a tripeptide, pyroglutamyl-histidyl-prolineamide, is formed in hypothalamus supraventricular & supraoptic nuclei neurons. After formation it is kept in median eminence of hypothalamus. Then it travels to pituitary portal vein system to pituitary gland anterior for controlling synthesis of TSH secretion. The gene for human preproTRH, located on chromosome 3, contains a 3.3-kb transcription unit that encodes six TRH molecules. The gene also encodes other neuropeptides that may be biologically significant. In the anterior pituitary gland, TSH and prolactin are synthesized by binding of TRH to receptors in thyrotrophs and prolactin synthesizing cells. TRH response is decreased by thyroid hormone by slow process whereas estrogen increases TRH response by increasing sensitivity in pituitary.

The response of the pituitary thyrotroph to TRH is bimodal: First, it stimulates release of stored hormone; and second, it stimulates gene activity, which increases hormone synthesis. The TRH receptor (TRH-R) is a member of the seven-transmembrane-spanning, GTP-binding, protein-coupled receptor family. The TRHR gene is located on chromosome 8. Large glycoprotein hormones such as TSH and LH bind to the extracellular portions of their receptors, but TRH, a small peptide, binds to the transmembrane helix 3 of the TRH-R. After binding to its receptor on the thyrotroph, TRH activates a G protein, which in turn activates phospholipase c to hydrolyze

phosphatidylinositol 4,5-bisphosphate (PIP₂) to inositol 1,4,5-trisphosphate (IP₃). IP₃ stimulates the release of intracellular Ca²⁺, which causes the first burst response of hormone release.

Simultaneously, there is generation of 1,2-diacylglycerol, which activates protein kinase C, thought to be responsible for the second and sustained phase of hormone secretion. The increases in intracellular Ca²⁺ and in protein kinase C may be involved in increased transcription of TSH. For thyroid hormone full biologic activity it should be glycosylation of TSH which is stimulated by TRH.

THYROTROPIN

Thyroid-stimulating hormone, or thyrotropin (TSH), is a glycoprotein synthesized and secreted by the thyrotrophs of the anterior pituitary gland. It has a molecular weight of about 28,000 and is composed of two noncovalently linked subunits, α and β . The α subunit is common to the two other pituitary glycoproteins, FSH and LH, and also to the placental hormone hCG; the β subunit is different for each glycoprotein hormone and confers specific binding properties and biologic activity. The human α subunit has an apoprotein core of 92 amino acids and contains two oligosaccharide chains; the TSH β subunit has an apoprotein core of 112 amino acids and contains one oligosaccharide chain. The α and β subunit amino acid chains of TSH each form "cysteine knot" by joining three coils which are interrupted. Mutations of the amino acids in either

chain can result in either decreased or increased TSH activity. Glycosylation takes place in the rough ER and the Golgi apparatus of the thyrotroph, where glucose, mannose, and fucose residues and terminal sulfate or sialic acid residues are linked to the apoprotein core. The function of these carbohydrate residues is not entirely clear, but it is likely that they enhance TSH biologic activity and modify its metabolic clearance rate. For example, deglycosylated TSH will bind to its receptor, but its biologic activity is markedly decreased and its metabolic clearance rate is markedly increased.

Thyroid hormone production is controlled by mainly TSH. This is attained by binding of TSH with its receptor called TSH-R which is unique and then it causes triggering of cAMP . The human TSH receptor (TSH-R) gene is located on chromosome 14q3. The TSH-R is a single-chain glycoprotein containing 764 amino acids. Like the TRH receptor of the anterior pituitary, the TSH-R in the thyroid follicular cell is a member of the seven-membrane spanning, GTP-binding protein-coupled receptor family. Structurally, it can be divided into two subunits: subunit A, containing 397 amino acids, representing the ectodomain which is involved in ligand binding; and subunit B, which includes the intramembrane and intracellular portion of the receptor involved in action of thyroid development, hormone production, and its release. The TSH-R is unique in that it has binding sites not only for TSH but also for TSH receptor antibody, which are found in patients with autoimmune hyperthyroidism (Graves' disease), and also for autoantibodies that bind to the

TSH receptor and block the action of TSH (TSH-R Ab [block]). These antibodies are also found in hypothyroidism and some thyroiditis

Mutations in the TSH-R have been associated with either spontaneous activation of the receptor and clinical hyperthyroidism or with resistance to TSH. Activating mutations involving the B subunit of the TSH-R have been found in solitary autonomous adenomas and in multinodular goiters as well as in rare cases of sporadic familial hyperthyroidism. Resistance to TSH due to mutations in either subunit of the receptor is related to high TSH levels.

EFFECTS OF TSH ON THE THYROID CELL

TSH has many actions on the thyroid cell. Most of its actions are mediated through the G protein-adenylyl cyclase-cAMP system, but activation of the phosphatidylinositol (PIP₂) system with increase in intracellular calcium may also be involved. The major actions of TSH include the following:

A. CHANGES IN THYROID CELL MORPHOLOGY

TSH rapidly induces pseudopods at the cell-colloid border, accelerating thyroglobulin resorption. Colloid content is diminished. Intracellular colloid droplets are formed and lysosome formation is stimulated, increasing thyroglobulin hydrolysis.

B. CELL GROWTH

Individual thyroid cells increase in size ; vascularity is increased; and, over a period of time, thyroid enlargement, or goiter, develops.

C. IODINE METABOLISM

TSH stimulates every steps of iodide metabolism, from increased iodide uptake and transport to increased iodination of thyroglobulin and increased secretion of thyroid hormones. The increase in cAMP mediates increased iodide transport, while PIP₂ hydrolysis and increased intracellular Ca²⁺ stimulate the iodination of thyroglobulin. The TSH effect on iodide transport is biphasic: Initially, it is depressed (iodide efflux); and then, after a lag of several hours, iodide uptake is increased. The efflux of iodide may be due to the rapid increase in hydrolysis of thyroglobulin with release of hormone and leakage of iodide out of the gland.

D. OTHER EFFECTS OF TSH

Other effects include increase in mitochondrial RNA for thyroglobulin and thyroperoxidase, with an increase in incorporation of I into MIT, DIT, T₃ and T₄; and increased lysosomal activity, with increased secretion of T₄ and T₃ from the gland. There is also increased activity of type 1 5'-deiodinase, conserving intrathyroidal iodine.

TSH has still other effects on the thyroid gland, including increase of glucose uptake, usage of oxygen, synthesis of carbondioxide, and oxidation of glucose is increased by urea cycle and HMP shunt. There is accelerated turnover

of phospholipids and stimulation of production of purine & pyrimidine precursors, with more production of RNA & DNA..

SERUM TSH

Normally, only α subunit and intact TSH are present in the serum. The level of α subunit is about 0.5–2 $\mu\text{g/L}$; it is elevated in old aged women who attained their menopause and in with TSH producing pituitary mass . The normal level of TSH ranges from 0.5 to 5 m U / L ; it is elevated in hypothyroidism and reduced in hyperthyroidism, whether endogenous or from excessive oral intake of thyroid hormones. The plasma half-life of TSH is half an hour, and the daily synthesis rate is about 40 to 150 mU/d.

CONTROL OF PITUITARY TSH PRODUCTION

The important factors controlling the synthesis and release of Thyroid stimulating hormone are in level of intrathyrotroph T_3 , controls mRNA for Thyroid stimulating hormone formation & its release; and TRH.

TSH synthesis and release are inhibited by high serum levels of T_4 and T_3 (hyperthyroidism) and stimulated by low levels of thyroid hormone (hypothyroidism). Some hormones and drugs inhibit TSH secretion like somatostatin, dopamine, bromocriptine, and glucocorticoids. During illness there will be suppression of TSH, and there may be a rebound rise in TSH as the patient recovers. The magnitude of these effects is variable; thus, the drugs mentioned above will suppress serum TSH, but it will usually be detectable. In contrast, hyperthyroidism will turn off TSH secretion entirely.

These observations are important clinically in interpreting serum TSH levels in patients receiving these medications. Secondary hypothyroidism is one due to pathology in hypothalamus or pituitary, where as tertiary hypothyroidism is due to damage of TRH producing neurons.

OTHER THYROID STIMULATORS & INHIBITORS

The thyroid follicle has a rich supply of capillaries that carry noradrenergic nerve fibers from the superior cervical ganglion and acetylcholine esterase-positive nerve fibers derived from the vagal nodose and thyroid ganglia. The parafollicular C cells secrete both calcitonin and calcitonin gene-related peptide (CGRP). In addition, growth factors such as insulin, IGF-I, and EGF and the autocrine actions of prostaglandins and cytokines may modify thyroid cell growth and hormone production. However, it is not yet clear how important these effects are in clinical situations.

ROLE OF PITUITARY & PERIPHERAL DEIODINASES

T₄ to T₃ is changed by pituitary type 2 5'-deiodinase at the brain and pituitary, providing the main source of intracellular T₃. Its increased activity in hypothyroidism provides in maintaining cerebral intracellular T₃ in the view of reducing serum T₄ concentrations. In hyperthyroidism, the reduction in its action provides in preventing overload of pituitary and neural cells with thyroid hormone. In contrary, type 1 5'-deiodinase is reducing in hypothyroidism, securing T₄, and more in hyperthyroidism, increasing the T₄ metabolism.

THYROIDAL AUTOREGULATION

Autoregulation may be defined as the capacity of the thyroid gland to modify its function to adapt to changes in the availability of iodine, independent of pituitary TSH. Thus, humans can maintain normal thyroid hormone secretion with iodide intakes varying from 50 µg to several milligrams per day. Some of the effects of iodide deficiency or excess are discussed above. The major adaptation to low iodide intake is the preferential synthesis of T₃ rather than T₄, increasing the metabolic effectiveness of the secreted hormone. Iodide excess, on the other hand, inhibits many thyroidal functions, including Iodide transport, production of cAMP, formation of H₂O₂, hormone production & its release and bondage of TSH and TSH –R Ab to its receptor. Some of these effects may be mediated by the formation of intrathyroidal iodinated fatty acids. The ability of the normal thyroid to “escape” from these inhibitory effects (Wolff-Chaikoff effect) allows the gland to continue to secrete hormone despite a high dietary iodide intake. It is important to note that this is different from the therapeutic effect of iodide in the treatment of Graves' disease. Here, the high levels of iodide inhibit thyroglobulin endocytosis and lysosomal activity, decreasing thyroid hormone release and lowering circulating hormone levels. In addition, the inhibition of TSH-R Ab [stim] activity reduces the vascularity of the gland, with beneficial consequences during surgery. This effect is also transient, lasting about 10 days to 2 weeks.

AUTOIMMUNE REGULATION

B lymphocytes are the major one in thyroid regulation by producing TSH receptor antibodies which can block the action of TSH or it can simulate TSH action by binding to various areas on the TSH receptor.

THE ACTION OF THYROID HORMONES

1. THE THYROID HORMONE RECEPTOR

Thyroid hormones, T_3 and T_4 , circulate in plasma largely bound to protein but in equilibrium with the free hormone. It is the free hormone that is transported, either by passive diffusion or by specific carriers, through the cell membrane, through the cell cytoplasm, to bind to a specific receptor in the cell nucleus. Inside the cell, T_4 is changed to T_3 by 5' deiodinase, implicating that T_4 is a proactive and T_3 the functional form of the hormone. In the human, there are two genes for the thyroid hormone receptor, alpha and beta. $TR\alpha$ is located on chromosome 17 and $TR\beta$ on chromosome 3. Each gene produces at least two products, $TR\alpha$ 1 and 2 and $TR\beta$ 1 and 2. Each has three domains: a ligand-independent domain at the amino terminal, a centrally located DNA binding area with two cysteine-zinc "fingers," and a ligand-binding domain at the carboxyl terminal. Note that $TR\alpha$ 2 does not bind T_3 and may actually inhibit T_3 action.

The concentration of these receptors in tissue varies with the stage of development and the tissue. For example, the brain contains mostly TR α , the liver mostly TR β , and cardiac muscle contains both. The binding affinity of T₃ analogs is directly proportionate to the biologic activity of the analog. Point mutations in the ligand-binding domain of the TR β gene are responsible for the syndrome of generalized resistance to thyroid hormone.

The thyroid hormone receptors may bind to the specific thyroid hormone response element (TRE) sites on DNA even in the absence of T₃ (—unlike the steroid hormone receptors). The TREs are located near—generally upstream with respect to the start of transcription—to the promoters where transcription of specific thyroid hormone-responsive genes is initiated. T₃ binding to the receptors results in stimulation—in some cases inhibition—of the transcription of these genes with consequent changes in the levels of the mRNAs transcribed from them. The changes in mRNA levels alter the levels of the protein product of these genes. These proteins then mediate the thyroid hormone response. These receptors often function as heterodimers with other transcription factors such as the retinoid X receptor and the retinoic acid receptor

2. PHYSIOLOGIC EFFECTS OF THYROID HORMONES

The transcriptional effects of T_3 characteristically demonstrate a lag time of hours or days to achieve full effect. These genomic actions result in a number of effects, including those on tissue growth, brain maturation, and increased heat production and oxygen consumption, which is due in part to increased activity of Na^+K^+ ATPase and in part to production of increased beta-adrenergic receptors. Some actions of T_3 are not genomic, such as reduction of pituitary type 2 5'-deiodinase and increase in glucose and amino acid transport. Some specific effects of thyroid hormones are summarized in what follows.

EFFECTS ON FETAL MATURATION

At fetal life of 11 weeks itself TSH and thyroid hormones will begin their functions. Because of the high placental content of type 3 5'-deiodinase, most maternal T_3 and T_4 are inactivated in the placenta, and very little free hormone reaches the fetal circulation. This little quantity of available hormone is essential for fetal brain maturation. However, after 11 wks of pregnancy, the fetus is largely dependent on its own thyroidal secretion. Although some fetal growth occurs in the absence of fetal thyroid hormone secretion, brain development and skeletal maturation are markedly impaired, resulting in cretinism (mental retardation and dwarfism).

EFFECTS ON OXYGEN CONSUMPTION, HEAT PRODUCTION, & FREE RADICAL FORMATION

T_3 increases O_2 consumption and heat production in part by stimulation of Na^+K^+ ATPase in all tissues except the brain, spleen, and testis. This contributes to the increased basal metabolic rate (O_2 consumption by the whole animal at rest) and the increased sensitivity to heat in hyperthyroidism—and the converse in hypothyroidism. Thyroid hormones also decrease superoxide dismutase levels, resulting in increased superoxide anion free radical formation. This may contribute to the deleterious effects of chronic hyperthyroidism.

CARDIOVASCULAR EFFECTS

T_3 induces transcription of α part of myosin heavy chain and depresses β heavy chain, making more cardiac muscle contractility. In addition T_3 fastens transcription of Ca^{2+} ATPase in the sarcoplasmic reticulum, raising diastolic tone of the heart; changes isoforms of Na^+K^+ ATPase genes; and raises beta-adrenergic receptors and the concentration of G proteins. So, thyroid hormones have marked positive inotropic and chronotropic effects on the heart. This makes, there is high cardiac output & hear rate in hyperthyroidism whereas low in hypothyroidism.

SYMPATHETIC EFFECTS

Thyroid hormones raises more number of beta-adrenergic receptors in heart & skeletal muscle, adipose tissue, and lymphocytes. It also slows the myocardial alpha-adrenergic receptors. They also may accelerate catecholamine action at a postreceptor site. Thus, response to catecholamines is more pronounced in hyperthyroidism, and treatment with beta-adrenergic blocking agents may be very helpful in controlling tachycardia and arrhythmias.

PULMONARY EFFECTS

Thyroid hormones maintain normal oxygen and carbondioxide demand by keeping respiratory centre active. In severe hypothyroidism, hypoventilation occurs, occasionally requiring assisted ventilation.

HEMATOPOIETIC EFFECTS

The increased cellular demand for O_2 in hyperthyroidism leads to increased production of erythropoietin and increased erythropoiesis. However, blood volume is usually not increased because of hemodilution and increased red cell turnover. Thyroid hormones increase the 2,3-diphosphoglycerate content of erythrocytes, so that it makes more displacement of O_2 from haemoglobin to tissues. The reverse occurs in hypothyroidism.

GASTROINTESTINAL EFFECTS

Thyroid hormones stimulate gut motility, which can result in increased motility and diarrhea in hyperthyroidism and slowed bowel transit and constipation in hypothyroidism. This may also contribute to the modest weight loss in hyperthyroidism and weight gain in hypothyroidism.

SKELETAL EFFECTS

Thyroid hormones stimulate increased bone turnover, increasing bone resorption and, to a lesser degree, bone formation. Thus, chronic hyperthyroidism may result in significant osteopenia and, in severe cases, modest hypercalcemia, hypercalciuria, and increased excretion of urinary hydroxyproline and pyridinium cross-links.

NEUROMUSCULAR EFFECTS

Although thyroid hormones stimulate increased synthesis of many structural proteins, in hyperthyroidism there is increased protein turnover and loss of muscle tissue, or myopathy. This may be associated with spontaneous creatinuria. Increased reflexes in hyperthyroidism is due to fast muscle contraction and relaxation or the reverse in hypothyroidism. Thyroid hormones are essential for normal development and function of the central nervous system, and failure of fetal thyroid function results in severe mental retardation. In the adult, hyperactivity in hyperthyroidism and sluggishness in hypothyroidism can be striking.

EFFECTS ON LIPID & CARBOHYDRATE METABOLISM

Hyperthyroidism increases liver glucose production and glycogen breakdown as well as gut glucose absorption. Thus, hyperthyroidism will exacerbate underlying diabetes mellitus. Cholesterol synthesis and degradation are both increased by thyroid hormones. The latter effect is due largely to an increase in the hepatic low-density lipoprotein (LDL) receptors, so that cholesterol levels decline with thyroid overactivity. Lipolysis is also increased, releasing fatty acids and glycerol. Conversely, cholesterol levels are elevated in hypothyroidism.

ENDOCRINE EFFECTS

Thyroid hormones increase the metabolic turnover of many hormones and pharmacologic agents. Increases the half life of cortisol. The production rate of cortisol will increase in the hyperthyroid patient with normal adrenal function, thus maintaining a normal circulating hormone level. However, in a patient with adrenal insufficiency, the development of hyperthyroidism or thyroid hormone treatment of hypothyroidism may unmask the adrenal disease. Ovulation may be impaired in both hyperthyroidism and hypothyroidism, resulting in infertility, which will be corrected by restoration of the euthyroid state. Serum prolactin levels are increased in about 40% of patients with hypothyroidism, presumably a manifestation of increased TRH release; this will revert to normal with T₄ therapy..

PHYSIOLOGIC CHANGES IN THYROID FUNCTION

THYROID FUNCTION IN THE FETUS

Prior to the development of independent fetal thyroid function, the fetus is dependent on maternal thyroid hormones for early neural development. However, by the 11th week of gestation, the hypophysial portal system has developed, and measurable TSH and TRH are present. At about the same time, the fetal thyroid begins to trap iodine. The secretion of thyroid hormone probably begins in mid gestation (18–20 weeks). TSH increases rapidly to peak levels at 24–28 weeks, and T_4 levels peak at 35–40 weeks. T_3 levels remain low during gestation; T_4 is converted to rT_3 by type 3 5-deiodinase during fetal development. At birth, there is a sudden marked rise in TSH, a rise in T_4 , a rise in T_3 , and a fall in rT_3 . These parameters gradually return to normal over the first month of life.

THYROID FUNCTION IN PREGNANCY

The striking change in thyroid parameters during pregnancy is the rise in TBG and consequent rise in total T_4 and total T_3 in the serum. The rise in TBG is due to estrogen-induced hepatic glycosylation of TBG with N-acetylgalactosamine, which prolongs the metabolic clearance rate of TBG. There is usually no change in thyroxine-binding prealbumin and little change in albumin. Although total T_4 and T_3 are increased, a new equilibrium develops between free and bound thyronines, and the levels of free T_4 and free T_3 are

normal. Other changes in pregnancy include an increase in iodide clearance, which, in areas of low iodine intake, may result in impaired hormone synthesis and a fall in T_4 , a rise in TSH, and thyroid enlargement. hCG, which peaks near the end of the first trimester, has a weak TSH agonist activity and may be responsible for the slight thyroid enlargement that occurs at that time. Maternal I^- crosses the placenta and supplies the fetal requirement; in large amounts, I^- can inhibit fetal thyroid function. Maternal TSH-R Ab [stim] and TSH-R Ab [block] can also cross the placenta and may be responsible for thyroid dysfunction in the fetus. As noted above, most maternal T_3 and T_4 are deiodinated by placental type 3 5-deiodinase and do not reach the fetus. However, antithyroid drugs such as propylthiouracil and methimazole do cross the placenta and in large doses will block fetal thyroid function.

CHANGES IN THYROID FUNCTION WITH AGING

Thyroxine turnover is highest in infants and children and gradually falls to adult levels after puberty. The T_4 turnover rate is then stable until after age 60, when it again drops slightly. Thus, replacement doses of levothyroxine will vary with age and other factors, and patients taking the drug must be monitored regularly.

EFFECTS OF ACUTE & CHRONIC ILLNESS ON THYROID FUNCTION (EUTHYROID SICK SYNDROME)

Acute or chronic illness may have striking effects on circulating thyroid hormone levels by modifying the peripheral metabolism of T_4 or by interference with T_4 binding to TBG. These effects can be classified as (1) the low T_3 syndrome or (2) the low T_3 - T_4 syndrome.

Inhibition of outer ring type 1 5'-deiodinase or activation of type 3 5-deiodinase accelerates conversion of T_4 to rT_3 and conversion of T_3 to 3,3'- T_2 . These reactions will markedly lower the circulating level of T_3 , resulting in the low T_3 syndrome. This occurs physiologically in the fetus and pathologically in circumstances of carbohydrate restriction, as in malnutrition, starvation, anorexia nervosa, and diabetes mellitus, and in patients with hepatic disease or major acute or chronic systemic illnesses. Drugs that inhibit type 1 5'-deiodinase also lower the circulating levels of T_3 ; corticosteroids, amiodarone, and iodinated dyes are the most effective, and propylthiouracil and propranolol are relatively weak. The pathogenesis of the low T_3 syndrome when associated with acute or chronic illness is thought to involve cytokines such as tumor necrosis factor, secreted by inflammatory cells, which inhibit type 1 5'-deiodinase, accelerating inner ring deiodination of T_4 .

T_3 levels are low; total T_4 levels are normal or slightly elevated; free T_4 often is slightly elevated; and rT_3 is elevated. TSH is normal. True

hypothyroidism can be ruled out by the normal T_4 , FT_4 , and TSH and by the elevated rT_3 .

Patients with the low T_3 - T_4 syndrome are usually much sicker, and indeed the mortality rate in this group of patients may approach 50%. Serum T_3 and T_4 levels are both low; FT_4 is usually normal; and rT_3 is elevated. TSH is usually normal, though it may be low if the patient is receiving dopamine or corticosteroids, which suppress TSH. The pathogenesis of this syndrome is thought to involve the liberation of unsaturated fatty acids, such as oleic acid, from anoxic or injured tissue, which inhibits the binding of T_4 to TBG. The syndrome can be differentiated from true hypothyroidism by the normal levels of free T_4 and TSH.

These abnormalities normalize when the patient recovers. Recovery is frequently accompanied by a transient elevation of the serum TSH that may be misinterpreted as hypothyroidism. In this setting, in the absence of clinically apparent hypothyroidism, it is best to avoid thyroid hormone therapy and to reevaluate at a later time following recovery. It is possible that intracellular hypothyroidism exists in these patients, but administration of T_3 or T_4 does not benefit the patient and may worsen the situation. Thus, these changes may represent a protective adaptation on the part of the organism to severe illness.

TESTS OF THYROID FUNCTION

The function of the thyroid gland may be evaluated in many different ways:

- (1) blood level of thyroid hormones,
- (2) study of the hypothalamic-pituitary-thyroid axis,
- (3) evaluation of iodine metabolism,
- (4) gland size measurement,
- (5) biopsy of gland ,
- (6) action on peripheral tissues by thyroid hormone,
- (7) magnitude of thyroid autoantibodies.

TESTS OF THYROID HORMONES IN BLOOD

The total serum T_4 and total serum T_3 are measured by radioimmunoassay or immunofluorescent assay. If the concentration of serum thyroid hormone binding proteins is normal, these measurements provide a reasonably reliable index of thyroid gland activity. However, changes in serum concentration of thyroid-binding proteins or the presence of drugs that modify the binding of T_4 or T_3 to TBP will modify the total T_4 and T_3 but not the amount of free hormone. Thus, further tests must be performed to assess the free hormone level that determines biologic activity.

Serum free thyroxine (FT_4) can be estimated using the free thyroxine index (FT_4I). This is the product of the total T_4 multiplied by the percentage of free T_4 as estimated by the amount of T_4 which binds to resin or

charcoal added to the system. A more precise estimate of free thyroxine is obtained by a two-step chemiluminescent immunoassay in which the thyroxine antibody system is modified to react with the free hormone. The normal range for FT₄ by this assay is 0.7–1.85 ng/dL (9–24 pmol/L). Although the FT₄I or the FT₄ is valid for normal subjects, these assays may not be valid in subjects with dysproteinemias and abnormal thyroxine-binding proteins (TBPs)—or in subjects taking medications modifying TBP or in subjects with the euthyroid sick syndrome. In these subjects, free thyroxine by equilibrium dialysis (FT₄D) will more accurately reflect the level of free thyroxine. Note that FT₄ does not measure T₃, so that patients receiving high oral doses of T₃ or with T₃ hyperthyroidism, FT₄ may be low despite the hyperthyroid state (T₃ toxicosis). Antiepileptic drugs such as phenytoin and carbamazepine and the antituberculous drug rifampin increase hepatic metabolism of T₄, resulting in a low total T₄, a low free T₄, and a low FT₄I. However, serum T₃ and serum TSH levels are normal, indicating that patients receiving these drugs are euthyroid. T₄ and FT₄I may be low in severe illness, but FT₄D and TSH are usually normal, which will distinguish these very ill patients from patients who are hypothyroid.

At times, FT₄I and FT₄D will be inappropriately elevated. For example, drugs such as iodinated contrast media, amiodarone, glucocorticoids, and propranolol inhibit type 1 5'-deiodinase and the conversion of T₄ to T₃ in peripheral tissues, resulting in elevation of total T₄, FT₄I, and FT₄D and

depression of T_3 . Hyperthyroidism is ruled out by the low T_3 and normal TSH. FT_4I and FT_4D are inappropriately elevated in the rare syndrome of generalized resistance to thyroid hormone. The presence of heparin in serum, even in the tiny amounts that would be found in a patient with a “heparin lock” indwelling intravenous catheter, will cause a spurious increase in FT_4D . This occurs in the test tube, since heparin activates lipoprotein lipase, releasing free fatty acids that displace T_4 from TBG.

Total T_3 can be measured in serum by immunoassay with specific T_3 antisera. The normal range in adults is 70–132 ng/dL (1.1–2 nmol/L). The measurement of total T_3 is most useful in the differential diagnosis of hyperthyroidism, because T_3 is preferentially secreted in early Graves' disease or toxic nodular goiter. In hyperthyroidism, this ratio will usually be well over 20, and it will be even higher in T_3 thyrotoxicosis. T_3 levels are often maintained in the normal range in hypothyroidism because TSH stimulation increases the relative secretion of T_3 ; thus, serum T_3 is not a good test for hypothyroidism.

T_3 is bound to TBG, and the total T_3 concentration in serum will vary with the level of TBG. Serum free T_3 (FT_3) can be measured by immunoassay or more precisely by equilibrium dialysis; the normal adult FT_3 is 230–420 pg/dL (3.5–6.5 pmol/L).

Reverse T_3 (rT_3) can be measured by radioimmunoassay. The serum concentration of rT_3 in adults is about one-third of the total T_3 concentration, with a range of 25–75 ng/dL (0.39–1.15 nmol/L). RT_3 can be used to

differentiate chronic illness from hypothyroidism because rT_3 levels are elevated in chronic illness and low in hypothyroidism. However, this differential diagnosis can be made by determination of TSH (see below), so that it is rarely necessary to measure rT_3 .

Thyroglobulin(Tg) can be measured in serum by double antibody radioimmunoassay. The normal range will vary with method and laboratory, but generally the normal range is less than 40 ng/mL ($< 40 \mu\text{g/L}$) in the euthyroid individual and less than 2 ng/mL ($< 2 \mu\text{g/L}$) in a totally thyroidectomized individual. The major problem with the test is that endogenous thyroglobulin antibodies interfere with the assay procedure and, depending on the method, may result in spuriously low or spuriously high values. Serum thyroglobulin is elevated in situations of thyroid overactivity such as Graves' disease and toxic multinodular goiter; in subacute or chronic thyroiditis, where it is released as a consequence of tissue damage; and in patients with large goiters, in whom the thyroglobulin level is proportionate to the size of the gland. Serum thyroglobulin determinations have been most useful in the management of patients with papillary or follicular thyroid carcinoma. Following thyroidectomy and ^{131}I therapy, thyroglobulin levels should be very low. In such a patient, serum thyroglobulin greater than 2 ng/dL ($> 2 \mu\text{g/L}$) indicates the presence of metastatic disease, and a rise in serum thyroglobulin in a patient with known metastases indicates progression of the disease.

EVALUATION OF THE HYPOTHALAMIC-PITUITARY-THYROID AXIS

It has not been clinically feasible to measure TRH in the peripheral circulation in humans. However, very sensitive methods for the measurement of TSH have been developed using monoclonal antibodies against human TSH. The general principle is this: One monoclonal TSH antibody is fixed to a solid matrix to bind serum TSH, and a second monoclonal TSH antibody labeled with isotope or enzyme or fluorescent tag will bind to a separate epitope on the TSH molecule. The quantity of TSH in the serum is thus proportionate to the quantity of bound second antibody. The earlier TSH radioimmunoassays, which could detect about 1 μU of TSH/mL, were adequate for the diagnosis of elevated TSH in hypothyroidism but could not detect suppressed TSH levels in hyperthyroidism. The “second generation” of “sensitive” TSH assays, using monoclonal antibodies, can detect about 0.1 $\mu\text{U}/\text{mL}$, and the “third generation” of “supersensitive” assays are sufficiently sensitive to detect about 0.01 $\mu\text{U}/\text{mL}$. This has allowed measurement of TSH well below the normal range of 0.5–5 $\mu\text{U}/\text{mL}$ (0.5–5 mU/L) and has enabled the clinician to detect partially and totally suppressed serum TSH levels. The level of FT_4 is inversely related to the logarithm of the TSH concentration. Thus, a small change in FT_4 may result in a large change in TSH. Serum TSH below 0.1 $\mu\text{U}/\text{mL}$ (0.1 mU/L) and an elevated FT_4 or FT_4I is indicative of hyperthyroidism. This may be due to Graves' disease, toxic nodular goiter, or high-dose thyroxine therapy. In the rare case of hyperthyroidism due to a TSH-

secreting pituitary tumor, FT₄I or FT₄ will be elevated and TSH will not be suppressed but will actually be normal or slightly elevated. An elevated TSH (> 10 μU/mL; 10 mU/L) and a low FT₄ or FT₄I is diagnostic of hypothyroidism. In patients with hypothyroidism due to a pituitary or hypothalamic tumor (central hypothyroidism), FT₄I or FT₄ will be low and TSH will not be elevated. This diagnosis can be confirmed by demonstrating the failure of serum TSH to increase following an injection of TRH. The TRH test is performed as follows: 200 μg of TRH is administered intravenously. Serum TSH is measured before to the injection and after half an hour and an hour afterward. The absence of a rise in TSH indicates either pituitary insufficiency or suppression. A modest or delayed rise may be seen in patients with hypothalamic disease and hypothyroidism. The test can also be used to differentiate the hyperthyroxinemia of the T₃ resistance syndrome from thyrotoxicosis due to a TSH-secreting pituitary tumor. TRH will produce a rise in TSH in the patient with a thyroid hormone resistance syndrome, whereas TSH-secreting tumors will not respond to TRH. Note that corticosteroids and dopamine inhibit TSH secretion, which will modify the interpretation of serum TSH levels in patients taking these drugs.

Serum TSH levels reflect the anterior pituitary gland sensing the level of circulating FT₄. High FT₄ levels suppress TSH and low FT₄ levels increase TSH release. Thus, the ultrasensitive measurement of TSH has become the most sensitive, most convenient, and most specific test for the diagnosis of both

hyperthyroidism and hypothyroidism. Indeed, a suppressed TSH correlates so well with impaired pituitary response to TRH that the simple measurement of serum TSH has replaced the TRH test in the diagnosis of hyperthyroidism.

IODINE METABOLISM & BIOSYNTHETIC ACTIVITY

Radioactive iodine allows assessment of the turnover of iodine by the thyroid gland in vivo. Iodine-123 is the ideal isotope for this purpose: It has a half-life of 13.3 hours and releases a 28-keV x-ray and a 159-keV gamma photon but no beta emissions. Thus, it is easily measured and causes little tissue damage. It is usually administered orally in a dose of 100–200 μ Ci, and radioactivity over the thyroid area is measured with a scintillation counter at 4 or 6 hours and again at 24 hours. The normal radioactive iodine uptake (RAIU) will vary with the iodide intake. In areas of low iodide intake and endemic goiter, the 24-hour RAIU may be as high as 60–90%. In hyperthyroidism due to Graves' disease or toxic nodular goiter, the 24-hour radioactive iodine uptake is markedly elevated, though if the iodide turnover is very rapid, the 5-hour uptake may be even higher than the 24-hour uptake.

Thyrotoxicosis with a very low thyroidal RAIU occurs in the following situations: (1) in subacute thyroiditis; (2) during the active phase of Hashimoto's thyroiditis, with release of preformed hormone, causing “spontaneously resolving thyrotoxicosis”; (3) in thyrotoxicosis factitia due to oral ingestion of a large amount of thyroid hormone; (4) as a result of excess iodide intake (eg, amiodarone therapy), inducing thyrotoxicosis in a patient with

latent Graves' disease or multinodular goiter, the low uptake being due to the huge iodide pool; (5) in struma ovarii; and (6) in ectopic functioning metastatic thyroid carcinoma after thyroidectomy.

Test	Symbol	Normal Range
Thyroxine	T4	4.5-12 µg/dL
Thiodothyronine	T3	90-200 ng/dL
Thyroid-stimulating hormone	TSH	0.4-4.5 µIU/mL
Free T4	FT4	0.7-1.6 ng/dL
Free T3	FT3	230-420 ng/L
Iodine-131 uptake	RAIU	8%-35% at 24 h

THYROID IMAGING

1. RADIONUCLIDE IMAGING

^{123}I and technetium Tc 99m pertechnetate ($^{99\text{m}}\text{Tc}$ as TcO_4) are useful for determining the functional activity of the thyroid gland. ^{123}I is administered orally in a dose of 200–300 μCi , and a scan of the thyroid is obtained at 8–24 hours. $^{99\text{m}}\text{TcO}_4$ is administered intravenously in a dose of 1–10 mCi, and the scan is obtained at 30–60 minutes. Images can be obtained with either a rectilinear scanner or a gamma camera. The rectilinear scanner moves back and forth over the area of interest; it produces a life-size picture, and special areas, such as nodules, can be marked directly on the scan. The gamma camera has a pinhole collimator, and the scan is obtained on a fluorescent screen and recorded on Polaroid film or a computer monitor. The camera has greater resolution, but special areas must be identified with a radioactive marker for clinical correlation. Radionuclide scans provide information about both the size and shape of the thyroid gland and the geographic distribution of functional activity in the gland. Functioning thyroid nodules are called “hot” nodules, and those not functioning are called “cold” nodules. The malignancy accounts only less than 1% as hot nodules and they turn into toxic and cause thyrotoxicosis. Among cold nodules 16% were malignant. Occasionally, a nodule will be hot with $^{99\text{m}}\text{TcO}_4$ and cold with ^{123}I , and a few of these nodules have been malignant. ^{131}I is the preferred isotope for huge substernal goiter & for distant metastases.

2. FLUORESCENT SCANNING

The iodine content can be determined and an image of the thyroid gland can be obtained by fluorescent scanning without administration of a radioisotope. An external source of americium-241 is beamed at the thyroid gland, and the resulting emission of 28.5 keV x-ray from iodide ions is recorded, producing an image of the thyroid gland similar to that obtained with ¹²³I. The advantage of this procedure is that the patient receives no radioisotope and the gland can be imaged even when it is loaded with iodine—as, for example, after intravenous contrast media. The disadvantage of this study is that it requires specialized equipment that may not be generally available.

THYROID ULTRASONOGRAPHY OR MAGNETIC RESONANCE IMAGING

A rough estimate of thyroid size and nodularity can be obtained from radionuclide scanning, but much better detail can be obtained by thyroid ultrasonography or MRI.

USG of thyroid is helpful in finding the size of gland or nodular size and for assessment of treatment. It is helpful also for differentiating cystic lesions from solid one. Substernal goiter cannot be assessed by USG.

MRI has more advanced technique and gives good picture of thyroid gland, posterior or substernal extension pathology. Both transverse and coronal images of the gland can be obtained, and lymph nodes as small as 1 cm can be

visualized. MRI is not useful in tracheal compression from a huge goiter, tracheal invasion by thyroid tumours, or metastases to lymph nodes.

THYROID BIOPSY

The best procedure for differentiating from benign and malignant disease is Fine-needle aspiration biopsy. It is a simple to perform and no admission required. The skin over the nodule is cleansed with alcohol, and, if desired, a small amount of 1% lidocaine can be injected intracutaneously for local anesthesia. A No. 25 3.75 cm needle is pierced in the gland and moved to and fro till a little quantity of blood comes in needle and it is taken out., and with a syringe the contents of the needle is put onto a sterile slide. A second clean slide is placed on top of the first slide, and a thin smear is obtained by drawing the slides apart quickly. Alternatively, a 10 mL or 20 mL syringe in an appropriate syringe holder can be used with a No. 23 one-inch needle to sample the nodule or to evacuate cystic contents.

Using Wright's or Giemsa's stain, fixed in alcohol and with Papanicolaou stain slides are fixed or made dry. The sensitivity (true-positive results divided by total cases of disease) is about 95%, and the specificity (true-negative results divided by total cases of no disease) is also about 95%. For best results, fine-needle aspiration biopsy it needs a fair amount of sample and cytologist experience.

EFFECTS OF THYROID HORMONES ON PERIPHERAL TISSUES

The definitive test of thyroid function would be a test of the effect of thyroid hormones on body tissues. Thyroid hormones increase heat production and oxygen consumption. A measurement of this basal oxygen in the intact organism became one of the first tests of thyroid function, the basal metabolic rate (BMR). However, this test is nonspecific and insensitive and is rarely used today. The speed of muscle stretching and relaxation is increased in hyperthyroidism and decreased in hypothyroidism.

Cardiac muscle contractility can also be measured as an index of thyroid hormone action. With echocardiography, it is relatively easy to measure such indices as the preejection period (PEP), the time from onset of the QRS complex to the opening of the aortic valve; or the left ventricular ejection time (LVET). These are prolonged in hypothyroidism and shortened in hyperthyroidism. Although these measurements are modified by coexistent cardiac disease, they may be the best objective tests for measuring the peripheral effects of thyroid hormone action.

Thyroid hormones influence the concentration of a number of enzymes and blood constituents. serum cholesterol is usually lowered in hyperthyroidism and elevated in hypothyroidism. Serum creatine kinase and lactic dehydrogenase, probably of skeletal muscle origin, are elevated in hypothyroidism and indeed, isoenzyme determination may be required to

differentiate the enzyme changes occurring in myocardial infarction from those occurring in myxedema.

Sex hormone-binding globulin (SHBG) and angiotensin-converting enzyme are also increased in hyperthyroidism and decreased in hypothyroidism. However, none of these biochemical or enzyme changes are sensitive or specific enough for diagnostic use.

MEASUREMENT OF THYROID AUTOANTIBODIES

Thyroid autoantibodies are

- (1) thyroglobulin antibody
- (2) thyroperoxidase antibody
- (3) TSH receptor antibody.

Thyroglobulin antibody and Thyroperoxidase antibody will be found by using hemagglutination, enzyme-linked immunosorbent assay (ELISA), or radioimmunoassay (RIA). The hemagglutination technique is much less sensitive than the ELISA or RIA methods. The incidence of positive TPO antibodies in normal men (by hemagglutination) was low about 2% and did not increase with age. On the other hand, high Tg Ab and TPO Ab titers by RIA are found in 97% of patients with Graves' disease or Hashimoto's thyroiditis.

Thyroglobulin antibodies are often high early in the course of Hashimoto's thyroiditis and decrease with time; TPO antibodies are usually measurable for the life of the patient. The titers of both Tg and TPO antibodies will decrease with time following institution of T₄ therapy in Hashimoto's thyroiditis or with

antithyroid therapy in Graves' disease. A strongly positive test for either of these antibodies is an indication of the presence of autoimmune thyroid disease but is not specific for the type of disease, ie, hyperthyroidism, hypothyroidism, or goiter.

The thyroid receptor stimulating antibody (TSH-R Ab) is characteristic of Graves' disease. It was originally measured by demonstrating prolonged discharge of radioiodine from the thyroid gland of the mouse after injection of serum from a patient with Graves' disease; it was then called long-acting thyroid stimulator (LATS). This laborious assay was now outdated and bioassay was being used using hamster ovary cells. Next, the rise in cAMP of thyroid is evaluated by incubation with serum or IgG. The results was positive in 80–90% of patients with Graves' disease and undetectable in healthy subjects or patients with Hashimoto's thyroiditis (without ophthalmopathy), nontoxic goiter, or toxic nodular goiter. It is most useful for the diagnosis of Graves' disease in patients with euthyroid ophthalmopathy or in predicting neonatal Graves' disease in the newborn of a mother with active or past Graves' disease.

The same type of assay can be used to detect TSH receptor-blocking antibody. In this assay, the increase in cAMP induced by TSH added to a human thyroid cell culture or the culture of hamster ovary cells containing the TSH-R gene is blocked by concurrent incubation with the patient's serum. The TSH-binding inhibition assay (TBII) measures the ability of serum IgG to inhibit the

binding of labeled TSH to a thyroid cell membrane preparation containing the TSH receptor. This technique is not as satisfactory as the bioassay because there are a variety of nonspecific interfering substances, such as thyroglobulin, which inhibit TSH binding. However, a modification of the TSH-binding inhibition assay using recombinant human TSH receptor has proved to be more reliable. Detection of a TSH receptor-blocking antibody in maternal serum may be very helpful in predicting the occurrence of congenital hypothyroidism in newborns of mothers with autoimmune thyroid disease.

SUMMARY: CLINICAL USE OF THYROID FUNCTION TESTS

The diagnosis of thyroid disease has been greatly simplified by the development of sensitive assays for TSH and free thyroxine. The estimate of free thyroxine, either FT₄I or FT₄, and a sensitive TSH determination are used both for the diagnosis of thyroid disease and for following patients receiving T₄ replacement or antithyroid drug therapy. An elevated TSH and low free thyroxine establish the diagnosis of hypothyroidism, and a suppressed TSH and elevated FT₄ establish the diagnosis of hyperthyroidism.

Other tests are available for special uses. In hypothyroidism, Tg Ab or TPO Ab tests will clarify the cause of the illness, and in hyperthyroidism elevation of free T₃, abnormal radioiodine uptake and scan, and a positive test for TSH-R Ab] may be useful. In patients with nodules or goiter, fine-needle aspiration biopsy will rule out malignancy; radioiodine scan may help to determine function; and thyroid ultrasound or MRI may be helpful in following

the size or growth of the goiter. Patients with known thyroid cancer are followed with serial thyroglobulin determinations, and ^{131}I scan or MRI may be useful for detection of metastatic disease.

HYPERTHYROIDISM & THYROTOXICOSIS

Hyperthyroidism is one condition where excess amount of thyroid hormone is synthesized. Thyrotoxicosis is a clinical diagnosis due to tissue exposure to high levels of thyroid hormone in blood. Sometimes it may be arise due to over intake of hormone or ectopic site production.

The various forms of thyrotoxicosis are

1. DIFFUSE TOXIC GOITER (GRAVES' DISEASE)

Graves' disease is the most common form of thyrotoxicosis and may occur at any age, more commonly in females than in males. The syndrome consists of one or more of the following features: (1) thyrotoxicosis, (2) goiter, (3) ophthalmopathy (exophthalmos), and (4) dermopathy (pretibial myxedema).

ETIOLOGY

Graves' disease is an autoimmune disease of unknown etiology.

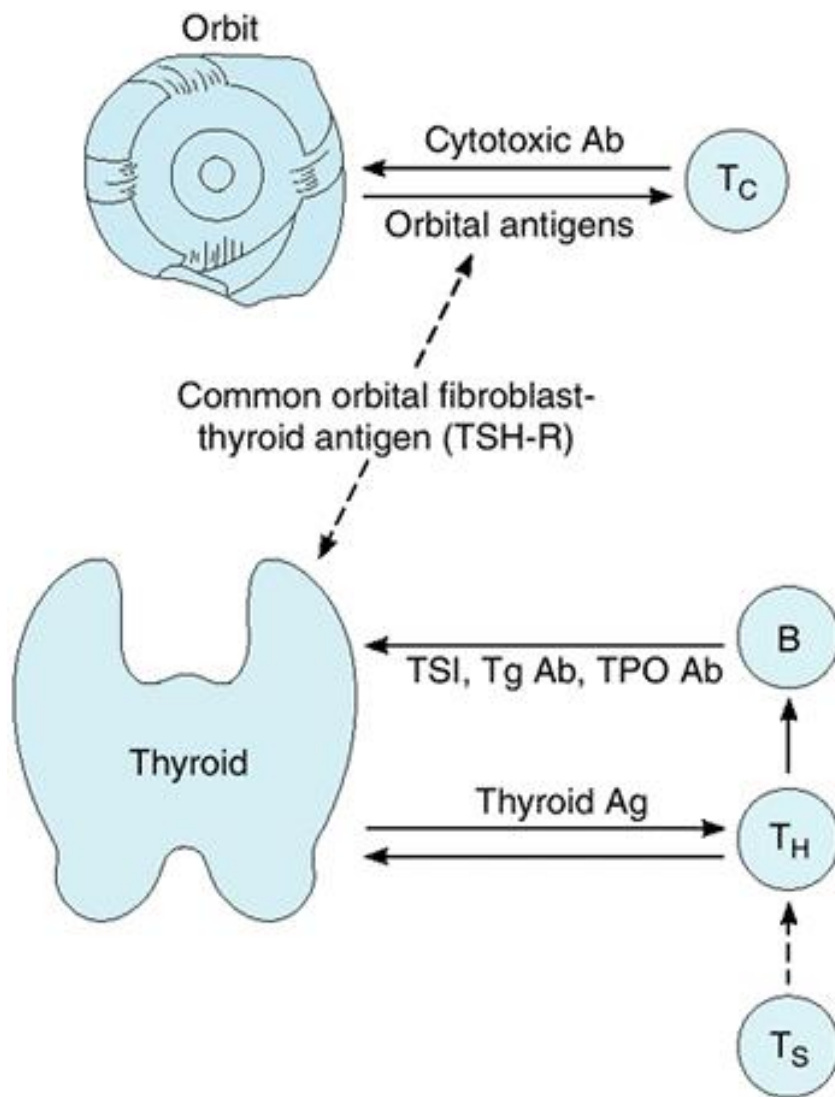
Nowadays it is suggested there is more hereditary risk of developing disease is around 15%. Females to male ratio is 5: 1 in developing disease and mean age of presentation would be 20 to 40 years.

PATHOGENESIS

In Graves' disease, T lymphocytes become activated to antigens in the thyroid gland and activate B lymphocytes to produce antibodies. One antibody is marked towards the TSH receptor site in the thyroid cell and has the ability to stimulate the thyroid cell to increased growth and function. The presence of this circulating antibody is positively correlated with active disease and with relapse of the disease. There is an strong hereditary predisposition, but still it's a question of debate which triggers acute reaction. There are various factors that may aggravate the immune response like ,(1) pregnancy, especially after delivery; (2) iodide deficient areas ; (3) treatment with lithium; (4)infections; and (5) glucocorticoid stoppage.

The mechanism of ophthalmopathy is due to cytotoxic lymphocytes and cytotoxic antibodies acts against to a antigen TSH-R present in orbital fibroblasts, orbital muscle, and thyroid tissue. Cytokines from these sensitized lymphocytes would cause inflammation of orbital fibroblasts and orbital myositis, resulting in enlarged orbital muscles, proptosis of the eye balls, and diplopia as well as redness, congestion, and conjunctival and periorbital edema.

The pathogenesis of thyroid dermopathy (pretibial myxedema) and the rare subperiosteal inflammation on the phalanges of the hands and feet (thyroid osteopathy) it may also involve lymphocyte cytokine stimulation of fibroblasts in these locations.



PATHOGENESIS OF GRAVE'S DISEASE

CLINICAL FEATURES

A. SYMPTOMS AND SIGNS

In younger individuals, common manifestations include increased heart beat, anxiety, easy tiredness, increased movements, loose stools, increased sweating, heat intolerance, increased loss of weight with increase in loss of appetite. Swelling of gland, eye signs, and mild high heart rate may be seen. Muscle weakness and loss of muscle mass may be so severe that the patient cannot rise from a chair without assistance. In children, rapid growth with accelerated bone maturation occurs.

In patients over age 60, cardiovascular and myopathic manifestations predominate; the most common presenting complaints are palpitation, dyspnea on exertion, tremor, nervousness, and weight loss.

The eye signs of Graves' disease have been classified by Werner. This classification is useful in describing the extent of the eye involvement.

The first letters of each class form the mnemonic "NO SPECS."

Class I involves upper lids spasm related with active thyrotoxicosis and subsides when thyrotoxicosis is controlled.

Classes II-VI denote infiltrative disease involving orbital muscles and orbital tissues.

Class II is associated with involvement of soft tissue with periorbital edema, congestion and edema of the conjunctiva.

Class III is proptosis found by the Hertel exophthalmometer.

Class IV consists of muscle involvement. The muscle most commonly involved in the infiltrative process is the inferior rectus, limiting upward gaze. Medial rectus is also affected so that lateral gaze is difficult.

Class V is involvement of cornea.

Class VI loss of vision from optic nerve involvement.

Thyroid ophthalmopathy is because of infiltration of muscles of orbit with lymphocytes and edema fluid formed because of inflammation. The orbit is a cone enclosed by bone, and swelling of the extraocular muscles within this closed space causing enlargement of the eyeball and restricted muscle movement, resulting in diplopia. Ocular muscle enlargement can be demonstrated by orbital CT scanning or MRI. When muscle swelling occurs posteriorly, toward the apex of the orbital cone, the optic nerve is compressed, which may cause loss of vision.



EYE CHANGES IN THYROID OPHTHALMOPATHY

Class	Definition
0	No signs or symptoms.
1	Only signs, no symptoms. (Signs limited to upper lid retraction, stare, lid lag.)
2	Soft tissue involvement (symptoms and signs).
3	Proptosis (measured with Hertel exophthalmometer). ²
4	Extraocular muscle involvement.
5	Corneal involvement.
6	Sight loss (optic nerve involvement).

CLASSIFICATION OF EYE CHANGES IN GRAVE'S DISEASE

Thyroid dermopathy is skin thickening in legs because of increased glycosaminoglycans . Rare condition involving two to three per 100 persons having Graves' disease. Often comes along with ophthalmopathy. TSH receptor antibody levels will be high.They will have hard skin and difficult to hold in hands. Sometimes the dermopathy involves the entire lower leg and may extend onto the feet. Bony involvement (osteopathy), with subperiosteal bone formation and swelling, is particularly evident in the metacarpal bones . This too is a relatively rare finding. A more common finding in Graves' disease is separation of the fingernails from their beds, or onycholysis.



GRAVE'S DERMOPATHY



GRAVE'S OSTEOPATHY

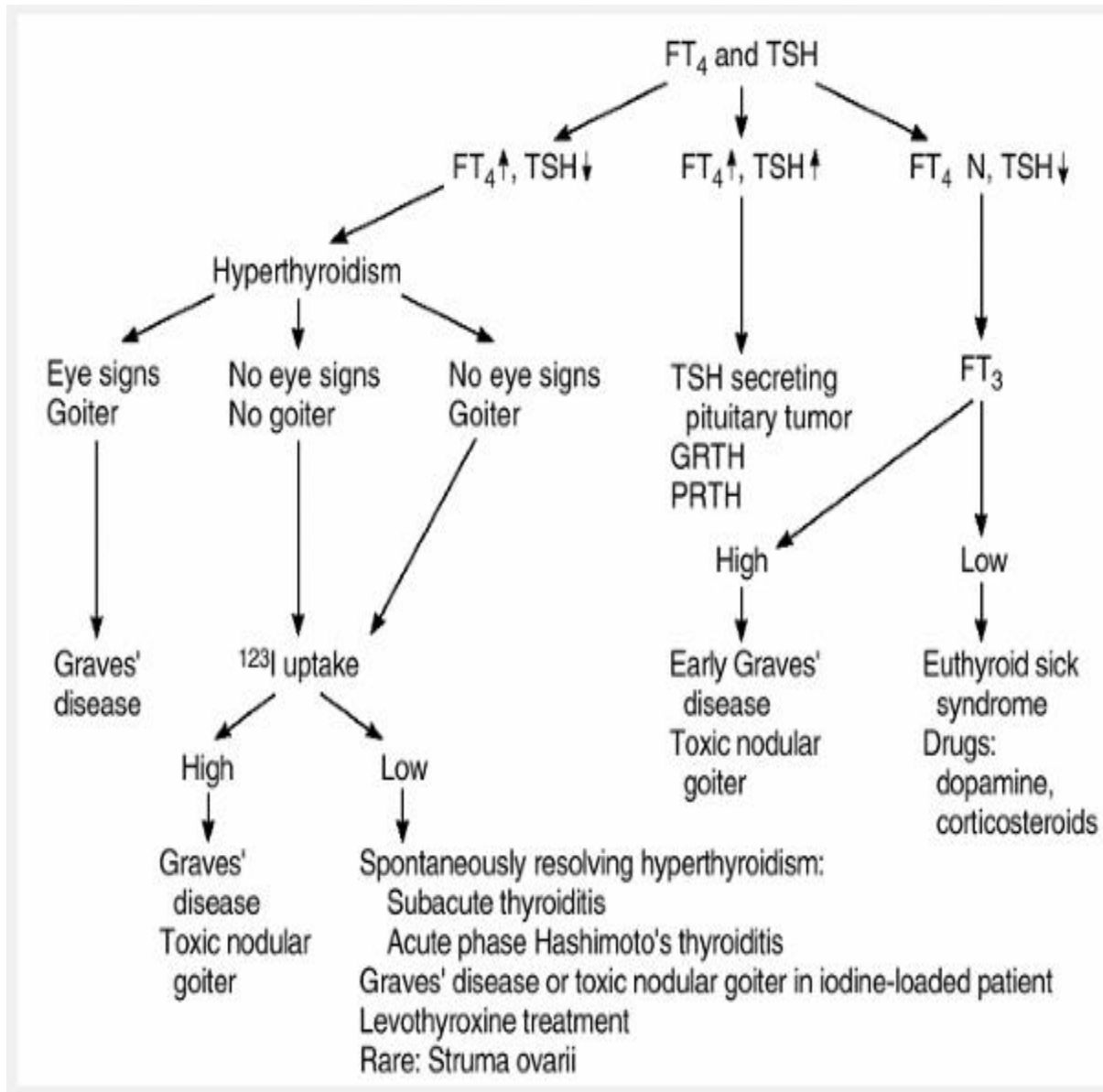
B. LABORATORY FINDINGS

Essentially, the combination of an increased free thyroxine T₄ and a decreased Thyroid stimulating hormone makes the diagnosis of hyperthyroidism. Ophthalmic signs are there, the diagnosis of Graves' disease is confirmed. Otherwise if absent, patient should undergo radioiodine uptake even in absence of goiter. Increased uptake is conclusive of Graves' disease or toxic nodular goiter. Decreased uptake is present in other hyperthyroid which is benign and thyroiditis. It can also be present in thyroxine treatment overload. Or, rarely, in association with a struma ovarii. If both FT₄ and TSH are elevated and radioiodine uptake is also elevated, consider a TSH-secreting pituitary tumor or generalized or pituitary resistance syndromes. If FT₄ is normal and TSH is suppressed, check FT₃, which will be elevated in early Graves' disease or in T₃-secreting toxic nodules. Low FT₃ will be found in the euthyroid sick syndrome or in patients receiving corticoids or dopamine.

Thyroid autoantibodies Tg Ab and TPO Ab are usually present in both Graves' disease and Hashimoto's thyroiditis, but TSH-R Ab is specific for Graves' disease. The ¹²³I or technetium scan is useful to evaluate the size of the gland or the presence of "hot" or "cold" nodules. CT and MRI scans of the orbit have revealed muscle enlargement in most patients with Graves' disease even when there is no clinical evidence of ophthalmopathy.

DIFFERENTIAL DIAGNOSIS

Graves' disease wont present in its usual manner. It can present with unlikely form where diagnosing is difficult. significant muscle wasting signifies severe myopathy. Thyrotoxic periodic paralysis is rare form and will have a sudden attack of flaccid paralysis and hypokalemia. The paralysis subsides naturally and can be prevented by potassium treatment and beta blockers. The illness is cured by appropriate treatment of the thyrotoxicosis. Patients with thyrocardiac disease present primarily with symptoms of heart involvement especially refractory atrial fibrillation insensitive to digoxin or with high-output heart failure. Half the number of patients have no previous heart problems and are reversed once treated thyrotoxicosis. In few aged patients will present with loss of weight , tiny goiter , decreased atrial fibrillation, and severe depression, with no evidence increased catecholamine reactivity. These placid patients have “apathetic hyperthyroidism.” Finally, some young women may present with amenorrhea or infertility as the primary symptom. In all of these instances, the diagnosis of hyperthyroidism can usually be made on the basis of the clinical and laboratory studies.



LABORATORY TESTS FOR DIAGNOSIS OF HYPERTHYROIDISM

COMPLICATIONS

Thyrotoxic crisis is medical emergency presenting with more pronounced clinical features of thyrotoxicosis. More commonly, it follows after a surgery, radioactive iodine therapy, or during a severe, stressful illness or disorder like uncontrolled diabetes, trauma, acute infection, severe drug reaction, or myocardial infarction.

The clinical features is due to increased metabolism and more adrenergic surge. High grade fever with increased sweating and flushing will be there. There is marked tachycardia, often with atrial fibrillation and high pulse pressure and occasionally with heart failure. Central nervous system symptoms include marked agitation, restlessness, delirium, and coma. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and jaundice. A fatal outcome will be associated with heart failure and shock.

TREATMENT OF GRAVES' DISEASE

Three modes of treatment

- (1) antithyroid drug therapy
- (2) surgery
- (3) radioactive iodine therapy.

A. ANTITHYROID DRUG THERAPY

In general, antithyroid drug therapy is most useful in young patients with small glands and mild disease. The drugs propylthiouracil or methimazole are given until the disease undergoes spontaneous remission. Treatment period varies from 6 months to 15 years. This mode of treatment has increased relapse rate. Antithyroid drugs usually started in high doses till patient becomes euthyroid, then maintenance therapy achieved. A common regimen consists of giving propylthiouracil, 100 mg every 6 hours initially, and then in 4–8 weeks reducing the dose to 50–200 mg once or twice daily. Propylthiouracil has one advantage over methimazole by inhibiting the T4 conversion to T3. Methimazole has a longer duration of action and is more useful if a single daily dose is desirable. FT4 and TSH are used in assessment of treatment.

An alternative method of therapy is combination of methimazole with levothyroxine to prevent hypothyroidism.

- Duration of therapy—The duration of therapy with antithyroid drugs in Graves' disease ranges from 6 months to 20 years . A sustained remission may be predicted in about 80% of treated patients in the following circumstances: (1) if the thyroid gland reverts to normal size; (2) if the disease can be suppressed with little dose of antithyroid drugs; (3) TSH-R Ab is should be no longer detectable in the serum.

B. SURGICAL TREATMENT

For large glands and MNG , subtotal thyroidectomy is done. The patient should be made euthyroid before surgery. Potassium iodide given before two weeks of surgery to reduce vascularity. There is still a debate in leaving how much thyroid tissue back. Most of them need postop thyroxine supplementation. Complications like nerve injury can occur.

C. RADIOACTIVE IODINE THERAPY

In old aged patients and in whom preexisting heart disease or other medical problems, severe thyrotoxicosis, ideal thing is to attain euthyroid state before therapy. For this , pretreatment with methimazole is given . Because it is usually desirable to destroy most of the gland in patients with underlying medical problems, the dose of ^{131}I may be slightly larger than is ordinarily given.

Major adverse effect of this therapy is hypothyroidism and it will be present in 80% of cases. They can be treated with thyroxine replacement therapy. Hypothyroidism may occur after any type of therapy for Graves' disease even after antithyroid drug therapy; in some patients, “burned-out” Graves' disease may be an end result of autoimmune thyroid disease.

Accordingly, all patients with Graves' disease require lifetime follow-up to be certain that they remain euthyroid.

D. OTHER MEDICAL MEASURES

1, In acute phase, beta-adrenergic blockers are used. Propranolol, 10–40 mg 6th hourly, will control heart rate, blood pressure and arrhythmia.

2, Adequate nutrition, including multivitamin supplements, is essential.

3, Barbiturates increase T₄ metabolism, and phenobarbital is used.

4, Iopodate sodium or iopanoic acid has been shown to inhibit both thyroid hormone synthesis and release and peripheral conversion of T₄ to T₃.

5, Cholestyramine, 4 g orally three times daily, will decrease serum T₄ by binding it in the intestine.

In a patient with a large toxic goiter and a severe allergic reaction to antithyroid drugs, iopodate sodium and beta blockade can be used effectively as preparation for surgery.

OTHER CAUSES OF HYPERTHYROIDISM

TOXIC ADENOMA

A adenoma secretes more T_3 and T_4 will cause hyperthyroidism. It is usually a “hot nodule” , gradually the size grows and masks the other part of the gland. Senior members are vulnerable. Routine hyperthyroid clinical features are seen. ophthalmopathy will be absent. On palpation nodule is seen with less thyroid tissue. TSH levels will be low and increase in T_3 . Toxic adenomas are always benign and follicular. Treated by using antithyroid drugs, radioactive iodine or unilateral lobectomy.

TOXIC MULTINODULAR GOITER

This is similar to toxic adenoma except radioiodine scan shows multiple functioning nodules.

SUBACUTE OR CHRONIC THYROIDITIS

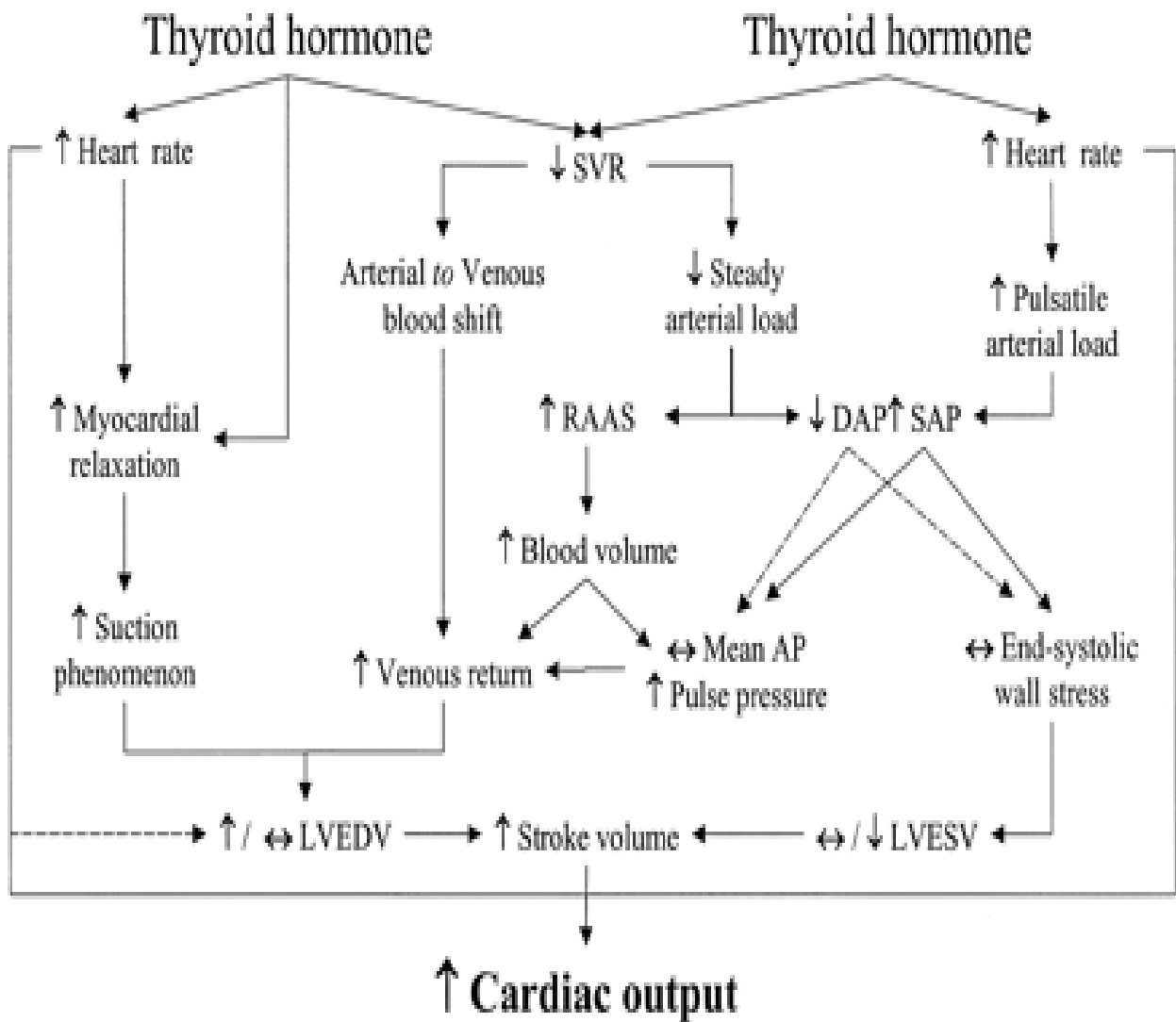
Subacute or chronic, may present with an acute release of T_4 and T_3 , producing symptoms of mild to severe thyrotoxicosis. These illnesses can be differentiated from other forms of thyrotoxicosis in that the radioiodine uptake is markedly suppressed, and the symptoms usually subside spontaneously over a period of weeks or months.

THYROTOXICOSIS FACTITIA

This is a psychoneurotic disturbance in which the patient ingests excessive amounts of thyroxine or thyroid hormone, usually for purposes of weight control. Psychotherapy is used.

CARDIOVASCULAR CHANGES IN HYPERTHYROID

- Increased Myocardial contractility
- Increased Cardiac output
- Increased Systolic/diastolic function
- Increased Systolic blood pressure
- Increased Blood volume
- Increased Venous resistance
- Decreased Arterial resistance
- Decreased Diastolic blood pressure
- Tachycardia at rest
- Systolic murmur
- Mitral valve prolapse
- Loud First heart sound
- Possible third heart sound



CARDIOVASCULAR CHANGES IN HYPERTHYROID

ELECTROCARDIOGRAPHIC FEATURES OF THYROTOXICOSIS:

Most common findings include;

- Sinus tachycardia
- Increased QRS voltages
- Atrial fibrillation

Other findings are;

- Non-specific ST and T wave changes.
- Supraventricular arrhythmias which includes,
 - premature atrial beats
 - paroxysmal supraventricular tachycardia
 - multifocal atrial tachycardia
 - atrial flutter.
- Ventricular extrasystoles

Parameter	Normal values	Hyperthyroidism
Blood volume (% of normal value)	100	105.5
Heart rate (bpm)	72–84	88–130
Cardiac output (L/min)	4.0–6.0	> 7.0
Systemic vascular resistance (dyn·sec/cm⁻⁵)	1500–1700	700–1200
Left ventricular ejection fraction (%)	> 50	> 65
Isovolumic relaxation time (msec)	60–80	25–40

AIMS AND OBJECTIVES

1. To study the clinical profile of hyperthyroidism at Government Stanley hospital.
2. To study echocardiographic findings in these patients.

MATERIALS AND METHODS

PLACE OF STUDY:

DEPARTMENT OF GENERAL MEDICINE, ENDOCRINOLOGY
OPD, MEDICAL OPD, MEDICAL WARDS, STANLEY MEDICAL
COLLEGE AND HOSPITAL, CHENNAI.

SAMPLE SIZE:

60

DURATION:

NOV 2013 TO NOV 2014.

STUDY DESIGN:

PROSPECTIVE OBSERVATIONAL STUDY

ETHICAL COMMITTEE APPROVAL:

THE ETHICAL COMMITTEE APPROVAL WAS OBTAINED FOR
THIS STUDY

PATIENT SELECTION:

ANY PATIENT COMING WITH SYMPTOMS SUGGESTIVE OF
HYPERTHYROID TO ENDOCRINOLOGY OPD, MEDICAL OPD
MEDICAL WARDS.

EXCLUSION CRITERIA:

PATIENTS WITH KNOWN HEART DISEASE.

CONSENT

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up for this study after getting a written / informed consent from these patients or their relatives in the local vernacular language.

STUDY SUBJECTS:

All the patients who fulfilled the inclusion criteria of any age and both genders were included in this study. The included patients were subjected to detailed history taking, complete physical examination and the relevant laboratory investigations as per a proforma, exclusively designed for the study.

RESULTS, OBSERVATION, DISCUSSION

The study includes total number of 60 patients. Data were collected and final analysis was made.

ANALYSIS OF DATA OF STUDY GROUP

AGE DISTRIBUTION:

AGE IN YRS	NUMBER OF PATIENTS	PERCENTAGE IN %
1-20	6	10
21-30	27	45
31-40	10	17
41-50	11	18
51 & ABOVE	6	10

Table1. Age distribution of study group

Among 60 patients studied, most patients were between the age group of 21 to 30 years 27 (45 %). Patients between 41 to 50 yrs were 11 (18%). Patients between 31-40 were 10 (17%). Followed by 6 patients were between 1 to 20 years and above 51 years of age. They contribute to 10% of study group.

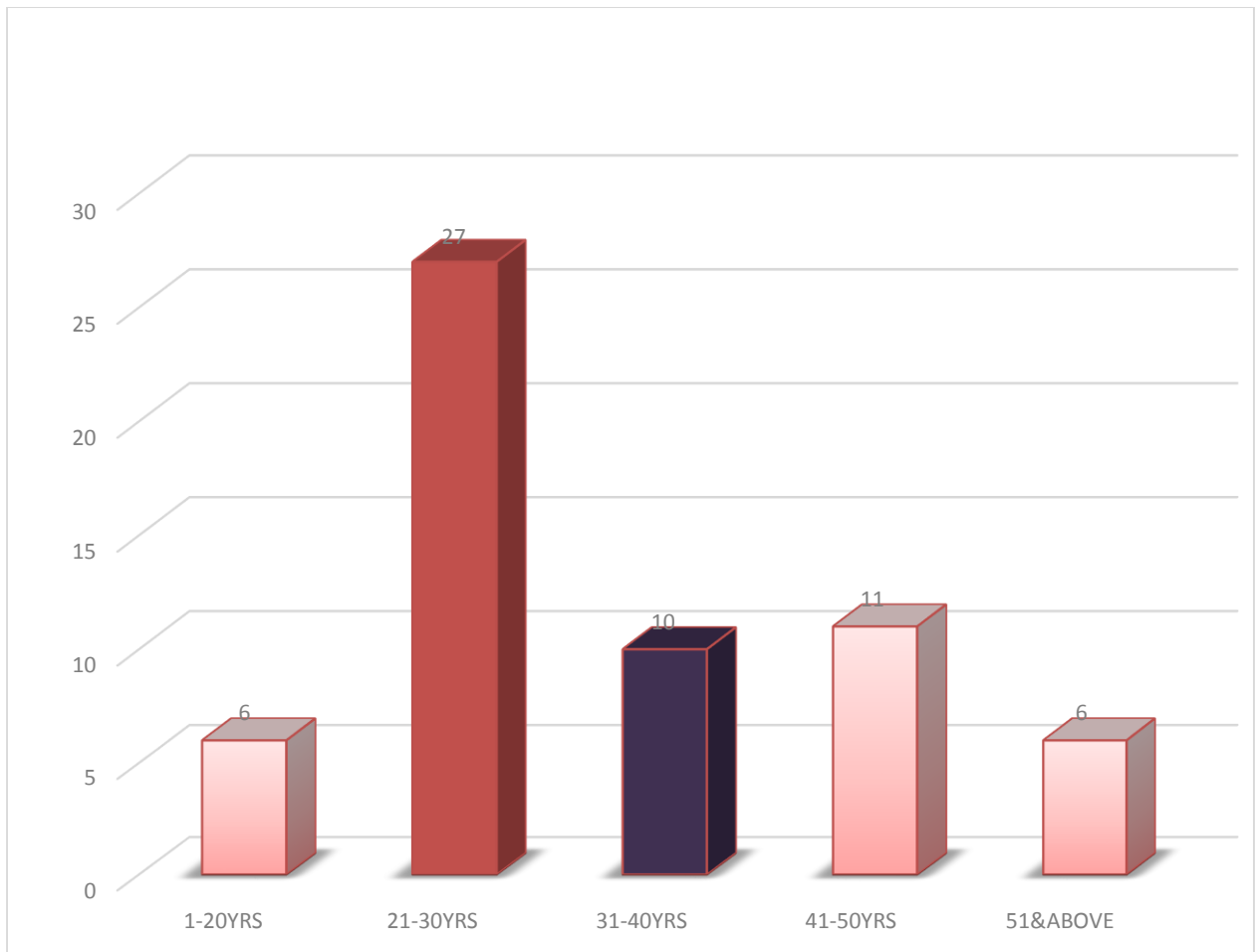


Fig1 : Graph depicting age distribution in group

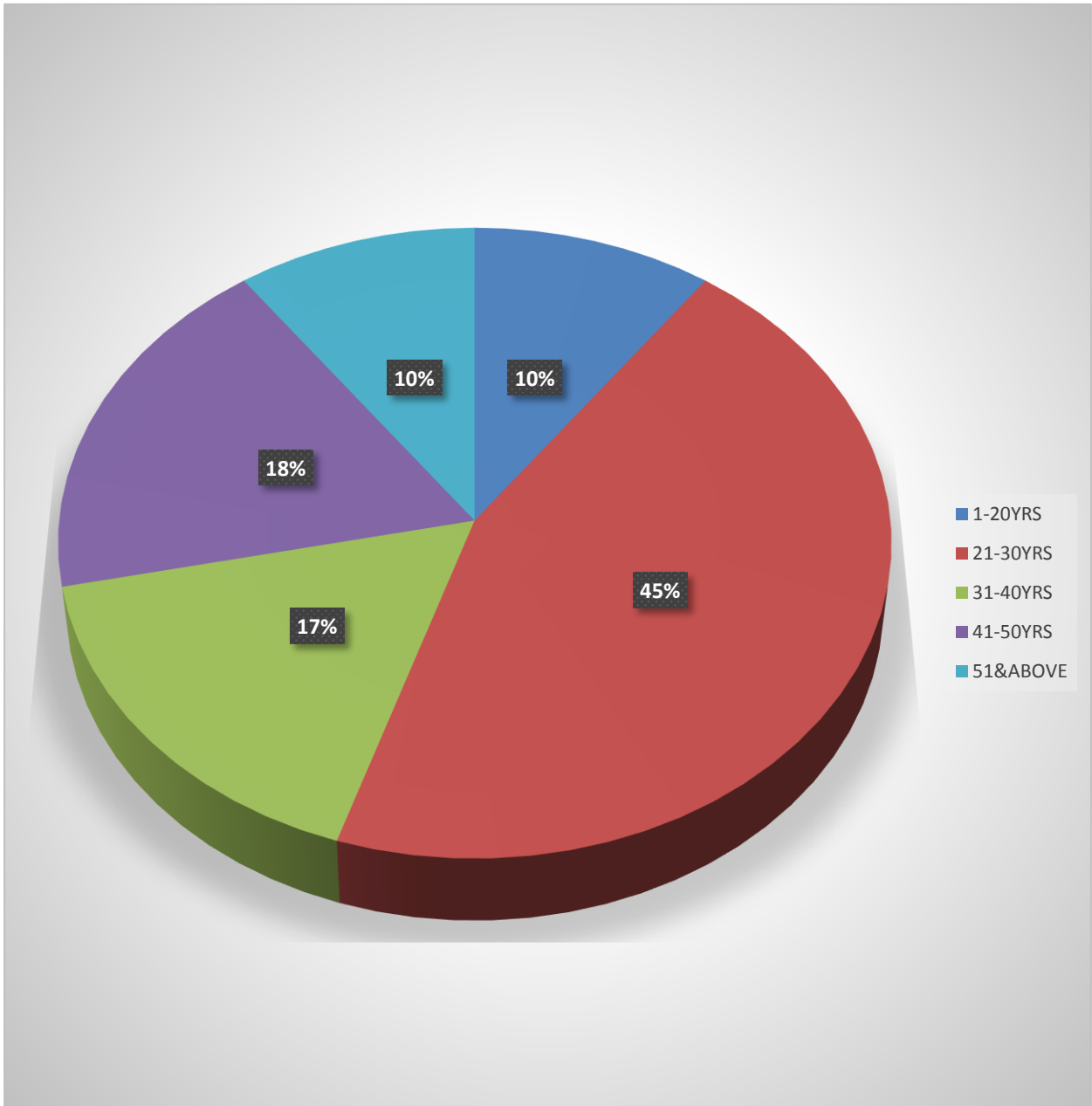


Fig2:Pie chart depicting age distribution instudy group

SEX DISTRIBUTION IN STUDY GROUP:

Among 60 patients in study, most of them were females. Female group in the study were 56 and male were only 4. Females were 93% and males were 7%. So according to my study in Stanley hospital incidence of hyperthyroidism was more among females.

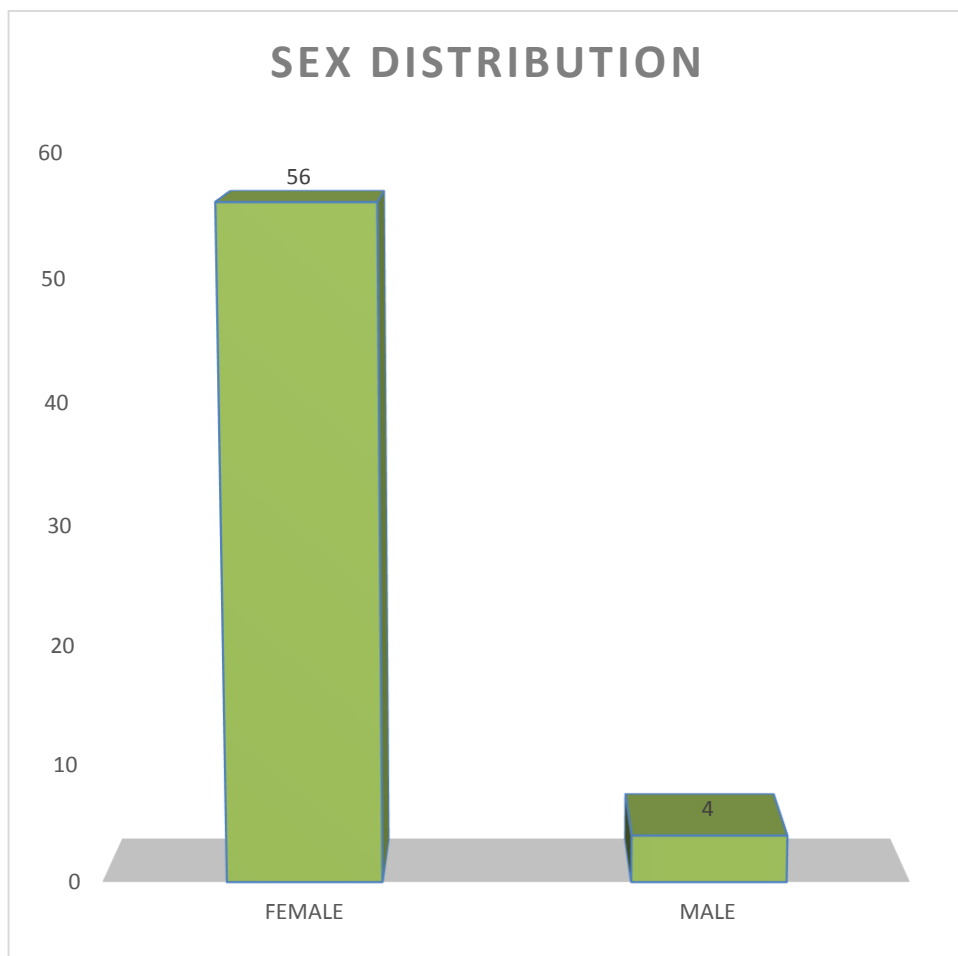


Fig3:Graph depicting sex distribution in study group

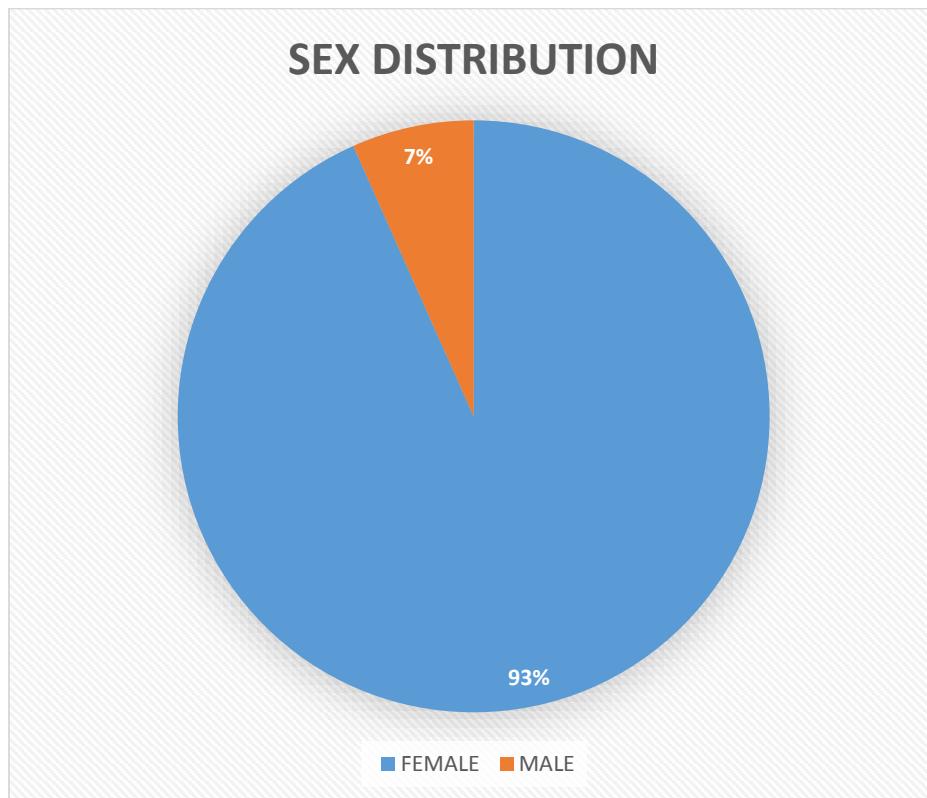


Fig4:Pie chart showing sex distribution in study group

SEX AND MARITAL STATUS DISTRIBUTION IN STUDY GROUP

Gender	Married		Unmarried		No. of patients	
	N	%	N	%	N	%
Male	3	75	1	25	4	7
Female	48	86	8	14	56	93
Total	51	80.5	9	19.5	60	100

Table 2: Sex and Marital status distribution in study group

In my study among 60 patients, 56 females and 4 were males. Out of these 56 patients, most of them were married. 48 females were married and 8 were unmarried. Among male population 3 were married and 1 was unmarried.

86 % of females were married and 14% were married. While in males 75% were married and 25 % were unmarried. So in my study in Stanley hospital , incidence of hyperthyroid was more among female married patients.

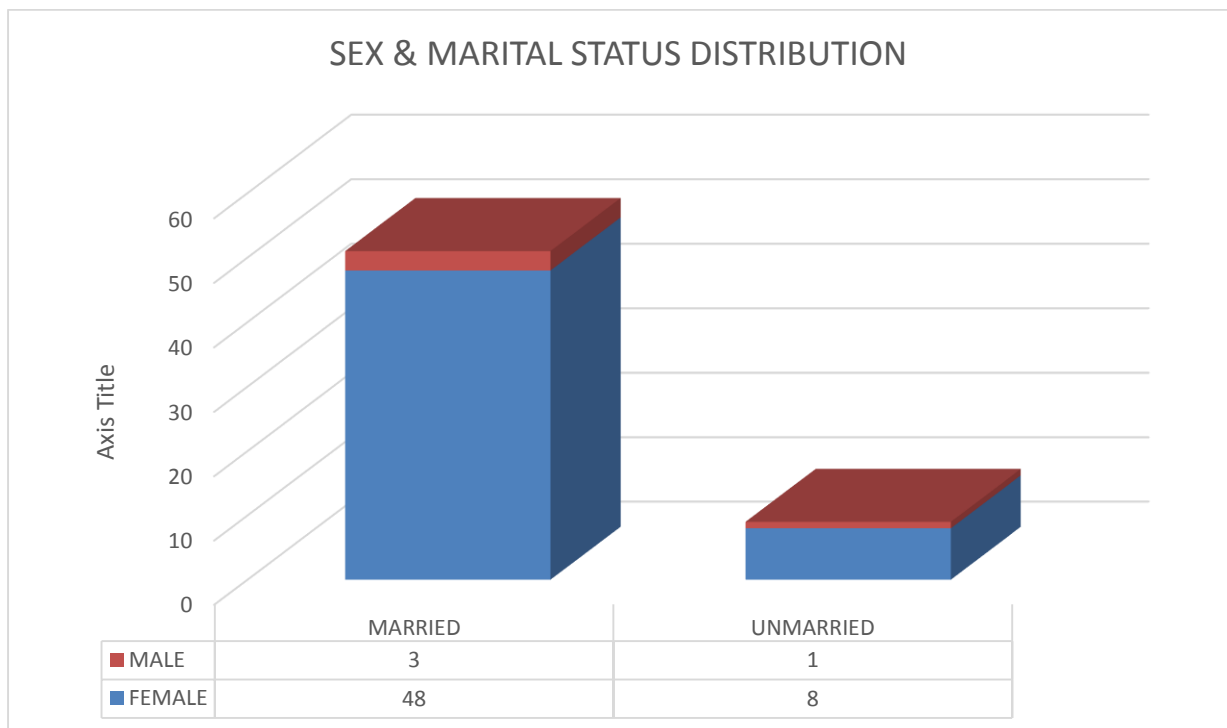


Fig5:Graph showing sex & marital status distribution in study group

SYMPTOM ANALYSIS DISTRIBUTION IN STUDY GROUP:

SYMPTOM ANALYSIS	NUMBR OF PATIENTS
Neck swelling	26
Palpitation	18
Diarrhoea	2
Weight loss & increased appetite	11
Heat intolerance	3
Hair loss	11
Menstrual irregularities	21
Tremors	12
Diplopia & proptosis	8

Table 3: Symptom analysis distribution in study group

In clinical features distribution in my study group of 60 patients , most patients came with multiple complaints rather than single complaint. Neck swelling and menstrual irregularities leads the top followed by weight loss and increased appetite and hair loss ,diplopia least were diarrhea and heat intolerance.

Neck swelling is present in 26 patients, palpitation in 18 patients, menstrual irregularities in 21 patients , tremors in 12 patients, weight loss and increased appetite in 11 patients , diplopia & proptosis in 8 patients. Least were diarrhea in 2 patients and heat intolerance in 3 patients.

So according to my study in Stanley hospital, major complaint was neck swelling & menstrual irregularities. Least were diarrhea and heat intolerance.

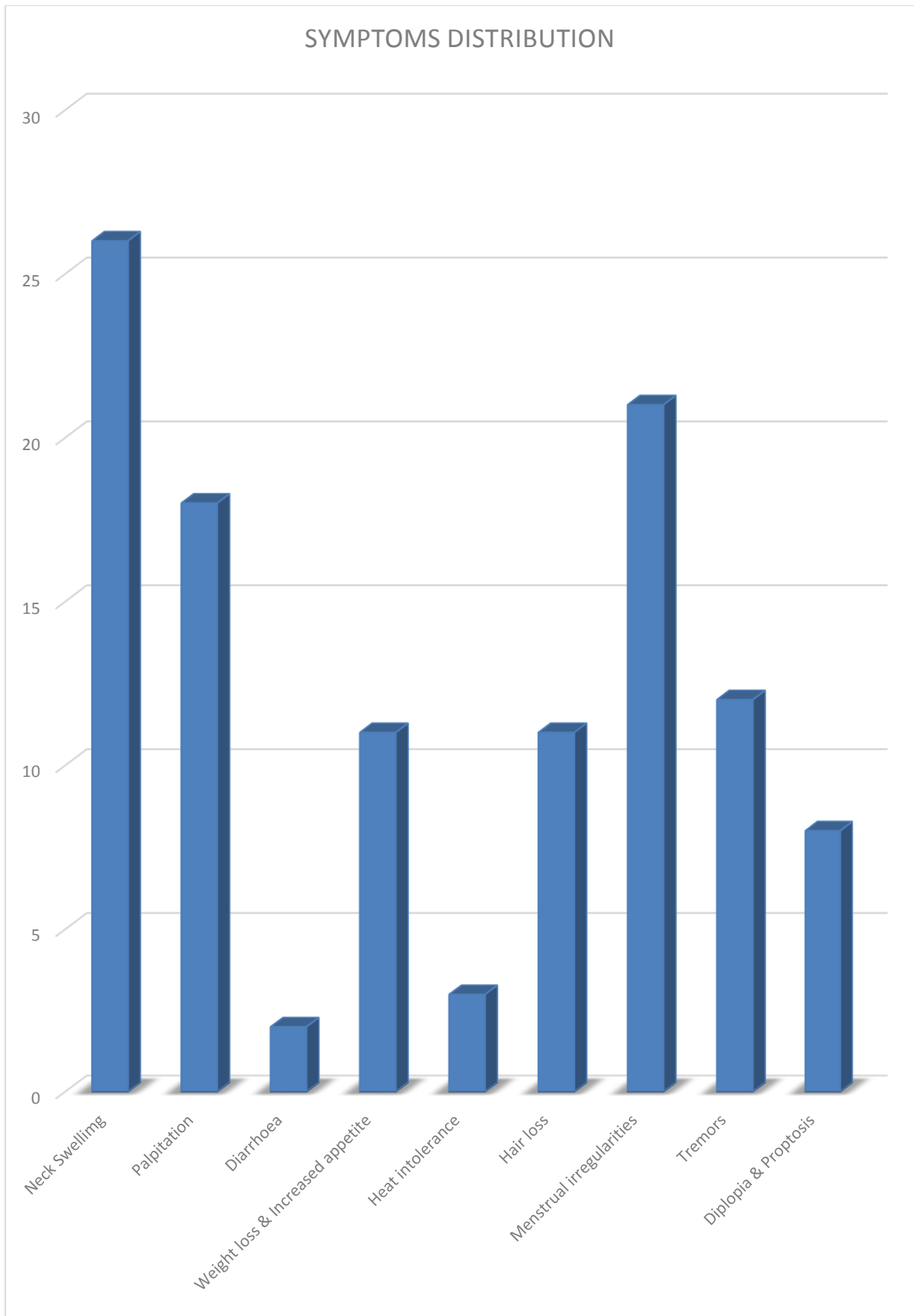


Fig6:Graph depicting symptom distribution in study group

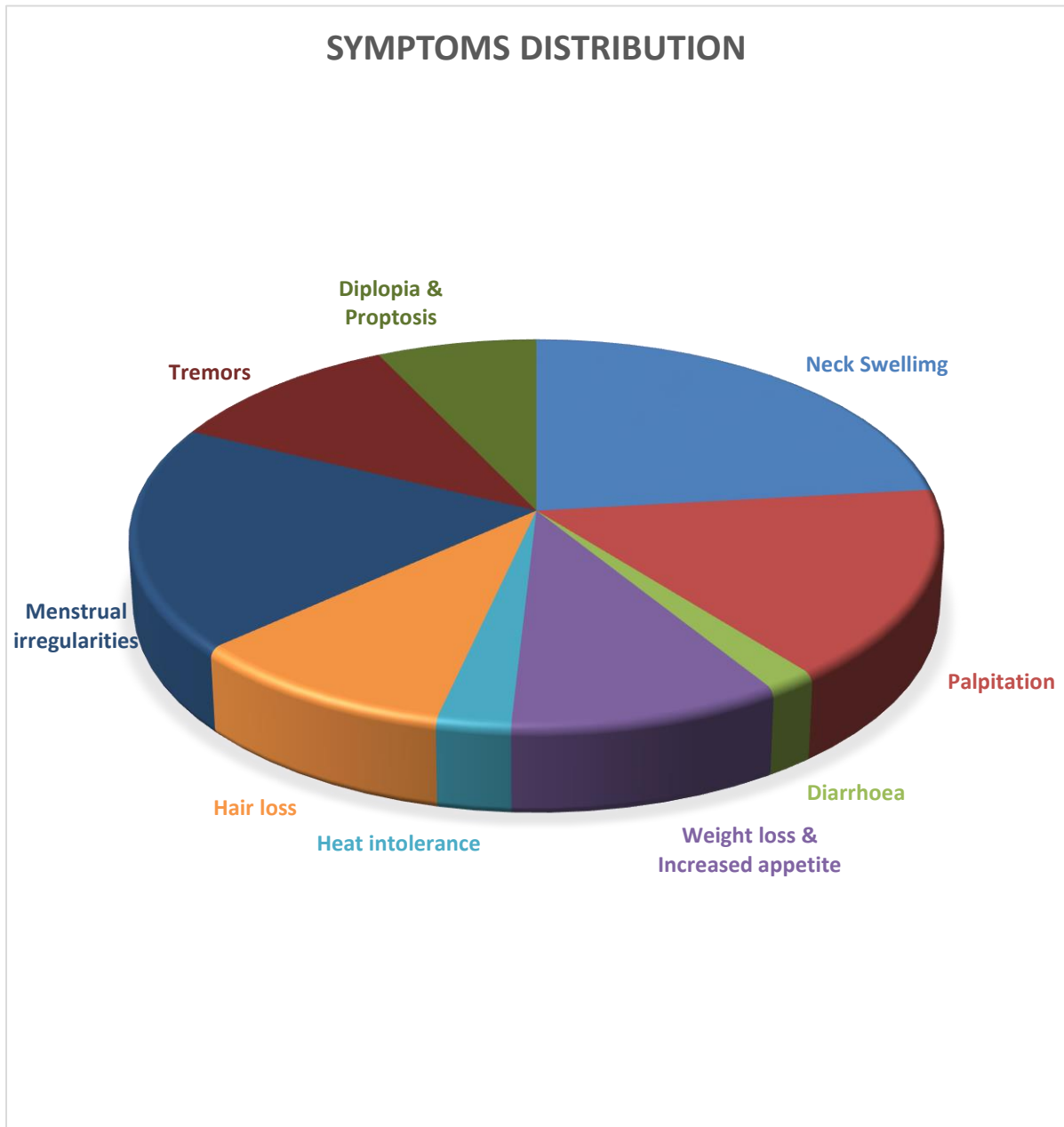


Fig7:Pie chart showing symptom distribution

Among 60 patients in study group, 40 members came with more than one symptoms that will be 67 %. Remaining 20 members alone had one symptom which will be 33%.

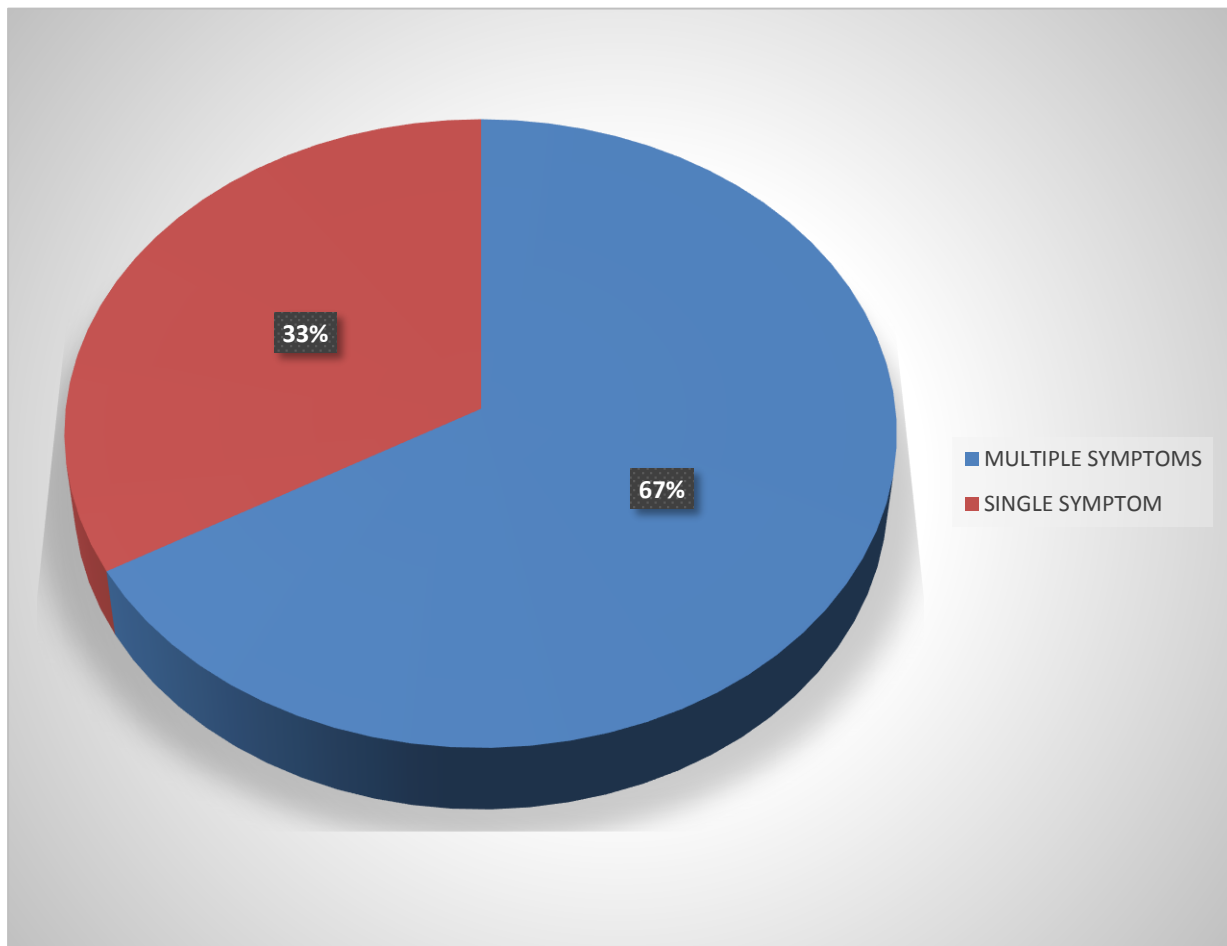


Fig8:Pie chart showing number of symptom distribution

CLINICAL FINDINGS DISTRIBUTION IN STUDY GROUP:

CLINICAL SIGNS	NUMBER OF PATIENTS	PERCENTAGE %
NORMAL	23	30
GOITER	20	27
TREMORS	13	17
SINUS TACHYCARDIA	10	13
EYE SIGNS	10	13

Table 4: Clinical findings distribution in study group

In study group, clinical signs were various entities. Most of the patients were clinically normal without no signs. They were 23 patients and contribute to 30 % Goiter is seen in 20 patients , which is 27 %, tremors were found in 13 patients

that is 17 %, sinus tachycardia and eye signs like lid lag sign, lid retraction etc were seen in 10 patients , about 13 %.

So according to my study, 30% were clinically normal and most common sign was goiter.

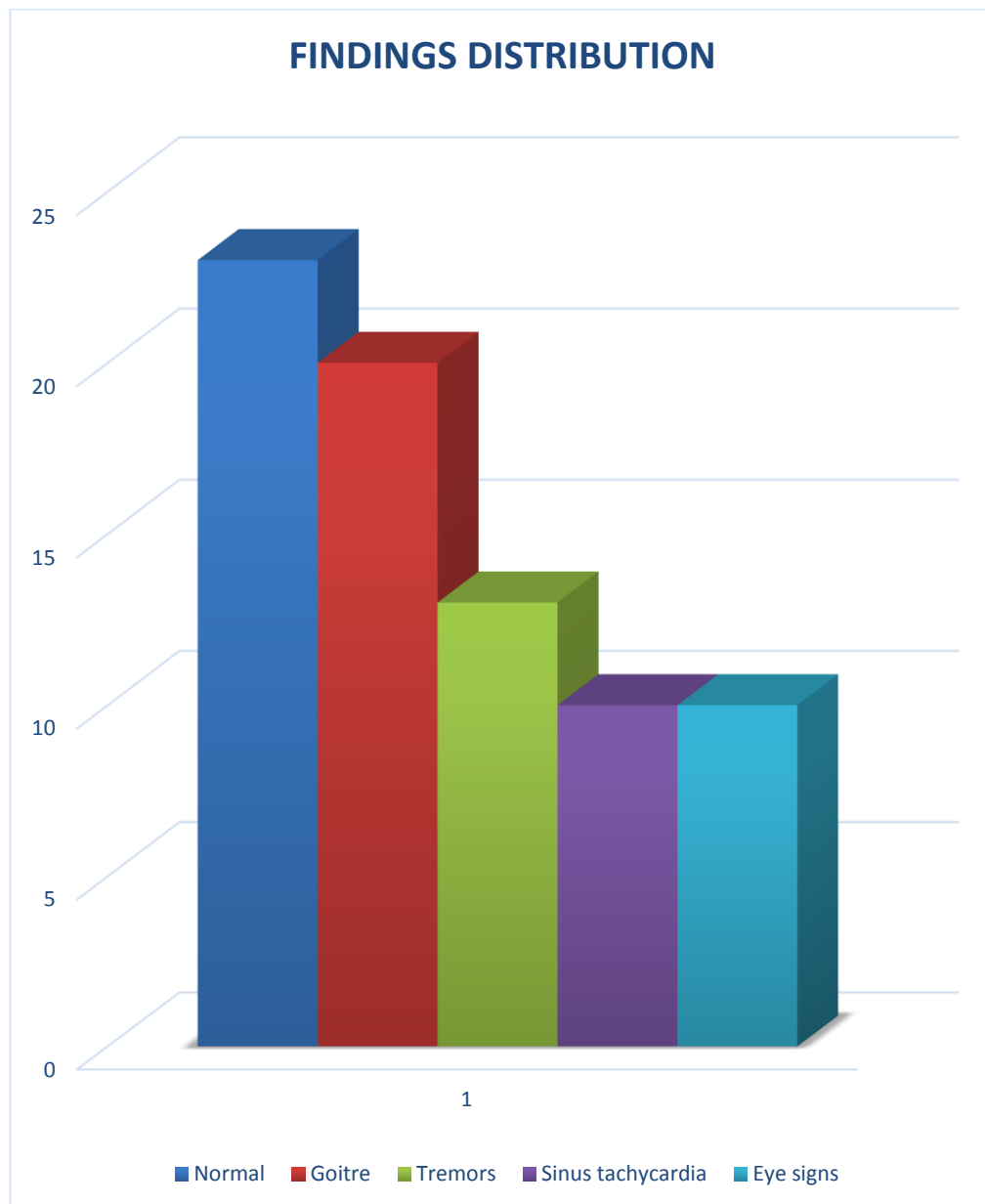


Fig9:Graph depicting clinical signs distribution in study group

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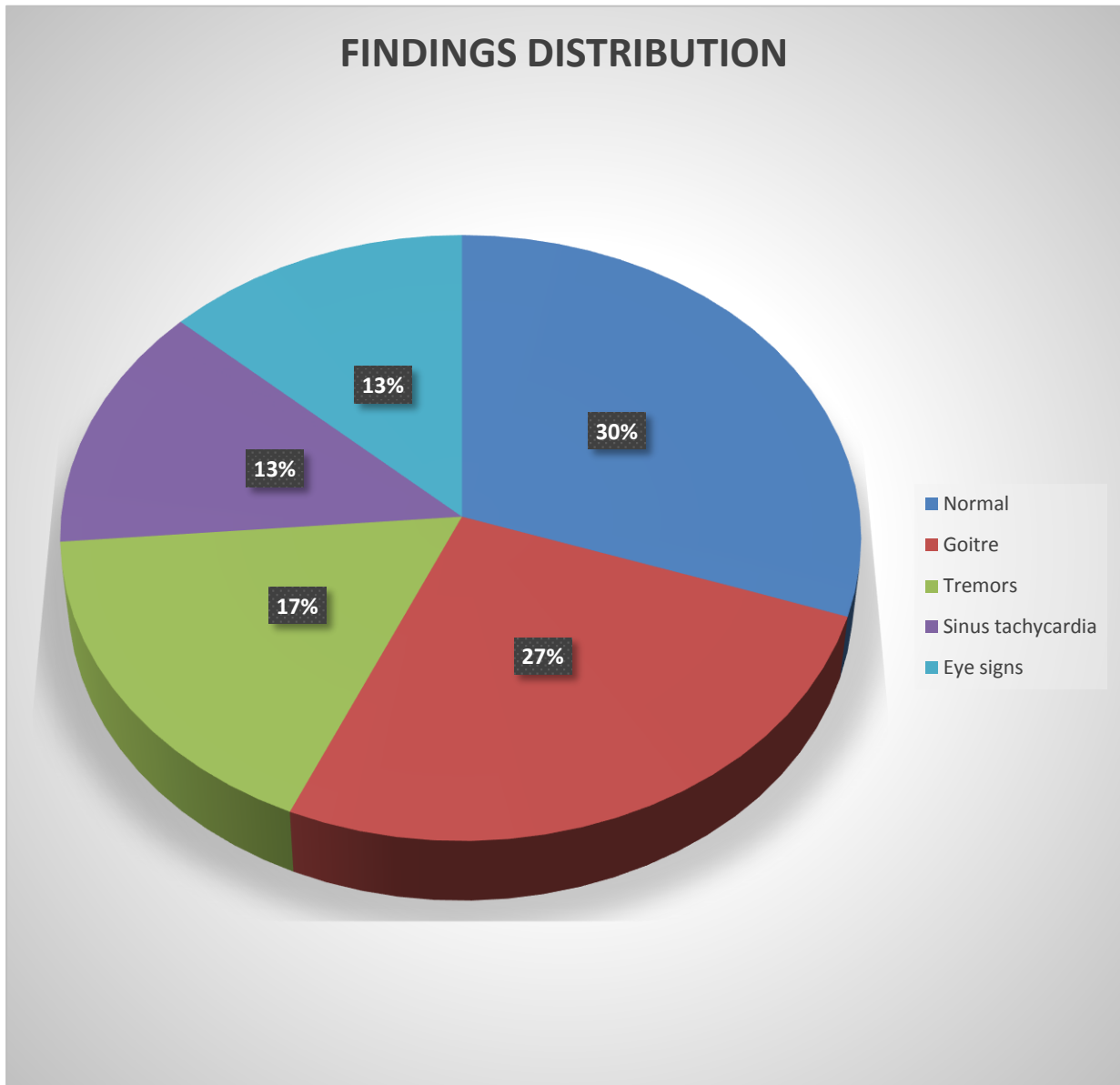


Fig10: Pie chart showing clinical sign distribution in study group

According to my study, in Stanley 38% were clinically had no signs, 40 % were having single findings. Remaining 22% had more than one findings.

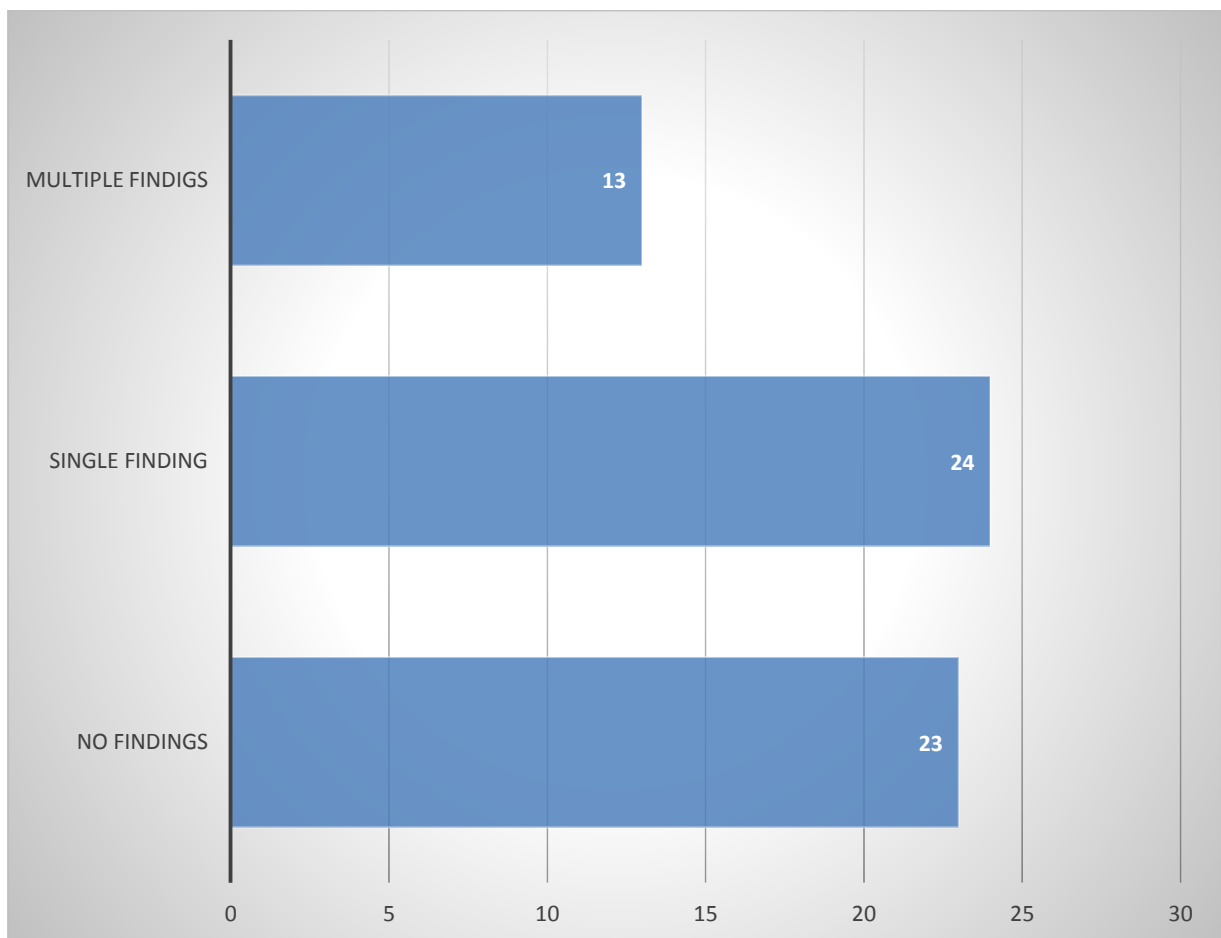


Fig11:Graph showing findings distribution in study group

TSH DISTRIBUTION IN STUDY GROUP:

All 60 patients were tested for thyroid function and thyroid stimulating hormone levels were analysed. All of them showed TSH of low range, which depicted all patients were primary hyperthyroid and no secondary hyperthyroid cases in Stanley hospital.

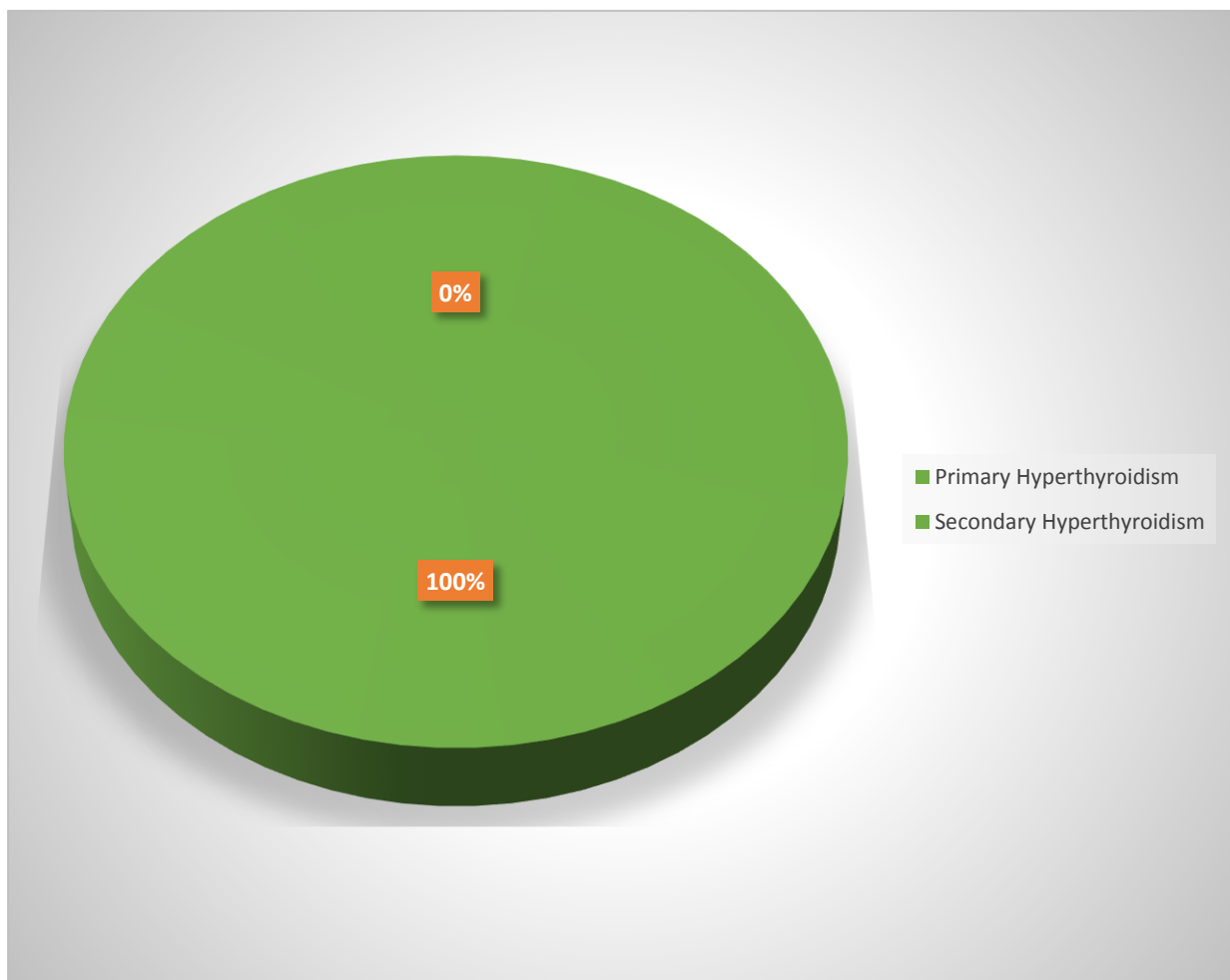


Fig12:Pie chart showing TSH distribution in study group

USG NECK FINDINGS DISTRIBUTION IN STUDY GROUP:

In study , all patients undergone ultra sound of neck to see the anatomy of the thyroid. Of these findings 37 persons had normal findings which is 62 % , Nodular goiter were found in 12 persons which is 20% and diffuse thyromegaly in 11 patients , that is 18%.

So according to my study, normal thyroid anatomy in ultrasound neck is present in Stanley hospital.

USG NECK FINDINGS	NUMBER OF PATIENTS	PERCENTAGE %
NORMAL	37	62
NODULAR GOITRE	12	20
THYROMEGALY	11	18

Table5: USG neck finding distribution in study group

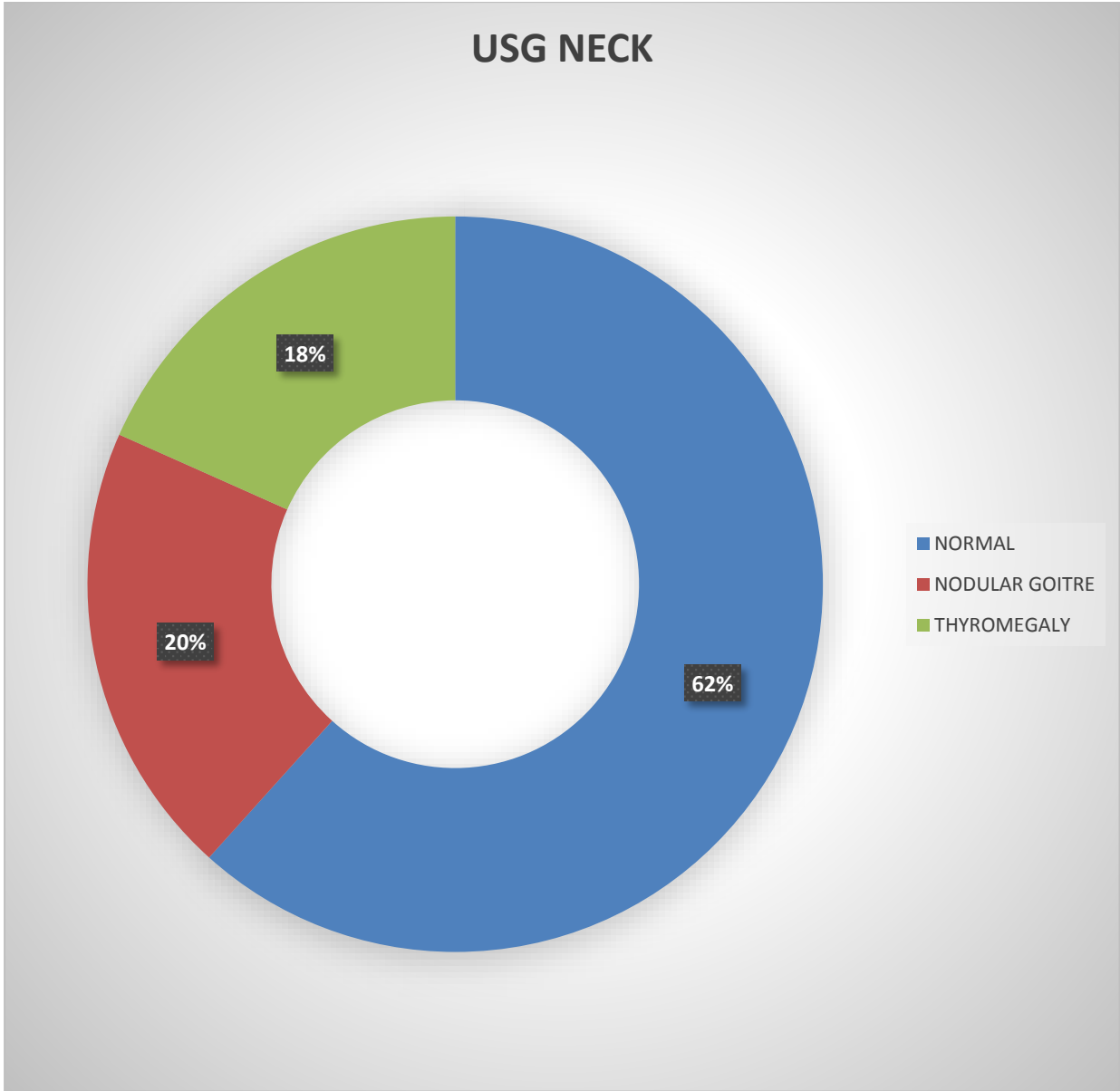


Fig13:Pie chart showing USG finding distribution in study group

FNAC FINDING DISTRIBUTION IN STUDY GROUP:

FNAC analysis was done among study group. Out of 60 cases cystic degeneration was present in 37 patients, that is 62%. Colloid goiter present in 13 patients , i.e. 22% and thyroiditis in around 10 persons which is 16%, mosly of hashimoto thyroiditis.

Cystic degeneration is the most common incidence in Stanley hospital.

FNAC FINDINGS	NUMBER OF PATIENTS	PERCENTAGE %
CYSTIC DEGENERATION	37	62
COLLOID GOITRE	13	22
THYROIDITIS	10	16

Table 6 : FNAC findings distribution in study group

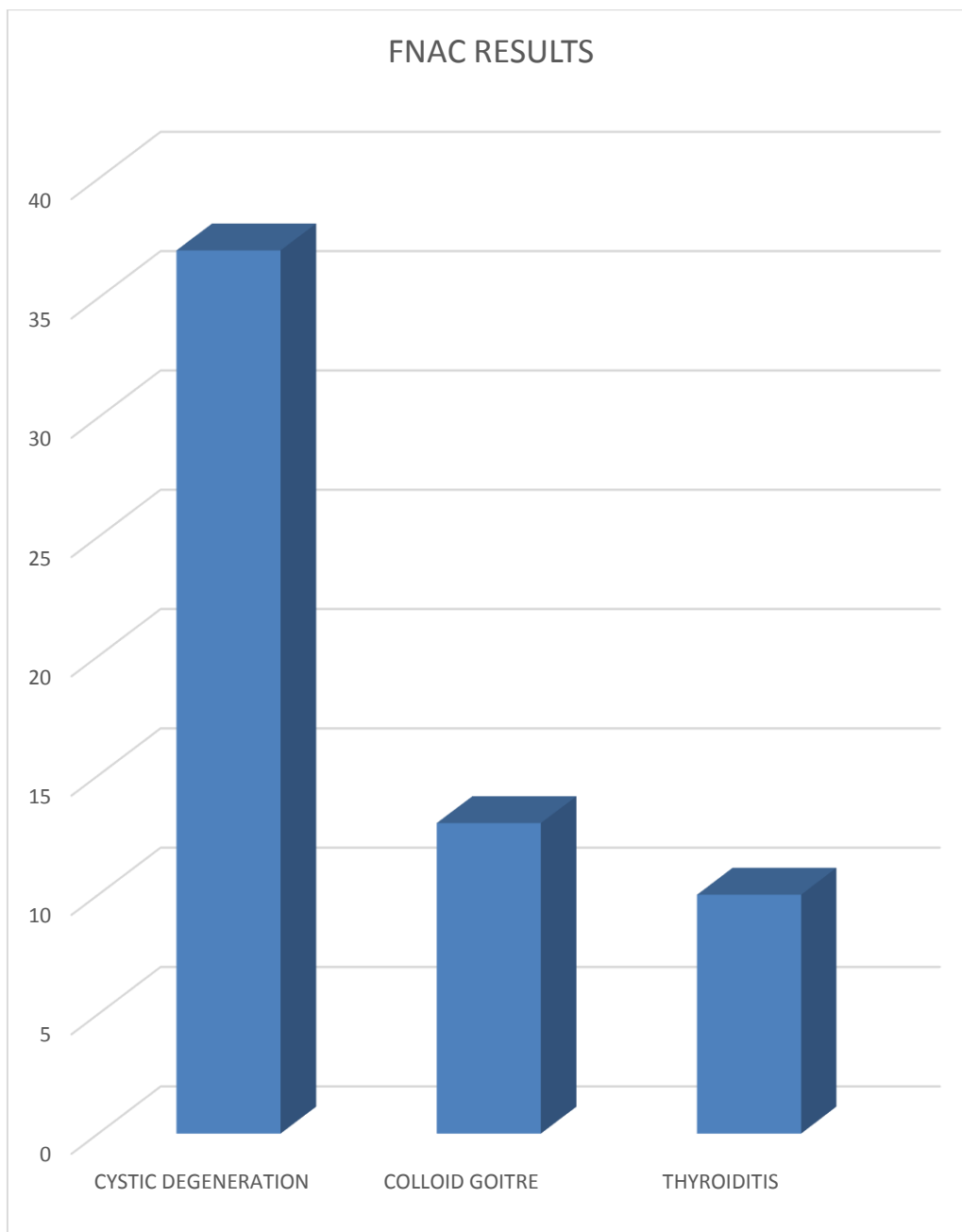


Fig14:Graph showing FNAC findings distribution in study group.

ANTIBODIES RESULTS DISTRIBUTION IN STUDY GROUP:

Out of 60 patients , 42 had normal Anti TPO & Anti Microsomal antibodies, which is 70% and 18 members had elevated antibody levels that is 30%.

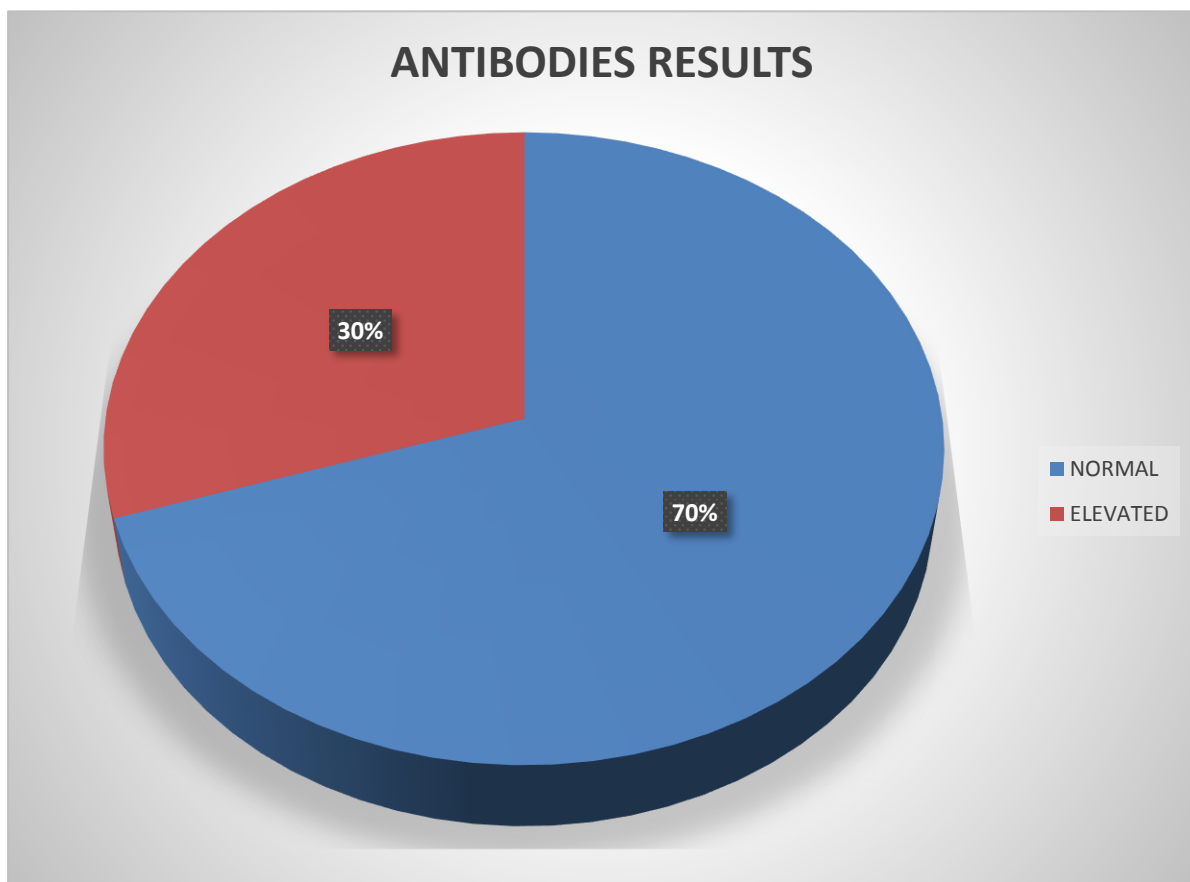


Fig15: Pie chart showing antibodies results distribution in study group

ECHOCARDIOGRAPHIC FINDINGS DISTRIBUTION IN STUDY GROUP:

ECHO FINDINGS	NUMBER OF PATIENTS	PERCENTAGE %
NORMAL	52	86.6
SYSTOLIC DYSFUNCTION	2	3.3
DIASTOLIC DYSFUNCTION	1	1.6
REGURGITANT LESION	1	1.6
CHAMBER ENLARGEMENT	2	3.3
PULMONARY HYPERTENSION	2	3.3

Table 7 :ECHO findings distribution in study group

Finally , echocardiogram was done in all 60 patients of the study group, 52 patients had normal echo with no abnormalities, which is 87% and remaining 8 (13%) had abnormal echo findings.

Various abnormal echo findings are as follows, Systolic dysfunction was seen in 2 persons (3.3%), Chamber enlargement which is left ventricle in 2 persons(3.3%), Pulmonary hypertension from mild to moderate in 2 persons(3.3%), Diastolic dysfunction and Regurgitant lesion in mitral valve were seen in 1 person each(1.6%).

So Echo findings in hyperthyroid were mostly normal except 8 cases in my study in Stanley hospital.

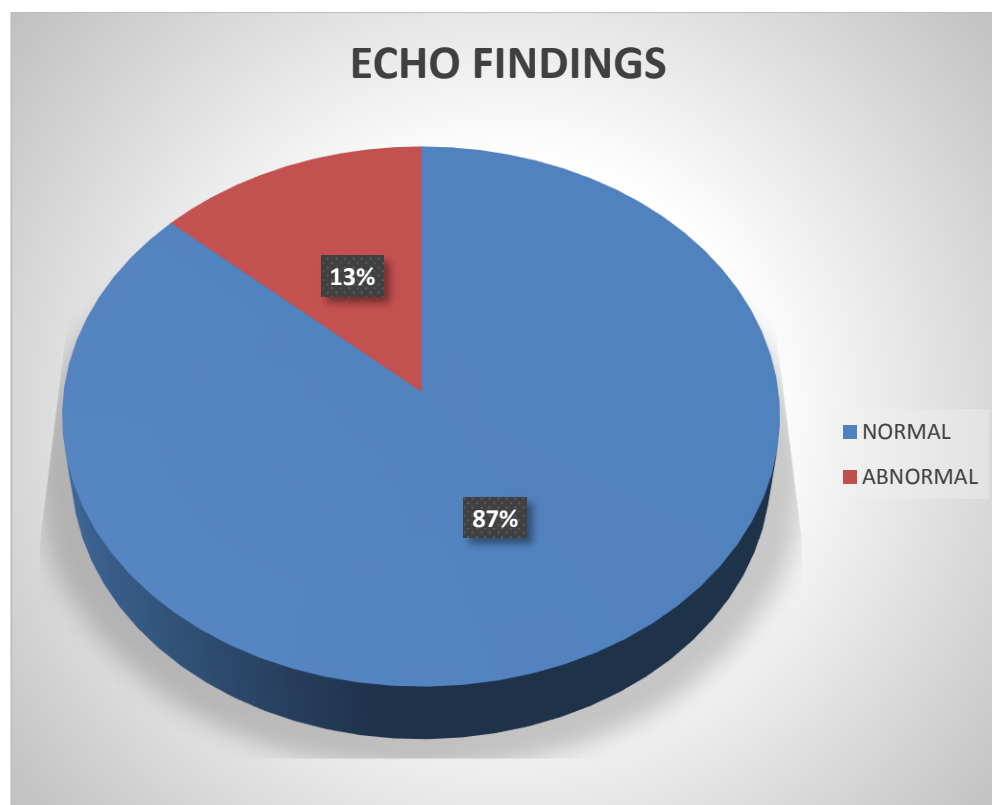


Fig17:Pie chart shoeing Echo findings distribution in study group

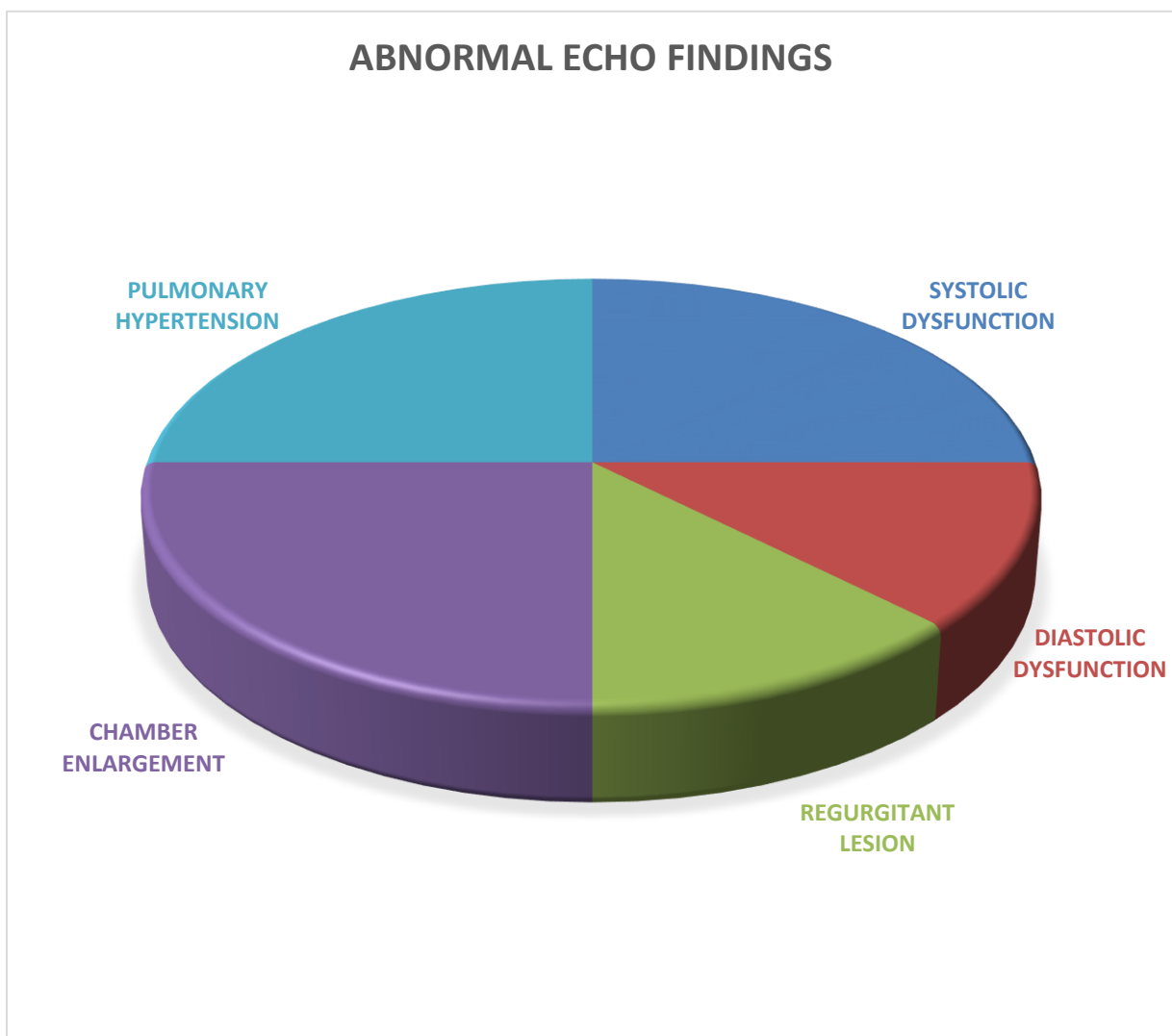


Fig 18: Pie chart showing Abnormal Echo findings distribution in Study group

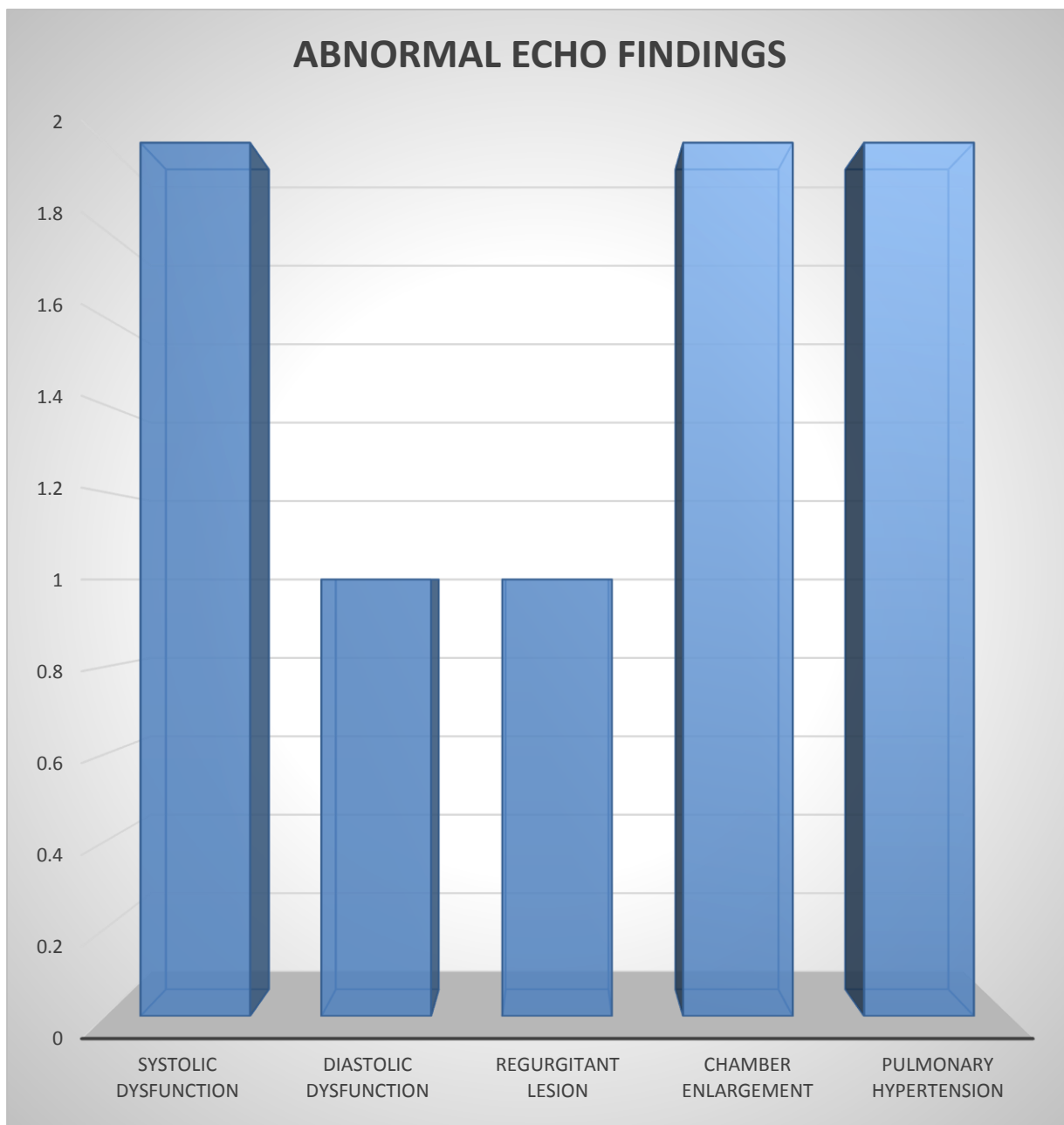


Fig19:Graph showing Abnormal Echo findings distribution in Study group

1)A study was conducted by Babul H Reddy et al to find out the prevalence of pulmonary hypertension in hyperthyroidism.It was a prospective study which included 25 consecutive patients of hyperthyroidism was tested for pulmonary hypertension at baseline and after achieving euthyroid state.They were studied for LV function,cardiac output and trans mitral flow velocity.40% of patients had pulmonary hypertension and 16% pulmonary venous hypertension which was reversed through achievement of euthyroid state.

2)A study conducted by Kahaly gj et al by using stress echocardiography on hyperthyroid patients and 42 patients were enrolled in the study.The stroke volume index,cardiac output, and ejection fraction were studied in the patients in hyperthyroid state, after treatment with propranolol and after achievement of euthyroid state.These parameters were substantially increased in hyperthyroid states and was blunted after propranolol treatment and reversed after achieving euthyroid state.Thus in hyperthyroidism the inotropic and chronotropic effects were increased which was reversed by achieving euthyroid state.

3)RC Anakwue et al studied the effects of thyrotoxicosis and the incidence of congestive heart failure in black community.The study included 50 patients who were thyrotoxic and CCF was determined clinically and echocardiographically.The study revealed that CCF can be present in thyrotoxicosis in spite of hyperdynamic condition may be due to autoimmunity andcongestive circulation.

4)SM Ansari et al studied the effects hyperthyroidism on heart.Echocardiography was done on 69 patients on patients who had presented with palpitations an tremors and radioimmunoassay confirmed hyperthyroidism.47 patients had cardiac pathology.Atrial fibrillation was the most common pathology found in hyperthyroid patients. The results showed that thyroid hormones had positive inotropic and chronotropic effect and echocardiography play an important role in recognizing the pathology of the heart.

CONCLUSION

- Hyperthyroidism is more common in females of younger age group commonly in third decade of life.
- Hyperthyroid patients mostly presents with neck swelling and palpitation and menstrual irregularities forms the significant complaint in my study.
- Half of the patients had clinically no findings and some had multi nodular goiter, eye signs were present in ten percentage of them.
- Hyperthyroid has significant effect on cardiac activity. It is a high output state. Causing systolic and diastolic dysfunction , pulmonary hypertension, left ventricle chamber enlargement , heart failure.
- Hyperthyroidism-related cardiac changes was largely asymptomatic and reversible after restoration to an euthyroid state. So hyperthyroidism should be considered as the reversible cause in cardiac morbidity.
- As a non-invasive method, echocardiography can play a vital role in recognizing the cardiac pathology in hyperthyroidism as well as to follow up the response to therapy.