Sudan University of Science & Technology

College of Graduate Studies

Assessment of Radioactive Iodine Treatment of Hyperthyroidism in Sudanese Patients

تقييم فعالية اليود المشع في علاج مرض فرط الغدة الدرقية لدي

المرضي السودانيين

A Thesis submitted for the fulfillment of the requirement of M.Sc. Degree in Nuclear Medicine Technology

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بسم الله الرحمن الرحيم

قال تعالي:

﴿وَالَّذِينَ جَاءُوا مِنْ بَعْدِهِمْ يَقُولُونَ رَبَّنَا اغْفِرْ لَنَا

وَلِإِخْوَانِنَا الَّذِينَ سَبَقُونَا بِالْإِيمَانِ وَلَا تَجْعَلْ فِي قُلُوبِنَا غِلًّا لِلَّذِينَ آمَنُوا رَبَّنَا إِنَّكَ ﴿﴾ رَءُوفٌ رَحِيمٌ

صدق الله العظيم

(سورة الحشر الآية : 10)

Dedication

This study is respectfully
Dedicated to
My family

Acknowledgment

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Abstract

Hyperthyroidism is considered as one of common pathological problem associated with thyroid gland, in which thyroid hormones level were increased. This a prospective study attended to assess the efficiency of thyroid treatment using I-131 in treatment of hyperthyroidism in Sudanese population, A 120 patients were treated using I131 at radiation and isotopes center of Khartoum in the period from 2012 to 2014. Imaging procedure was done using Tc99m radiopharmaceutical where the Tc99m/ Mo99m Generator was used to produce Tc99m, dose caliber and Dual head Gama camera was used to scan these patient. The level of thyroid hormone were recorded before, and after 3, 6, 9, and 12 month after treatment in order to assess the decrement level of these hormone and therefore performing a quantitative assessment of hyperthyroidism treatment, the result showed that the mean value of these hormones was 6.9, 4.2, 2.8, and 2.5 (nmol/L) for T3, 222.1, 134, 119, 119.2 and 113.4 (nmol/L) for T4, and 0.37, 6.34, 5.3, 2.8, and 2.3 (nmol/L) for TSH respectively. Pair sample two tailed test was performed; a significant difference between the thyroid hormone level was noted before the RAI treatment and after 3, 6, 9, and 12 month later after the treatment, at Confidence level of (CL=95%) and (p value= 0.05), the test were significant at P= 0.000. Causative disease of hyperthyroid function found to be due to Graves' disease in 45

patients (54%) of the collected samples, 28 patients (23.3%) by TMNG, 30 patients (25%) due to diffuse toxic goiter and 8 patients (6.7%) related to the autonomous toxic nodules. This study concludes that hyperthyroidism treatment using I131 considered effective and cause significant difference in thyroid hormone level after treatment.

المستخلص

يعتبرمرض فرط نشاط الغدة الدرقية واحد من المشاكل المرضية الشائعة المرتبطة بالغدة الدرقية، التي تحدث فيها زيادة في افراز هرمونات الغدة الدرقية. أجريت هذه الدراسة لتقييم فعالية علاج الغدة الدرقية باستخدام اليود 131 المشع في علاج مرض فرط نشاط الغدة الدرقية في المرضي السودانيين. تم علاج 120 مريض باستخدام اليود 131 المشع في المركز القومي للعلاج بالأشعة والطب النووي في الخرطوم في الفترة من عام 2012 إلى عام 2015.استخدم عنصر التكنيشيوم المشع المستخلص من مولد التكنيشيوم-المولبدنيم وجهاز معايرة الجرعات و جهاز القاما كاميرا لعمل مسح الغدة وقياس نسبة اخذ الغدة لليود.

سجلت مستويات هرمون الغدة الدرقية قبل العلاج باليود المشع و 3 و 6 و 9 و 12 شهرا بعد العلاج من أجل تقييم مستوى نقصان هذه الهرمونات، ومن ثم إجراء تقييم كمي لعلاج فرط نشاط الغدة الدرقية، وأظهرت النتائج أن متوسط قيم هذه الهرمونات 6.9، 4.2، 2.8، و 2.5 (نانو مول / لتر) للثايرونين ثلاثي اليود و 222.1، 134، 119، 119.2 و 113.4 (نانو مول / لتر) للثايروكسين و 0.37، 6.34، 5.3، 2.8، و 2.3 (نان ومول / لتر) للهرمون المحفز للغدة الدرقية على التوالي. تم إجراء عينة الزوج ثنائي الذيل وجد ان هنالك اختلافا كبيرا بين مستوى الهرمونات قبل العلاج باليود المشع وبعد 3، 6 و 9 و 12 شهر بعد العلاج، وعند مستوى الثقة (٪95 = CL) و (نسبه خطاء =0.05)، كانت نسبة الخطاء التي نتجت من الفحص تساوي 0.000. وجد ان المرض المسبب لفرط زياده نشاط الغدة الدرقية يعود إلى مرض قريفز في 45 مريض يمثلون (٪54) من العينات التي تم جمعها، 28 مريض (٪23.3) الي تضخم الغدة الدرقية

متعدد العقيدات سامة و 30 مريض (25٪)تضخم الغدة الدقية المنتشرة السامة و 8 مرضي (6.7٪) العقيدات السامة المستقلة.

خلصت هذه الدراسة الي ان علاج فرط نشاط الغدة الدرقية باستخدام اليود المشع يعتبر فعالا واحدث اختلافا كبيرا في مستوى هرمون الغدة الدرقية بعد العلاج.

Abbreviations

ATA	**American Thyroid Association**
ATP	**Adenosine Triphosphate**
BI-213	**bismuth-213**
cAMP	**cyclic Adenosine monophosphate**
cGY	**centigray**
cm	**centimeter**
CT	**Computerized Tomography**
DIT	**deoxyribonucleic acid**
DNA	**di-iodide tyrosine**
Fig.	**Figure**

GD	Graves' Disease
Ho-166	Holmium-166
I123	Iodine-123
I125	Iodine-125
I131	Iodine-131
JTA	Japanese Thyroid Association
KeV	Kilo Electron Volt
LAO	Left Anterior Oblique
Mbq	Mega Electron Volt
mCi	Mill curie
MeV	mono-iodide tyrosine
MIT	Mega Becquerel
mL	milli Liter
MRI	Magnetic Resonance Imaging
mU/L	milli-international units per liter
NIS	Sodium Iodide Symporter
PTU	Propyl thiouracil
RAI	Radioactive iodine

RAIU	**Radioactive iodine uptake**
RAO	**Right anterior oblique**
RICK	**Rick& isotope center Khartoum**
RNA	**Ribonucleic acid**
RXR	**Retinoid x receptor**
SPSS	**Statistical package for social sciences**
SSKI	**Strong solution of potassium iodide**
T I/2	**Half-life**
T3	**Tri-iodothyronine**
T4	**Thyroxine**
Tc99m	**Technetium**
TFT	**Thyrotropin-releasing hormone**
TRH	**Thyroid function test**
TSH	**Thyroid stimulating hormone**
TSI	**Thyroid simulating immunoglobulin**
U/ml	**Units per milliliter**
Y-90	**Yttrium 90**

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Chapter One

Chapter One

1.1 Introduction

The thyroid is made up of the isthmus which overlying the 2nd and 3rd rings of the trachea, the lateral lobes which each extending from the side of the thyroid cartilage downwards to the 6th tracheal ring and an inconstant pyramidal lobe which projecting upwards from the isthmus, usually on the left side, which represents a remnant of the embryological descent of the thyroid. The thyroid gland is enclosed in the pretracheal fascia, covered by the strap muscles and overlapped by the sternocleidomastoids. The anterior jugular veins course over the isthmus. When the thyroid enlarges, the strap muscles stretch and adhere to the gland so that, at operation, they often appear to be thin layers of fascia. On the deep aspect of the thyroid lie the larynx and trachea, with the pharynx and oesophagus behind and the carotid sheath on either side. Two nerves lie in close relationship to the gland; in the groove between the trachea and oesophagus lies the recurrent laryngeal nerve and deep to the upper pole lies the external branch of the superior laryngeal nerve passing to the cricothyroid muscle (Abdallah YMY et al, 2014 Adam et al, 2005).

Hyperthyroidism is a condition in which the body has too much thyroid hormone or overactive tissue within the thyroid gland, resulting in overproduction and thus an excess of circulating free thyroid hormones: thyroxine (T_4), tri-iodothyronine (T_3), or both. Symptoms may include weight loss, nervousness, irritability, increased perspiration, a racing heart, hand tremors, anxiety, difficulty sleeping, increased

bowel movements, fine brittle hair, and muscular weakness especially in the upper arms and thighs. In Graves' disease, a bulging of one or both eyes may occur. A classification of hyperthyroidism causes had been made by William et.al 2005, in which he stated that 95% associated with increased radioiodine uptake in patient with Graves' and Plummer's disease. Many treatment options had been proposed since 1941 and have since evolved to the treatment modality of choice for the majority of adult patients, particularly in the USA. The effectiveness of radioiodine treatment for hyperthyroidism is due to radiation-induced cellular damage resulting from high-energy beta emission, the magnitude of which is directly proportional to the radiation dose received by the thyroid gland (Fred et al, 2006).

This paper aimed to discuss the role of thyroid treatment of hyperthyroidism by using of I^{131} radioisotopes in Sudanese population.Nuclear Medicine is the section of science that utilizes the properties of radiopharmaceuticals in order to derive clinical information of the human physiology and biochemistry. The radiopharmaceutical follows its physiological pathway and it is concentrated on specific organs and tissues for short periods of time. Then, the patient is positioned under a nuclear medicine equipment which can detect the radiation emitted by the human body resulting in images of the biodistribution of the radiopharmaceutical. In Nuclear Medicine, there are two main methods of patient imaging, the imaging with Planar Imaging, Dynamic Imaging or SPECT and the PET. During the last decade, hybrid systems have been developed integrating the CT technique with either. Hyperthyroidism refers to any condition in which the body has too much thyroid hormone or overactive tissue within the thyroid gland, resulting in

overproduction and thus an excess of circulating free thyroid hormones: [thyroxine](#) (T_4), tri-iodothyronine (T_3), or both. Symptoms may include weight loss, nervousness, irritability, increased perspiration, a racing heart, hand tremors, anxiety, difficulty sleeping, increased bowel movements, fine brittle hair, and muscular weakness especially in the upper arms and thighs. In Graves' disease, a bulging of one or both eyes may occur. A physical examination and laboratory tests that measure the amount of thyroid hormone (thyroxine, or T4, and triiodothyronine, or T_3) and thyroid-stimulating hormone (TSH) in your blood are necessary and thyroid scan and uptake. Measurement of antibodies in the blood that attack the thyroid (antithyroid antibodies) may help in diagnosing the cause of hyperthyroidism (Fred et al 2006).

Therapy for hyperthyroidism is generally safe and effective, but no one treatment is best for all patients with hyperthyroidism, The appropriate choice of treatment will be influenced by your age, the type of hyperthyroidism that you have, the severity of your hyperthyroidism, other medical conditions that may be affecting your health. The three basic approaches to the therapy of primary hyperthyroidism are firstly; antithyroid drugs, such as thiomides, △ropylthiouracil and methimizole, secondly; surgery and thirdly; ^{131}I therapy. Iodine131 regarded as the treatment of choice for hyperthyroidism in patients older than 30 years and in patient of any age in whom hyperthyroidism is accompanied by medical complications or in whom other treatments have failed. Although Antithyroid drugs are frequently used as initial approach to the control of diffuse toxic goiter (Greaves disease); such drugs are generally not used in the treatment of toxic nodules or multinodular

goiter. In significant number of patients with Graves ' disease, Antithyroid drugs produced intolerable side effects, does not adequately control the disease, or result in patient compliance problem. In these patients and in patients with toxic nodular disease, ^{131}I therapy is of considerable value. Iodine-131therapy is also of considerable value in patients with recurrent hyperthyroidism after previous thyroidectomy when repeat surgery would cause enhanced risks; in children who have experienced toxicity to Antithyroid drugs; and in patient refused other therapy (Fred et al, 2006).

1.2 Problem of the study

Thyroid hyper function may be related to many more underlying causes leading to significant change in much system and may lead to many syndromes due to overexpression of thyroid hormone in serum. In significant number of patients with hyperthyroidism, antithyroid drug therapy produces intolerable side effects and does not adequately control the disease ,or result in patient compliance problem, in these patients and in patients with toxic nodular disease, I-131 therapy is of considerable value. Iodine 131 therapy is also of great value in patient with recurrent hyperthyroidism after previous thyroidectomy.

1.3 Study Objective:

1.3.1 General Objective:

The main objective of this study is to assess radioactive iodine as a treatment of hyperthyroidism, in order to assess the efficiency of the treatment.

1.3.2 Specific Objective:

• To measure thyroid profile and uptake before radioactive iodine therapy.

• To evaluate the response of hyperthyroidism to radioactive iodine therapy.

• To find the association between the doses delivered to the patients and thyroid profile and uptake.

• To find the relationship between the thyroid uptake and laboratory thyroid profile (TFT).

1.4 Significant of the Study:

The thyroid plays an important role in regulating the body's metabolism and calcium balance so any thyroid functions disturbance affects the body. This study was highlighted on the assessment of treatment of hyperthyroidism related to its causative factor in which radioactive iodine considered as the first line of treatment in the most of hyperthyroidism patients where the other medical management can lead to lesser response rate and outcome.

1.5 Overview of the Study:

The following thesis was laid out into five chapters. Chapter one was deals with introduction, problem of the study, hypothesis and objectives. Chapter two will highlights the literature review (part one about anatomy pathophysiology and treatments of hyperthyroidism parts two about radioactive iodine, Chapter three will care about methodology, Chapter four about results and discussion and Chapter Five will show the conclusion, recommendation, references and appendices.

Chapter Two

Chapter Two

Literature Review

2.1Thyroid Anatomy:

The thyroid gland is situated in the neck in front of the larynx and trachea at the level of the 5th, 6th and 7th cervical and 1st thoracic vertebrae. It resembles a butterfly in shape, consisting of two lobes; one on either side of the thyroid cartilage and upper cartilaginous rings of the trachea (Anne et al, 2001).The name of the gland is derived from the Greek word for shield. Because of its embryological development from pharyngeal pouches and descent, ectopic tissue can be found anywhere from the foramen caecum at the base of the tongue to the myocardium. The pyramidal lobe extends towards the hyoid bone and is a remnant of the thyroglossal duct. The normal adult thyroid gland weighs approximately15–20 g. The gland consists of many follicles of varying size lined by epithelium made up of cuboidal and columnar follicular cells, which secrete toward the large lumen of the follicle containing colloid. The thyroid gland is 50–75% colloid by weight (Harold, 2006).The gland is enclosed in the pretracheal fascia, covered by the strap muscles and overlapped by the sternocleidomastoids. The anterior jugular veins course over the isthmus. When the thyroid enlarges, the strap muscles stretch and adhere to the gland so that, at operation, they often appear to be thin layers of fascia (Harold, 2006).
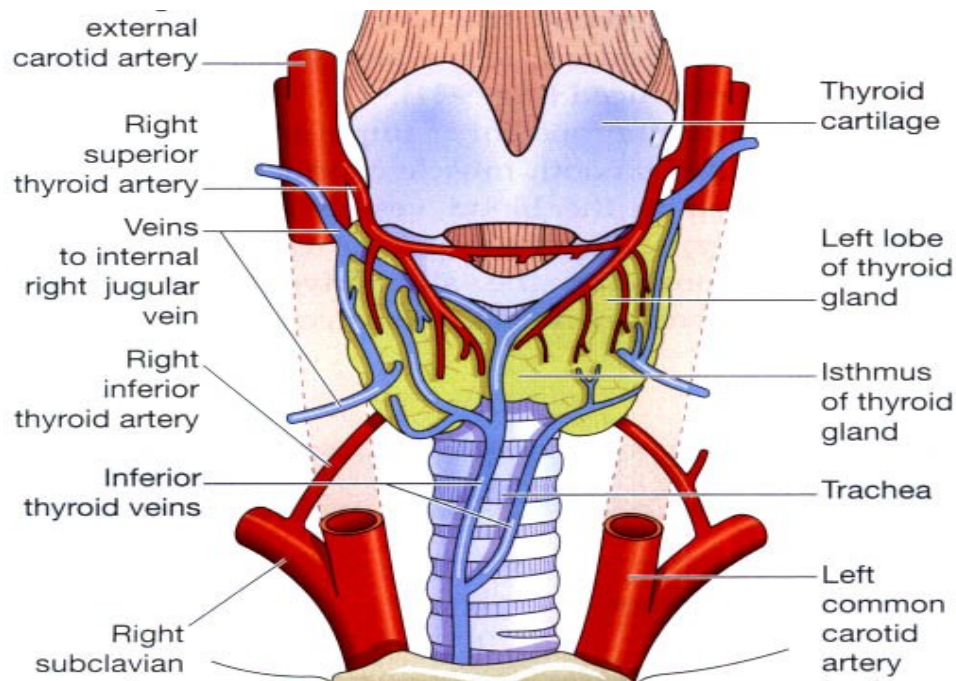
Figure (2.1): showed the anatomy, blood supply, nerve supply of thyroid gland and its relationships. (James H. et al 2006)

2.2 physiology of Thyroid Gland:

The thyroid gland is composed of large numbers of closed follicles (100 to 300 micrometers in diameter) filled with a secretory substance called colloid and lined with cuboidal epithelial cells that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein thyroglobulin, which contains the thyroid hormones within its molecule. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex (Cooper, 2003).

2.2.1 Thyroid Metabolic Hormones:

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The thyroid secretes two major hormones, thyroxine and triiodothyronine, commonly called T4 and T3, respectively (Besser et al, 2002).

Both of these hormones profoundly increase the metabolic rate of the body. Complete lack of thyroid secretion usually causes the basal metabolic rate to fall 40 to 50 per cent below normal, and extreme excesses of thyroid secretion can increase the basal metabolic rate to 60 to 100 per cent above normal. Thyroid secretion is controlled primarily by thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. The thyroid gland also secretes calcitonin, an important hormone for calcium metabolism (Burger, 2004).

The Synthesis and Secretion of the Thyroid Metabolic Hormones: About 93 per cent of the metabolically active hormones secreted by the thyroid gland are thyroxine, and 7 per cent tri-iodothyronine. However, almost all the thyroxine is eventually converted to tri-iodothyronine in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Tri-iodothyronine is about four times as potent as thyroxine, but it is present in

the blood in much smaller quantities and persists for a much shorter time than does thyroxine(Burger, 2004).To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride(Besser et al, 2002).Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides(Burger 2004). Normally, most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones (Dayan, 2001).

The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell (Dohan, 2003). This is called iodide trapping. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells. Iodine is essential for synthesis of thyroid hormones. After oral ingestion, iodine is rapidly reduced to iodide in the upper small intestine.

More than 90% of the iodide is systemically absorbed within 60 minutes of oral ingestion. It distributes in the blood as an extracellular ion similar to chloride. Most leaves the extracellular space through thyroid extraction (20%) or urinary excretion (80%).Some is taken up by the salivary glands and gastric mucosa, which secrete into the gastrointestinal tract(James et al, 2006).

2.2.2Iodide Trapping and Organification:

The thyroid follicular cell traps iodide by means of a high energy sodium iodide "thyroid pump" that concentrates iodine intracellularly at 25–500 times the plasma concentration. Trapping can be blocked competitively by monovalent anions (e.g., perchlorate). In the normal thyroid, organification promptly follows trapping .The iodide is oxidized by thyroid peroxidase at the follicular cell colloid interface to neutral iodine, which binds to tyrosine residues on thyroglobulin. These mono- and di-iodinated tyrosines (MIT, DIT) couple to form T3 and T4, which are stored in the colloid filled follicular lumen. Organification can be blocked by drugs such as propylthiouracil and methimazole (James et al, 2006).

2.2.3Thyroid Hormone Storage and Release:

Thyroid stimulating hormone (TSH) initiates iodide uptake and organification, as well as release of thyroid hormone through hydrolysis of thyroglobulin. Thyroglobulindoes not normally enter the bloodstream except during disease states (e.g., thyroiditis or thyroid cancer). The normal thyroid gland contains

a 1-month supply of hormone, thus drugs blocking hormone synthesis (e.g., propylthiouracil) do not become fully effective in controlling hyperthyroidism until intrathyroidal stores are depleted (James et al, 2006), *Thyroid-Pituitary Feedback:* The thyroid-pituitary feedback mechanism is very sensitive to circulating serum thyroid hormone levels and is the dominant method of adjusting TSH secretion . When serum thyroid hormone levels are increased, the serum TSH is suppressed; when serum thyroid hormone levels are low, serum TSH increases. The major hormone released by the thyroid is T4, which is transported to peripheral tissues by thyroid-binding proteins and converted to the more metabolically active T3at peripheral tissue site of action (James et al, 2006).
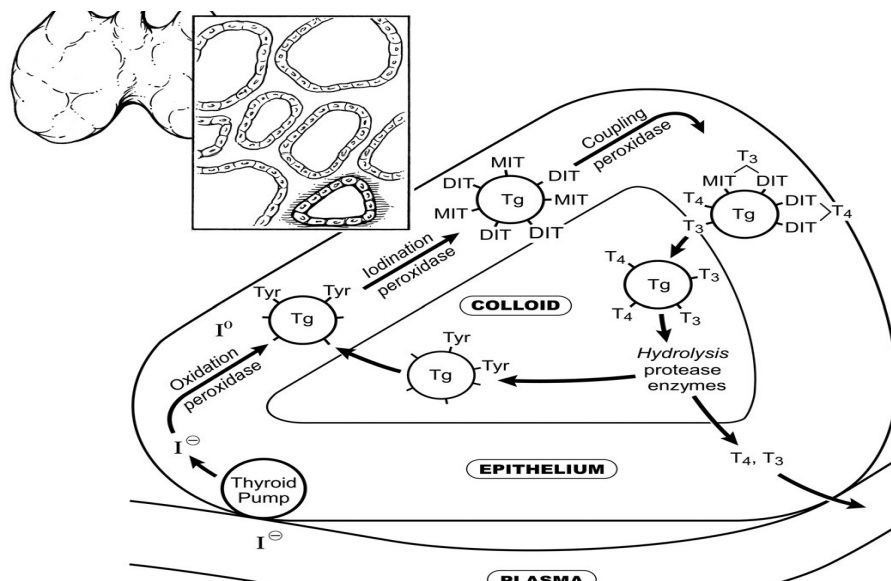
Figure (2-2): Iodine metabolism(James H.et al, 2006).
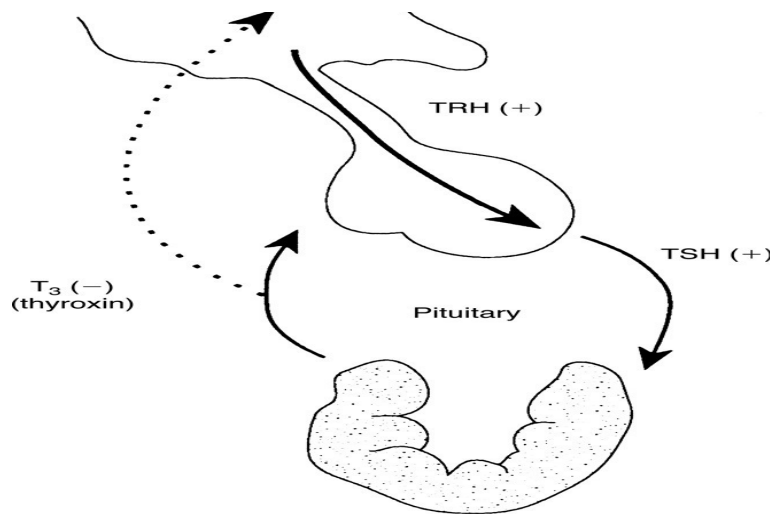
Figure (2-3): Thyroid-pituitary feedback loop **(**James H.et al, 2006(.

2.2.4 Thyroglobulin & chemistry of thyroxine and tri-iodothyronine:

2.2.4.1 Formation and Secretion of Thyroglobulin by the Thyroid Cells: The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin, with a molecular weight of about 335, 000(Marino et al, 2000). Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and

even afterward as stored hormones in the follicular colloid (Marino et al, 2000).

2.2.4.2 Oxidation of the iodide ion: The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an oxidized form of iodine, either nascent iodine (Dohan et al 2003) or I3 _, that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provide a potent system capable of oxidizing iodides (Marino et al, 2000).The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero (Marino et al, 2000).The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but very slowly with the amino acid tyrosine. In the thyroid cells, however, the oxidized iodine is associated with an *iodinase* enzyme that causes the process to occur within seconds or minutes. Therefore, almost as rapidly as the thyroglobulin molecule is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle, iodine binds with about one sixth of the tyrosine amino acids within the thyroglobulin molecule(Marino et al,

2000).Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another. The major hormonal product of the coupling reaction is the molecule thyroxine that remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine, which represents about one fifteenth of the final hormones (Besser, 2002).

2.2.4.3 Storage of thyroglobulin: The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months (Ye, 2001).Release of thyroxine and triiodothyronine from the thyroid gland: Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and tri-iodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form pinocytic vesicles that enter the apex of the thyroid cell. Then

lysosomes in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple proteases among the enzymes digest the thyroglobulin molecules and release thyroxine and tri-iodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood .About three quarters of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remains monoiodotyrosine and diiodotyrosine. During the digestion of the thyroglobulin molecule to cause release of thyroxine and tri-iodothyronine, these iodinated tyrosines also are freed from the thyroglobulin molecules. However, they are not secreted into the blood. Instead, their iodine is cleaved from them by a deiodinase enzyme that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine-deficient because of failure of this recycling process (Marino et al, 2000).

2.2.4.4 Daily rate of secretion of thyroxine and tri-iodothyronine:

About 93 per cent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 per cent is triiodothyronine. However, during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine. Therefore, the hormone finally delivered to and used by the tissues is mainly triiodothyronine, a total of about 35 micrograms of triiodothyronine per day (Yen, 2001).

2.2.4.5 Transport of thyroxine and triiodothyronine to tissues thyroxine and triiodothyronine are bound to plasma proteins: On entering the blood, over 99 per cent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with thyroxine-binding globulin and much less so with thyroxine-binding pre-albumin and albumin (Yen, 2001).

2.2.4.6 T4 and T3 are released slowly to tissue cells: Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances in particular, thyroxine is released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine because of its lower affinity is released to the cells in about 1 day(Yen, 2001).On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks (Yen, 2001).

After injection of a large quantity of thyroxine into a human being, essentially no effect on the metabolic rate can be discerned for 2 to 3 days, thereby demonstrating that there is a long latent period before thyroxine activity begins. Once activity does begin, it increases progressively and reaches a maximum in 10 to 12 days. Thereafter, it decreases with a half-life of about 15 days. Some of the activity persists for as long as 6 weeks to 2 months.

The actions of triiodothyronine occur about four times as rapidly as those of thyroxine, with a latent period as short as 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days. Most of the latency and prolonged period of action of these hormones are probably caused by their binding with proteins both in the plasma and in the tissue cells, followed by their slow release (Silva, 2003).

2.2.5. Physiologic of thyroid gland:

2.2.5.1 Thyroid hormones increase the transcription of large numbers of genes: The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes. Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is generalized increase in functional activity throughout the body (Silva, 2003).

2.2.5.2Most of the thyroxine secreted by the thyroid is converted to triiodothyronine: Before acting on the genes to increase genetic transcription, one iodide is removed from almost all the thyroxine, thus forming triiodothyronine. Intracellular thyroid hormone receptors have a very high affinity for triiodothyronine. Consequently, more than 90 per cent of the thyroid hormone molecules that bind with the receptors are triiodothyronine (James et al, 2006).

2.2.5.3 Thyroid Hormones Activate Nuclear Receptors: The thyroid hormone receptors are either attached to the DNA genetic strands or located

in proximity to them. The thyroid hormone receptor usually forms a heterodimer with retinoid X receptor (RXR) at specific thyroid hormone response elements on the DNA. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins.

However, not all the proteins are increased by similar percentages some only slightly, and others at least as much as six fold. It is believed that most, if not all, of the actions of thyroid hormone result from the subsequent enzymatic and other functions of these new proteins (Fred et al, 2006).

2.2.5.4 Thyroid hormones increase cellular metabolic activity: The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 per cent above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated. Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased. The growth rate of young people is greatly accelerated. The mental processes are excited, and the activities of most of the other endocrine glands are increased (Silva JE, 2003).

2.2.5.5 Thyroid Hormones Increase the Number and Activity of Mitochondria: When thyroxine or triiodothyronine is given to an animal, the

mitochondria in most cells of the animal's body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, one of the principal functions of thyroxin might be simply to increase the number and activity of mitochondria, which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. However, the increase in them number and activity of mitochondria could be the result of increased activity of the cells as well as the cause of the increase (Silva, 2003).

2.2.5.6 Thyroid hormones increase active transport of ions through cell membranes: One of the enzymes that increase its activity in response to thyroid hormone is Na+-K+-ATPase. This in turn increases the rate of transport of both sodium and potassium ions through the cell membranes of some tissues. Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms by which thyroid hormone increases the body's metabolic rate. In fact, thyroid hormone also causes the cell membranes of most cells to become leaky to sodium ions, which further activates the sodium pump and further increases heat production (Fred et al, 2006).

2.2.5.6 Effect of thyroid hormone on growth: Thyroid hormone has both general and specific effects on growth. For instance, it has long been known that thyroid hormone is essential for the metamorphic change of the tadpole into the frog. In humans, the effect of thyroid hormone on growth is manifest

mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so that the duration of growth and the eventual height of the adult may actually be shortened. An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded, and the brain remains smaller than normal. Without specific thyroid therapy within days or weeks after birth, the child without a thyroid gland will remain mentally deficient throughout life (Silva, 2003).

**2.2.5.7 Effects of thyroid hormone on specific bodily mechanisms stimulation of carbohydrate metabolism*:* Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract, and even increased insulin secretion with its resultant secondary effects on carbohydrate metabolism.

All these effects probably result from the overall increase in cellular metabolic enzymes caused by thyroid hormone (Silva, 2000).

2.2.5.8 Stimulation of fat metabolism: Essentially all aspects of fat metabolism are also enhanced under the influence of thyroid hormone. In particular, lipids are mobilized rapidly from the fat tissue, which decreases the fat stores of the body to a greater extent than almost any other tissue element. This also increases the free fatty acid concentration in the plasma and greatly accelerates the oxidation of free fatty acids by the cells (Silva, 2000).

2.2.5.9 Effect on plasma and liver fats: Increased thyroid hormone decreases the concentrations of cholesterol, phospholipids, and triglycerides in the plasma, even though it increases the free fatty acids. Conversely, decreased thyroid secretion greatly increases the plasma concentrations of cholesterol, phospholipids, and triglycerides and almost always causes excessive deposition of fat in the liver as well. The large increase in circulating plasma cholesterol in prolonged hypothyroidism is often associated with severe atherosclerosis (Silva, 2000).

One of the mechanisms by which thyroid hormone decreases the plasma cholesterol concentration is to increase significantly the rate of cholesterol secretion in the bile and consequent loss in the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells (Silva, 2000).

2.2.5.10 Increased requirement for vitamins: Because thyroid hormone increases the quantities of many bodily enzymes and because vitamins are essential parts of some of the enzymes or coenzymes, thyroid hormone causes increased need for vitamins. Therefore, a relative vitamin deficiency can occur when excess thyroid hormone is secreted, unless at the same time increased quantities of vitamins are made available (Silva, 2000).

2.2.5.11 Increased basal metabolic rate*:* Because thyroid hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate 60 to 100 per cent above normal. Conversely, when no thyroid hormone is produced, the basal metabolic rate falls almost to one-half normal. Extreme amounts of the hormones are required to cause very high basal metabolic rates (Silva, 2000).

2.2.5.12 Decreased body weight: Greatly increased thyroid hormone almost always decreases the body weight, and greatly decreased hormone almost always increases the body weight; these effects do not always occur, because thyroid hormone also increases the appetite, and this may counterbalance the change in the metabolic rate (Silva, 2006).

2.2.5.13 Effect of thyroid hormones on the cardiovascular system increased blood flow and cardiac output: Increased metabolism in the tissues causes more rapid utilization of oxygen than normal and release of greater than normal quantities of metabolic end products from the tissues.

These effects cause vasodilation in most body tissues, thus increasing blood flow. The rate of blood flow in the skin especially increases because of the increased need for heat elimination from the body. As a consequence of the increased blood flow, cardiac output also increases, sometimes rising to 60 per cent or more above normal when excessive thyroid hormone is present and falling to only 50 per cent of normal in very severe hypothyroidism (Zhang et al, 2000).

2.2.5.14 Increased heart rate: The heart rate increases considerably more under the influence of thyroid hormone than would be expected from the increase in cardiac output. Therefore, thyroid hormone seems to have a direct effect on the excitability of the heart, which in turn increases the heart rate. This effect is of particular importance because the heart rate is one of the sensitive physical signs that the clinician uses in determining whether a patient has excessive or diminished thyroid hormone production (Zhang et al, 2000).

I2.2.5.15 increased heart strength: The increased enzymatic activity caused by increased thyroid hormone production apparently increases the strength of the heart when only a slight excess of thyroid hormone is secreted. This is analogous to the increase in heart strength that occurs in mild fevers and during exercise. However, when thyroid hormone is increased markedly, the heart muscle strength becomes depressed because of long-term excessive protein catabolism. Indeed, some severely thyrotoxic patients die of cardiac decompensation secondary to myocardial failure and

to increased cardiac load imposed by the increase in cardiac output; (Zhang et al, 2000).

2.2.5.16 Normal arterial pressure*:* The mean arterial pressure usually remains about normal after administration of thyroid hormone. Because of increased blood flow through the tissues between heartbeats, the pulse pressure is often increased, with the systolic pressure elevated in hyperthyroidism 10 to 15 mm Hg and the diastolic pressure reduced a corresponding amount (Zhang et al, 2000).

2.2.5.17 Increased respiration: The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration. Increased gastrointestinal motility: In addition to increased appetite and food intake, thyroid hormone increases both the rates of secretion of the digestive juices and the motility of the gastrointestinal tract. Hyperthyroidism often results in diarrhea. Lack of thyroid hormone can cause constipation (Zhang et al, 2000).

2.2.5.18 Excitatory effects on the central nervous system: In general, thyroid hormone increases the rapidity of cerebration but also often dissociates this; conversely, lack of thyroid hormone decreases this function. The hyperthyroid individual is likely to have extreme nervousness and many psychoneurotic tendencies, such as anxiety complexes, extreme worry, and paranoia (Zhang et al, 2000).

2.2.5.19 Effect on the function of the muscles: Slight increase in thyroid hormone usually makes the muscles react with vigor, but when the quantity of hormone becomes excessive, the muscles become weakened because of excess protein catabolism. Conversely, lack of thyroid hormone causes the muscles to become sluggish, and they relax slowly after a contraction (Zhang et al, 2000).

2.2.5.20 Muscle tremor: One of the most characteristic signs of hyperthyroidism is a fine muscle tremor. This is not the coarse tremor that occurs in Parkinson's disease or in shivering, because it occurs at the rapid frequency of 10 to 15 times per second. The tremor can be observed easily by placing a sheet of paper on the extended fingers and noting the degree of vibration of the paper. This tremor is believed to be caused by increased reactivity of the neuronal synapses in the areas of the spinal cord that control muscle tone. The tremor is an important means for assessing the degree of thyroid hormone effect on the central nervous system (Zhang et al, 2000).

2.2.5.21 Effect on sleep: Because of the exhausting effect of thyroid hormone on the musculature and on the central nervous system, the hyperthyroid subject often has a feeling of constant tiredness, but because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep. Conversely, extreme somnolence is characteristic of hypothyroidism, with sleep sometimes lasting 12 to 14 hours a day (Zhang et al, 2000).

2.2.5.22 Effect on other endocrine glands: Increased thyroid hormone increases the rates of secretion of most other endocrine glands, but it also increases the need of the tissues for the hormones. For instance, increased thyroxine secretion increases the rate of glucose metabolism everywhere in the body and therefore causes a corresponding need for increased insulin secretion by the pancreas. Also, thyroid hormone increases many metabolic activities related to bone formation and, as a consequence, increases the need for parathyroid hormone. Thyroid hormone also increases the rate at which adrenal glucocorticoids are inactivated by the liver. This leads to feedback increase in adrenocorticotropic hormone production by the anterior pituitary and, therefore, increased rate of glucocorticoid secretion by the adrenal glands (Zhang et al, 2000).

2.2.5.23 Effect of thyroid hormone on sexual function: For normal sexual function, thyroid secretion needs to be approximately normal. In men, lack of thyroid hormone is likely to cause loss of libido; great excesses of the hormone, however, sometimes cause impotence. In women, lack of thyroid hormone often causes menorrhagia and polymenorrhea that is, respectively, excessive and frequent menstrual bleeding. Yet, strangely enough, in other women thyroid lack may cause irregular periods and occasionally even amenorrhea. A hypothyroid woman, like a man, is likely to have greatly decreased libido. To make the picture still more confusing, in the hyperthyroid woman, oligomenorrhea, which means greatly reduced

bleeding, is common, and occasionally amenorrhea results(Zhang et al, 2000).

The action of thyroid hormone on the gonads cannot be pinpointed to a specific function but probably results from a combination of direct metabolic effects on the gonads as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones that control the sexual functions (Larsen et al, 2003).

2.2.5.23 Regulation of thyroid hormone secretion: To maintain normal levels of metabolic activity in the body, precisely the right amount of thyroid hormone must be secreted at all times; to achieve this, specific feedback mechanisms operate through then hypothalamus and anterior pituitary gland to control the rate of thyroid secretion. These mechanisms are as follows (Larsen et.al, 2003).

2.2.5.24 TSH (from the anterior pituitary gland) increases thyroid secretion: TSH, also known as thyrotropin, is an anterior pituitary hormone, a glycoprotein with a molecular weight of about 28,000. This hormone increases the secretion of thyroxine and triiodothyronine by the thyroid gland. Its specific effects on the thyroid gland are as follows:

Firstly; increased proteolysis of the thyroglobulin that has already been stored in the follicles, with resultant release of the thyroid hormones into the circulating blood and diminishment of the follicular substance itself. Secondly; Increased activity of the iodide pump, which increases the rate of

"iodide trapping" in the glandular cells, sometimes increasing the ratio of intracellular to extracellular iodide concentration in the glandular substance to as much as eight times normal. And increased iodination of tyrosine to form the thyroid hormones. 4. Increased size and increased secretory activity of the thyroid cells 5. Increased number of thyroid cells plus a change from cuboidal to columnar cells and much enfolding of the thyroid epithelium into the follicles .In summary, TSH increases all the known secretory activities of the thyroid glandular cells. The most important early effect after administration of TSH is to initiate proteolysis of the thyroglobulin, which causes release of thyroxine and triiodothyronine into the blood within 30 minutes. The other effects require hours or even days and weeks to develop fully (Larsen et al, 2003).

2.2.5.25 Cyclic adenosine monophosphate mediates the stimulatory effect of TSH: In the past, it was difficult to explain the many and varied effects of TSH on the thyroid cell. It is now clear that most, if not all, of these effects result from activation of the "second messenger" cyclicadenosine monophosphate (cAMP) system of the cell. The first event in this activation is binding of TSH with specific TSH receptors on the basal membrane surfaces of the thyroid cell. This then activates adenylyl cyclase in the membrane, which increases the formation of cAMP inside the cell. Finally, the cAMP acts as a second messenger to activate protein kinase, which causes multiple phosphorylations throughout the cell. The result is both an immediate increase in secretion of thyroid hormones and prolonged growth of the

thyroid glandular tissue itself. This method for control of thyroid cell activity is similar to the function of cAMP as a "second messenger" in many other target tissues of the body (Szkudlinski et al, 2002).

2.2.5.26: Anterior pituitary secretion of TSH is regulated by thyrotropin-releasing hormone from the hypothalamus: Anterior pituitary secretion of TSH is controlled by a hypothalamic hormone, thyrotropin-releasinghormone (TRH), which is secreted by nerve endings in the median eminence of the hypothalamus. From the median eminence, the TRH is then transported to the anterior pituitary by way of the hypothalamic chypophysial portal blood. TRH has been obtained in pure form. It is a simple substance, a tripeptide amide pyroglutamyl-histidylproline- amide. TRH directly affects the anterior pituitary gland cells to increase their output of TSH. When the blood portal system from the hypothalamus to the anterior pituitary gland becomes blocked, the rate of secretion of TSH by the anterior pituitary decreases greatly but is not reduced to zero. The molecular mechanism by which TRH causes the TSH-secreting cells of the anterior pituitary to produce TSH is first to bind with TRH receptors in the pituitary cell membrane. This in turn activates the phospholipase second messenger system inside the pituitary cells to produce large amounts of phospholipase C, followed by a cascade of other second messengers, including calcium ions and diacylglycerol, which eventually leads to TSH release (Szkudlinsk et al, 2002).

2.2.5.27 Effects of cold and other neurogenic stimuli on TRH and TSH secretion: One of the best-known stimuli for increasing the rate of TRH secretion by the hypothalamus, and therefore TSH secretion by the anterior pituitary gland, is exposure of an animal to cold. This effect almost certainly results from excitation of the hypothalamic centers for body temperature control.

Exposure of rats for several weeks to severe cold increases the output of thyroid hormones sometimes to more than 100 per cent of normal and can increase the basal metabolic rate as much as 50 per cent. Indeed, persons moving to arctic regions have been known to develop basal metabolic rates 15 to 20 per cent above normal (Szkudlinski, et al 2002).

Various emotional reactions can also affect the output of TRH and TSH and therefore indirectly affect the secretion of thyroid hormones. Excitement and anxiety conditions that greatly stimulate the sympathetic nervous system cause an acute decrease in secretion of TSH, perhaps because these states increase the metabolic rate and body heat and therefore exert an inverse effect on the heat control center. Neither these emotional effects nor the effect of cold is observed after the hypophysial stalk has been cut, demonstrating that both of these effects are mediated by way of the hypothalamus (Szkudlinski, et al 2002).

2.2.5.28 Feedback effect of thyroid hormone to decrease anterior pituitary secretion of TSH: Increased thyroid hormone in the body fluids

decreases secretion of TSH by the anterior pituitary. When the rate of thyroid hormone secretion rises to about 1.75 times normal, the rate of TSH secretion falls essentially to zero. Almost all this feedback depressant effect occurs even when the anterior pituitary has been separated from the hypothalamus. Therefore, as shown in Figure 2-1, it is probable that increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by a direct effect on the anterior pituitary gland itself. Regardless of the mechanism of the feedback, its effect is to maintain an almost constant concentration of free thyroid hormones in the circulating body fluids (Szkudlinski et al, 2002).

2.3Antithyroid substances:

Drugs that suppress thyroid secretion are called antithyroid substances. The best known of these substances are thiocyanate, propylthiouracil, and high concentrations of inorganic iodides. The mechanism by which each of these blocks thyroid secretion is different from the others, and they can be explained as follows (Silva, 2003).

2.3.1 Thiocyanate ions decrease iodide trapping: The same active pump that transports iodide ions into the thyroid cells can also pump thiocyanate ions, perchlorate ions, and nitrate ions. Therefore, the

administration of thiocyanate (or one of the other ions as well) in high enough concentration can cause competitive inhibition of iodide transport into the cell that is, inhibition of the iodide-trapping mechanism. The decreased availability of iodide in the glandular cells does not stop the formation of thyroglobulin; it merely prevents the thyroglobulin that is formed from becoming iodinated and therefore from forming the thyroid hormones. This deficiency of the thyroid hormones in turn leads to increased secretion of TSH by the anterior pituitary gland, which causes overgrowth of the thyroid gland even though the gland still does not form adequate quantities of thyroid hormones. Therefore, the use of thiocyanates and some other ions to block thyroid secretion can lead to development of a greatly enlarged thyroid gland, which is called a goiter (Silva, 2003).

2.3.2 Propylthiouracil decreases thyroid hormone formation:

Propylthiouracil (and other, similar compounds, such as methimazole and carbimazole) prevents formation of thyroid hormone from iodides and tyrosine. The mechanism of this is partly to block the peroxidase enzymethat is required for iodination of tyrosine and partly to block the coupling of two iodinated tyrosines to form thyroxine or triiodothyronine. Propylthiouracil, like thiocyanate, does not prevent formation of thyroglobulin. The absence of thyroxine and triiodothyronine in the thyroglobulin can lead to tremendous feedback enhancement of TSH secretion by the anterior pituitary gland, thus promoting growth of the glandular tissue and forming a goiter (Silva, 2003).

2.3.3 Iodides in high concentrations decrease thyroid activity and thyroid gland size:

When iodides are present in the blood in high concentration (100 times the normal plasma level), most activities of the thyroid gland are decreased, but often they remain decreased for only a few weeks. The effect is to reduce the rate of iodide trapping, so that the rate of iodination of tyrosine to form thyroid hormones is also decreased. Even more important, the normal endocytosis of colloid from the follicles by the thyroid glandular cells is paralyzed by the high iodide concentrations. Because this is the first step in release of the thyroid hormones from the storage colloid, there is almost immediate shutdown of thyroid hormone secretion into the blood. Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood supply, in contradistinction to the opposite effects caused by most of the other antithyroid agents. For this reason, iodides are frequently administered to patients for 2 to 3 weeks before surgical removal of the thyroid gland to decrease the necessary amount of surgery, especially to decrease the amount of bleeding (Fred et al, 2006).

2.4Thyroid pathology:

2.4.1Hyperthyroidism:

Most effects of hyperthyroidism are obvious from the preceding discussion of the various physiologic effects of thyroid hormone. However, some specific effects should be mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism (Silva2003).Causes of hyperthyroidism (toxic goiter, thyrotoxicosis, Graves' disease): In most patients with hyperthyroidism, the thyroid gland is increased to two to three time's normal size, with tremendous hyperplasia and in-folding of the follicular cell lining into the follicles, so that the number of cells is increased greatly. Also, each cell increases its rate of secretion several fold; radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates 5 to 15 times normal. The changes in the thyroid gland in most instances are similar to those caused by excessive TSH. However, plasma TSH concentrations are less than normal rather than enhanced in almost all patients and often are essentially zero. However, other substances that have actions similar to those of TSH are found in the blood of almost all these patients. These substances are immunoglobulin antibodies that bind with the same membrane receptors that bind TSH. They induce continual activation of the cAMP system of the cells, with resultant development of hyperthyroidism. These antibodies are called thyroid-stimulating immunoglobulin and are designated TSI. They have a prolonged

stimulating effect on the thyroid gland, lasting for as long as 12 hours, in contrast to a little over 1 hour for TSH. The high level of thyroid hormone secretion caused by TSI in turn suppresses anterior pituitary formation of TSH (Stassi et al, 2002).

The antibodies that cause hyperthyroidism almost certainly occur as the result of autoimmunity that has developed against thyroid tissue. Presumably, at some time in the history of the person, an excess of thyroid cell antigens was released from the thyroid cells, and this has resulted in the formation of antibodies against the thyroid gland itself (Stassi et al, 2002).

Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism, in that it usually is not associated with evidence of any autoimmune disease. An interesting effect of the adenoma is that as long as it continues to secrete large quantities of thyroid hormone, secretory function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland (Tomer et al, 2003).

Symptoms of Hyperthyroidism: The symptoms of hyperthyroidism are obvious from the preceding discussion of the physiology of the thyroid hormones: (1) a high state of excitability, (2) intolerance to heat, (3) increased sweating, (4) mild to extreme weight loss (sometimes as much as

100 pounds), (5) varying degrees of diarrhea,(Besser GM, 2002) muscle weakness,(Burger AG, 2003) nervousness or other psychic disorders,(Cooper DS, 2003) extreme fatigue but inability to sleep, and tremor of the hands(Stassi et al, 2002)

Exophthalmos: Most people with hyperthyroidism develop some degree of protrusion of the eyeballs. This condition is called exophthalmos. A major degree of exophthalmos occurs in about one third of hyperthyroid patients, and the condition sometimes becomes so severe that the eyeball protrusion stretches the optic nerve enough to damage vision. Much more often, the eyes are damaged because the eyelids do not close completely when the person blinks or is asleep. As a result, the epithelial surfaces of the eyes become dry and irritated and often infected, resulting in ulceration of the cornea. The cause of the protruding eyes is edematous swelling of the retro-orbital tissues and degenerative changes in the extranodular muscles. In most patients, immunoglobulins can be found in the blood that reacts with the eye muscles. Furthermore, the concentration of these immunoglobulins is usually highest in patients who have high concentrations of TSIs. Therefore, there is much reason to believe that exophthalmos, like hyperthyroidism itself, is an autoimmune process. The exophthalmos usually is greatly ameliorated with treatment of the hyperthyroidism (Stassi et al, 2002).

Diagnostic Tests for Hyperthyroidism: For the usual case of hyperthyroidism, the most accurate diagnostic test is direct measurement of the concentration of "free" thyroxine (and sometimes triiodothyronine) in the

plasma, using appropriate radioimmunoassay procedures. Other tests that are sometimes used are as follows: The basal metabolic rate is usually increased to +30 to +60 in severe hyperthyroidism; the concentration of TSH in the plasma is measured by radioimmunoassay. In the usual type of thyrotoxicosis, anterior pituitary secretion of TSH is so completely suppressed by the large amounts of circulating thyroxine and triiodothyronine that there is almost no plasma TSH. And the concentration of TSI is measured by radioimmunoassay. This is usually high in thyrotoxicosis but low in thyroid adenoma (Larsen et al, 2003).

Physiology of treatment in hyperthyroidism: The most direct treatment for hyperthyroidism is surgical removal of most of the thyroid gland. In general, it is desirable to prepare the patient for surgical removal of the gland before the operation. This is done by administering propylthiouracil, usually for several weeks, until the basal metabolic rate of the patient has returned to normal. Then, administration of high concentrations of iodides for 1 to 2 weeks immediately before operation causes the gland itself to recede in size and its blood supply to diminish. By using these preoperative procedures, the operative mortality is less than 1 in 1000 in the better hospitals, whereas before development of modern procedures, operative mortality was 1 in 25(Fred et al, 2006).

Treatment of the hyperplastic thyroid gland with radioactive iodine: Eighty to 90 per cent of an injected dose of iodide is absorbed by the hyperplastic, toxic thyroid gland within1 day after injection. If this injected

iodine is radioactive, it can destroy most of the secretory cells of the thyroid gland. Usually 5 millicuries of radioactive iodine is given to the patient, whose condition is reassessed several weeks later. If the patient is still hyperthyroid, additional doses are administered until normal thyroid status is reached (Silva, 2003).

2.4.2 Hypothyroidism:

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism, but there are a few physiologic mechanisms peculiar to hypothyroidism. Hypothyroidism, like hyperthyroidism, probably is initiated by autoimmunity against the thyroid gland, but immunity that destroys the gland rather than stimulates it. The thyroid glands of most of these patients first have autoimmune "thyroiditis," which means thyroid inflammation.

This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called thyroid goiter, as follows(Roberts et al, 2004).

Physiologic characteristics of hypothyroidism: Whether hypothyroidism is due to thyroiditis, endemic colloid goiter, idiopathic colloid goiter, destruction of the thyroid gland by irradiation, or surgical removal of the thyroid gland, the physiologic effects are the same. They include fatigue and extreme somnolence with sleeping up to 12 to 14 hours a day, extreme muscular sluggishness, slowed heart rate, decreased cardiac output,

decreased blood volume, sometimes increased body weight, constipation, mental sluggishness, failure of many trophic functions in the body evidenced by depressed growth of hair and scaliness of the skin, development of a froglike husky voice, and, in severe cases, development of an edematous appearance throughout the body called myxedema (Roberts et al, 2004).

Myxedema: Myxedema develops in the patient with almost total lack of thyroid hormone function. In this condition, for reasons not explained, greatly increased quantities of hyaluronic acid and chondroitin sulfate bound with protein form excessive tissue gel in the interstitial spaces and this causes the total quantity of interstitial fluid to increase. Because of the gel nature of the excess fluid, it is mainly immobile, and the edema is the nonpitting type (Roberts et al, 2004).

Atherosclerosis in hypothyroidism: As pointed out earlier, lack of thyroid hormone increases the quantity of blood cholesterol because of altered fat and cholesterol metabolism and diminished liver excretion of cholesterol in the bile. The increase in blood cholesterol is usually associated with increased atherosclerosis.

Therefore, many hypothyroid patients, particularly those with myxedema, develop atherosclerosis, which in turn results in peripheral vascular disease, deafness, and coronary artery disease with consequent early death (Roberts et al, 2004).

Diagnostic tests in hypothyroidism: The tests already described for diagnosis of hyperthyroidism give opposite results in hypothyroidism. The free thyroxine in the blood is low. The basal metabolic rate in myxedema ranges between -30 and -50. And the secretion of TSH by the anterior pituitary when a test dose of TRH is administered is usually greatly increased (except in those rare instances of hypothyroidism caused by depressed response of the pituitary gland to TRH) (Roberts et al, 2004).

Treatment of Hypothyroidism: The effect of thyroxine on the basal metabolic rate, demonstrating that the hormone normally has duration of action of more than 1 month. Consequently, it is easy to maintain a steady level of thyroid hormone activity in the body by daily oral ingestion of a tablet or more containing thyroxine. Furthermore, proper treatment of the hypothyroid patient results in such complete normality that formerly myxedematous patients have lived into their 90s after treatment for more than 50 years (Roberts et al, 2004).

Cretinism: Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood. This condition is characterized especially by failure of body growth and by mental retardation. It results from congenital lack of a thyroid gland (congenital cretinism), from failure of the thyroid gland to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (endemic cretinism). The severity of endemic cretinism varies greatly, depending on the amount of iodine in the diet, and whole populaces of an endemic geographic iodine-deficient soil area have been

known to have cretinoid tendencies. A neonate without a thyroid gland may have normal appearance and function because it was supplied with some (but usually not enough) thyroid hormone by the mother while in utero, but a few weeks after birth, the neonate's movements become sluggish and both physical and mental growth begin to be greatly retarded. Treatment of the neonate with cretinism at any time with adequate iodine or thyroxine usually causes normal return of physical growth, but unless the cretinism is treated within a few weeks after birth, mental growth remains permanently retarded. This results from retardation of the growth, branching, and myelination of the neuronal cells of the central nervous system at this critical time in the normal development of the mental powers. Skeletal growth in the child with cretinism is characteristically more inhibited than is soft tissue growth. As a result of this disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the child with cretinism an obese, stocky, and short appearance. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the child (Roberts et al, 2004).

2.5 Thyroid Scintigraphy:

2.5.1 Thyroid Radiopharmaceuticals:

Radioiodine: Because radioiodine is selectively trapped and organified by the thyroid and incorporated into thyroid hormone, radioactive iodine is an ideal physiological radiotracer ,providing clinically important physiological

information regarding thyroid function. I-123 and I-131 are the two radiopharmaceuticals used clinically. Because of the rapid absorption, prompt uptake, and organification of iodine, radioactivity is detectable in the thyroid gland within minutes and normally reaches the thyroid follicular lumen by 20–30 minutes. A progressive increase in thyroid uptake normally occurs over 24hours. The time delay between radioiodine ingestion and imaging (e.g., 2–6 hours for routine I-123thyroid imaging and 1–3 days for I-131) is dictated more by the desire for background clearance and a high target to-background ratio than by slow gland uptake. Radioiodine is also taken up in the salivary glands stomach, and to a lesser extent, choroid plexus. It is not concentrated in these organs. The kidneys and gastrointestinal tract serve as the excretory route (James et al, 2006).

Iodine I-131: Physics: The physical half-life of I-131 is 8 days. It undergoes beta minus decay and emits a principle primary gamma photon of 364 keV. The 364-keVgamma photons are not optimal for modern-day gamma cameras. Camera count detection sensitivity for I-131 is poor; approximately half of the photons penetrate the typical three-eighths-inch crystal and thus are not detected. Septal penetration of the collimator by the high-energy emissions results in image degradation. High energy beta particles are also emitted, the principle one being 0.606 MeV (James et al, 2006).

Dosimetry, The high-energy beta emissions and long physical half-life of I-131 result in relatively high radiation to the patient, particularly to the thyroid (approximately 1 rad/μCi). This high radiation absorbed dose severely

limits the dose that can be administered, further impacting on image quality (James et al, 2006).
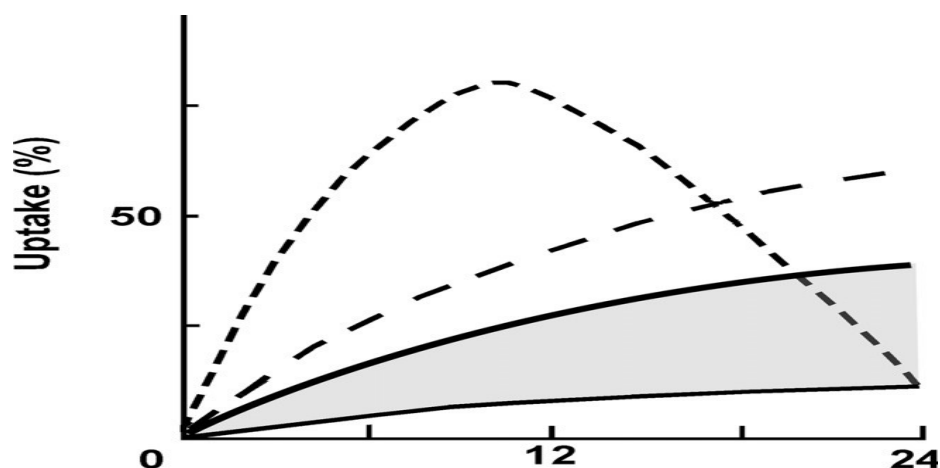
Figure (2-4): Thyroid radioiodine uptake. Radioiodine uptake normally increases progressively over 24 hours (gray area) and is between 10 and 30% at 24 hours. (James H.et al, 2006).

Iodine I-123: Physics I-123 decays by electron capture with a half-life of 13.2 hours. The principal gamma emission is a 159 keV photon which is well-suited for gamma cameras. There are a small percentage of higher energy emissions (2.4% 440–625 keV) and 0.15% (625–784 keV).There are no particulate emissions (James et al, 2006).

Dosimetry, Methods used for I-123 production in the United States today result in long-lived radionuclide impurities. In the past, I[123] was contaminated with I-124and I-125. The maximal levels of identified impurities are Te-121 (0.05%) and I-125 (0.06%). The thyroid receives 1.5–2.6 rads (15–25% RAIU) from a 200 µCi dose of I[123].The considerably lower radiation dosimetry of I-

123compared to I^{131} allows administration of 200–400 µCi of I-123 for routine thyroid scanning compared to 50 µCi of I-131. This higher administered dose results inconsiderably better image quality (James et al, 2006).

Tc-99m Pertechnetate: Because of Tc-99m pertechnetate's low cost and ready availability from molybdenum-99/Tc-99m generator systems, it has long served as an alternative to radioiodine for thyroid scintigraphy. Physics: The 140-keV photopeak of Tc-99m is ideal for use with the gamma camera. It has a short 6-hour half-life and no particulate emissions. Pharmacokinetics: In contrast to the oral administration of radioiodine, Tc-99m Pertechnetate is administered intravenously.Tc-99m is trapped by the thyroid in an identical manner as iodide, but it is not organified nor incorporated into thyroid hormone. Because it is not organified, it is not retained in the thyroid. Thus, thyroid imaging is performed at peak uptake 20–30 minutes after injection. Dosimetry: The lack of particulate emissions and the short half-life of6 hour's results in relatively low radiation dosimetry to the thyroid. Thus, the allowable administered activity of Tc-99m Pertechnetate (3–5 mCi) is considerably higher that I-123 for routine thyroid scans. The large photon flux provides high quality images (James et al, 2006).

Table (2-1): Physical Characteristic of Thyroid Radiopharmaceuticals

	Tc-99m	I-123	I-131
Mode of decay	Isometric transition	Electron capture	Beta minus
Physical half-life(t1/2)	6 hr	13.2 hr	8.1 days
Photon energy	140 keV	159 keV	364 keV
Abundance	89%	83.4%	81%
Beta emissions			606 keV

(James H.et al, 2006).

Table (2-2): Dosimetry of Thyroid Radiopharmaceuticals

	Tc-99m (rads/5 mCi, cGY/18MBq) 5	I-123 (rads/200 µCi,) cGy/7.5 MBq)	I-131 (rads/50 µCi, cGy/3.7 MBq)
Thyroid	0.600	1.5 to 2.6*	39.000 to 65.000
Bladder wall	0.430	0.070	0.150
Stomach	0.250	0.050	0.085

Small intestine	0.550	0.030	0.003
Red marrow	0.100	0.060	0.007
Testis	0.050	0.027	0.006
Ovaries	0.150	0.072	0.009
TOTAL BODY	0.070	0.009	0.035

(James H.et al, 2006).

*Lower estimate assumes a 15% RAIU and higher estimate assumes a 25% RAIU, both at time of calibration.

2.5.2 Special Considerations and Precautions:

Food and Medications Containing Iodine: Stable iodine contained in foods and medications can interfere with radionuclide thyroid studies. Expansion of the iodine pool due to ingestion or parenteral administration of iodine containing agents results in a reduced percent radioiodine uptake (%RAIU) by the thyroid. Increasing amounts of iodine in the normal diet over the years has resulted in a lower normal value for the %RAIU. Suppression of uptake by exogenous iodine may preclude successful imaging or accurate uptake measurements.

As little as 1 mg of stable iodine can cause marked reduction of uptake and 10 mg can effectively block the gland (98% reduction). Radiographic contrast media are a common source of iodine that interferes with radioiodine thyroid

studies. A food and drug history should be obtained from all patients prior to undergoing thyroid imaging and uptake studies. Chronic renal failure impairs iodide clearance, expands the iodide pool, and thus lowers the %RAIU. Hypothyroidism slows clearance of radioactive iodine from the body; hyperthyroidism increases the clearance rate (James et al, 2006).

Pregnancy: The fetal thyroid concentrates radioiodine after 10–12 weeks of gestation. Radioiodine crosses the placenta and significant exposure of the fetal thyroid can occur after therapeutic doses to the mother, resulting in fetal hypothyroidism and even cretinism (James et al, 2006).

Nursing Mother: Radioiodine is excreted in human breast milk. Because of its long half-life, nursing should be discontinued after diagnostic or therapeutic studies with I-131.With I-123, it has generally been recommended that breastfeeding may resume after 2–3 days. With Tc-99m Pertechnetate, nursing can be resumed after 24 hours (James et al, 2006).

Patient Information: Thyroid studies must always be interpreted in light of the patient's clinical history, thyroid physical examination, and, importantly, with knowledge of the patient's serum thyroid function studies (James et al, 2006).

2.5.3 Methodology for thyroid uptake studies and thyroid scans:

Thyroid uptake studies and thyroid scans are often performed at the same clinic visit. However, they are usually acquired with different instrumentation, providing different but complementary information. Thyroid scans are acquired with a gamma camera. Thyroid uptake studies are most commonly acquired with a non-imaging gamma scintillation probe detector. Camera-based methods are sometimes used and will be discussed. A thyroid uptake provides quantitative information regarding the percent of the administered activity taken up by the thyroid (James et al, 2006).

Radioiodine Percent Uptake: Both I-131 and I-123 can be used for calculation of the %RAIU or the percent of the administered radioactive iodine taken up by the thyroid. Clinical indications for uptake determinations are few, but important. Indications: The most common clinical indication for a %RAIU study is to aid in the differential diagnosis of newly diagnosed thyrotoxicosis. In most cases, the referring physician seeks to differentiate Graves' disease, the most common cause for thyrotoxicosis, from other causes (e.g., thyroiditis, the second most common cause). Therapy of Graves' disease is quite different than that for other causes. The %RAIU is elevated in Graves' disease, but suppressed or decreased in most other causes of thyrotoxicosis with diffuse goiter, such as thyroiditis (James et al, 2006).

Methodology: Medications that might interfere with thyroid uptake should be discontinued for an appropriate length of time. Patients should have nothing by mouth for 4 hours prior to the study to assure good radioiodine absorption. I-123 and I-131 are usually administered in capsule form rather

than liquid. The unit-dosed capsule formulation minimizes airborne exposure of radioiodine to technologists and is convenient for handling (James et al 2006).

When a scan is not needed, 5–10 µCi I-131 or 50–100µCi I-123 is adequate for an uptake because of the probe's high detection sensitivity compared to a gamma camera. When a scan is indicated, both can be performed using the scan dose of I-123 (200 300 µCi). The standard% RAIU uptake is acquired at 24 hours. In some clinics, a 2–6 hour uptake is also routinely performed .A non-imaging gamma scintillation probe detector is used for radioiodine thyroid uptake studies. It has a 2-cmthick × 2-cm diameter sodium iodine crystal with an open cone-shaped single-hole lead collimator coupled to a photomultiplier tube and electronics. Room background activity is determined. The radioiodine capsule is placed in a Lucite neck phantom and activity counted with the probe detector placed at a standardized distance of 30cm. The capsule is administered to the patient. The probe is placed 30cm from the anterior surface of the patient's neck, such that the entire gland can be detected by the probe but most extra thyroidal activity is not. The patient's neck (background) is counted. At the uptake times (2–6 hours and/or 24 hours), counts are obtained for the neck and the patient's thigh (background). The percent radioiodine uptake is calculated according to this formula:

$$\%RAIU\text{ (background corrected)} = \frac{\text{Neck counts/min}}{\text{Administered dose capsule counts}} \times 100$$

In the past, a standard reference capsule similar in activity to the administered capsule was counted initially and at the uptake intervals. The purpose of the standard was to correct for decay. A dose-to-standard ratio was determined to correct for the difference in standard and administered dose. In present-day uptake probe-computer systems, decay is automatically corrected (James et al, 2006).

Table (2-3): Clinical Frequency of Various Causes for Hyperthyroidism.

Clinical Frequency of Various Causes for Thyrotoxicosis(Hyperthyroidism)	
Graves' disease	70%
Thyroiditis	20%
Toxic multinodular goiter	5%
Toxic adenoma	5%
Others	<1%

(James et al, 2006).

Tc-99m Pertechnetate Uptake: The advantages of using Tc-99m Pertechnetate as an alternative to radioiodine to calculate an uptake includes its favorable radiation dosimetry, a particular consideration for children, and that the study can be completed within 30 minutes with uptake results available soon thereafter. The disadvantages of the Tc-99mpertechnetate uptake include a less well-defined normal range, the standard practice of calculating the therapy dose based on the radioiodine uptake, and the lack of software for this calculation on some newer camera computer systems (James et al, 2006).

Methodology: A scintillation probe is not used for a Tc-99m uptake because of the high neck and body background. This is a gamma camera technique for calculating the percent uptake, similar to that used for thyroid cancer scans. Before and after inject if theTc-99m Pertechnetate, the syringe is imaged with the gamma camera (preinjection counts minus postinjection residual counts = administered counts). Twenty minutes after injection, the thyroid scan is acquired on computer. Regions of interest are drawn on computer for the thyroid, thyroid background, and the syringes. Areas of interest are normalized for pixel size and thyroid and syringe counts are normalized for time of acquisition (James et al 2006).

The percent uptake is calculated*:*

Tc-99m Pertechnetate % uptake $= \dfrac{Thyroid\ counts - Background\ counts}{Injected} \times 100$

counts – R counts

Normal Tc-99m uptake ranges from 0.3–4.5%. Accuracy is less than with the %RAIU.A simple qualitative approach has been used to estimate uptake by obtaining images with the salivary glands in the same field-of-view as the thyroid. In the euthyroid patient, relative uptake in the salivary and thyroid glands is similar. With hyperthyroidism, thyroid uptake is considerably greater than salivary gland uptake.

Thyroid Scintigraphy: The thyroid scan depicts the entire gland in a single image and permits direct correlation of physical findings with abnormalities in the image. The combination of gamma camera and pinhole collimator offers the flexibility of obtaining multiple-view high-resolution images of the thyroid. Pinhole collimator magnification provides image resolution superior to parallel-hole collimators in the range of 5mm, compared to 1–2 cm with a parallel-hole collimator.

Thyroid Examination, The thyroid gland should be routinely examined by palpation at the time of imaging in order to estimate the size of the gland and to confirm the presence and location of nodules. A radioactive marker source (122-keV Cobalt-57 or Tc-99m) can then be placed over the palpated nodule for anatomical and functional correlation (James et al. 2006).

Methodology: Procedure Radioiodine is administered orally. The usual I-123 thyroid scintigraphy dose is 200–300 μCi. The scan is usually acquired at 2–6

hours after administration but may be acquired at the time of the 24-hour %RAIU. The higher count rate obtainable at 2–6 hours allows for shorter imaging time and better image quality. The low count rate at 24 hours requires longer acquisition time which increases the likelihood of patient movement. With Tc-99m Pertechnetate, 3–5 mCi is administered intravenously and imaging begins 20–30 minutes after injection. For both radiopharmaceuticals, a standard or large field-of-view gamma camera is used, equipped with a pinhole collimator that has an interchangeable lead pinhole insert of 3- to 6-mm in internal diameter placed in its distal aspect. Smaller diameter inserts provide higher resolution but lower sensitivity. A 15–20% photopeak window is set at 159 keV forI-123 and at 140 keV for Tc-99m. Imaging protocols for thyroid imaging for the two radiopharmaceuticals are similar and described in more detail in Boxes 5-6 and 5-7.The patient is positioned supine with the neck hyper extended so that the plane of the thyroid gland is parallel to the crystal face of the camera. The thyroid gland should fill approximately two-thirds of the field of view. This is achieved with a 6–8 cm distance from the collimator to the surface of the neck. Magnification increases as the pinhole collimator approaches the neck.

On one image, a radioactive marker (Tc-99m orCobalt-57) or computer cursor is placed at the sterna notch and on the right. A 4- to5-cm line source marker or two point sources 4–5 cm apart may be placed on the neck just lateral to the thyroid lobes and parallel to their long axis to estimate the size of the thyroid and nodules. Because of the three-dimensional nature of the gland

and pinhole collimator distortion, this is an approximate measurement and does not obviate physical exam size estimation (James et al. 2006).
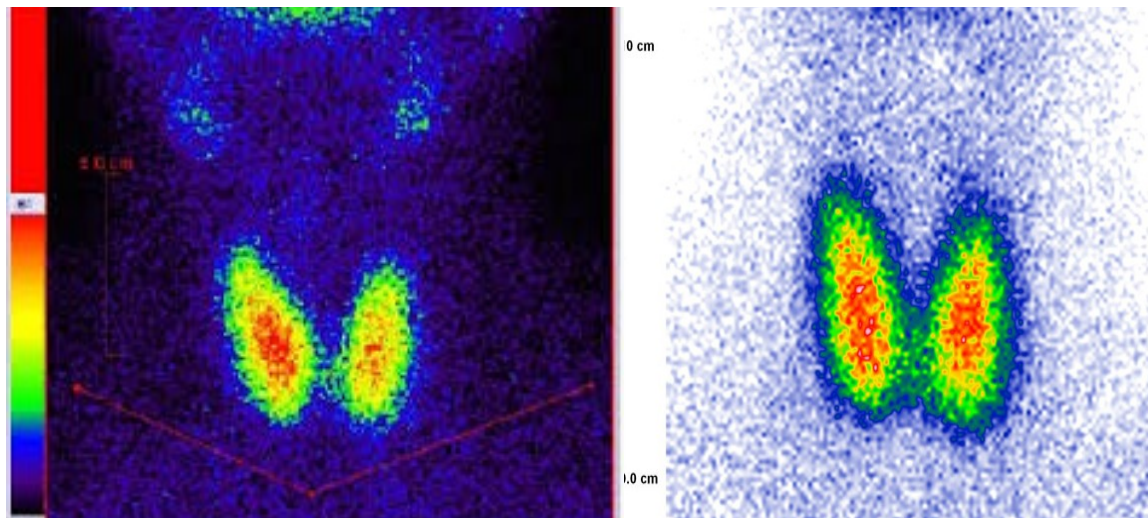
Figure (2-5): Normal I-123 thyroid scan (NM department RICK).

Images are routinely obtained in the anterior, right anterior oblique (RAO), and left anterior oblique (LAO) views. Each image is obtained for 100,000counts. It is preferable for the patient to remain in one position while the camera and collimator are moved to the different projections, thus making images more reproducible between patients and resulting in less image distortion and patient motion.

Additional images with a radioactive marker may be indicated to determine whether a palpable nodule takes up the radiopharmaceutical (i.e., a hot or cold nodule). Special care should be taken to avoid the parallax effect of pinhole collimator. The parallax effect results in a change in the relationship between a near and distant object when viewed from different angles. With a

pinhole collimator, this can result in misregistration of the relationship between the nodule and the marker or, in the case of a suspected substernal goiter, the suprasternal notch marker and the thyroid. The effect can be minimized in several ways. One method is to obtain an image with the collimator at an increased distance from the thyroid, decreasing the effect of magnification and distortion. A second method is to place the marker region of interest in the center of the field-of-view. Finally, a parallel-hole collimator might be used for the marker image (James et al. 2006).

Iodide I-131 Scan*: Because of the high radiation dose the thyroid with I-131, clinical indications for I-131thyroid scans are limited to confirming the thyroid origin of a mediastinal mass (substernal goiter) and for thyroid cancer scintigraphy. The advantage of I-131 is that delayed imaging allows for improved target-to-background ratio, thus improving delectability. For the substernal goiter, 50 µCi I-131 is administered orally. A large-field-of-view gamma camera equipped with a high-energy parallel-hole collimator is used. A 20–30%window is centered at 364 keV. A radioactive marker should be placed at the suprasternal notch (James et al, 2006).

2.5.4Clinical indications for thyroid uptake studies:

Thyrotoxicosis: Thyrotoxicosis is characterized by hyper metabolism due to increased circulating thyroid hormone. Hyperthyroidism is thyrotoxicosis caused by a hyperfunctioning thyroid gland (e.g., Graves' disease or toxic

nodular goiter. Examples of thyrotoxicosis not caused by a hyperfunctioning thyroid gland are subacute thyroiditis, thyroiditis factitia, and struma ovarii.

Clinical Diagnosis: The symptoms of thyrotoxicosis are those of increased metabolism such as weight loss, tachycardia, palpitations, heat intolerance, hyperhidrosis, and anxiety. However, these symptoms are nonspecific and require confirmation with serum thyroid function studies. A suppressed serum thyroid stimulating hormone (TSH) less than0.1 mU/L is the most sensitive test for diagnosis of thyrotoxicosis. The suppressed TSH is caused by negative feedback on the pituitary from the elevated serum thyroid hormone. The only exception to a suppressed TSH with thyrotoxicosis is a rare hypothalamic or pituitary etiology.
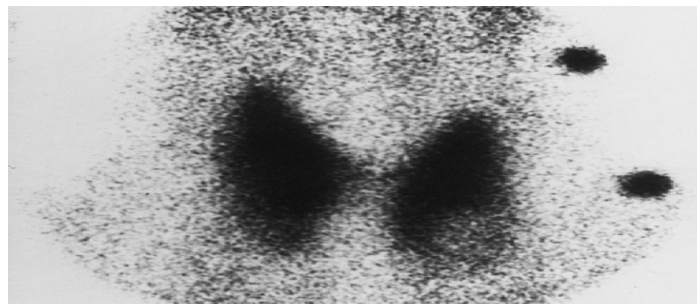

Figure (2-6): Solitary cold nodule (James et al, 2006).

Diseases with Increased %RAIU: The list of diseases producing thyrotoxicosis with an "elevated "uptake (*see* Box 5-4) includes entities where the uptake may be in the normal range (e.g., toxic nodules).This can be viewed as elevated in the sense that the normal response to

thyrotoxicosis is suppression of TSH byT-4 feedback to the pituitary with subsequent suppression of iodine uptake and thus %RAIU. Graves' disease: Between 70% and 80% of patient presenting with thyrotoxicosis have Graves' disease as the etiology? This autoimmune disease is most commonly seen in middle-aged females but also occurs in children and the elderly. Thyroid-stimulating immunoglobulins similar to TSH bind to the follicular cells causing hyperplasia and autonomous thyroid hyperfunction. The diagnosis of Graves' disease is often straightforward, such as thyrotoxicosis, diffuse goiter without nodules, characteristic exophthalmopathy, and pretibial dermopathy. However, in many patients the diagnosis is suspected but uncertain. An elevated %RAIU, usually in the range of 50–80%, confirms the diagnosis of Graves' disease and excludes most other causes. A Tc-99m Pertechnetate uptake in Graves' disease is typically greater than4.0%. A thyroid scan is often not necessary to confirm Graves' disease if physical examination or sonography is consistent with diffuse goiter without nodules. Multinodular Toxic Goiter Sometimes referred to as Plummer's disease, multinodular goiter often presents in older patients with tachyarrhythmias, weight loss, Diseases with Suppressed %RAIU.

Subacute Thyroiditis: The most common reason for thyrotoxicosis associated with a decreased %RAIU is subacute thyroiditis. There are several causes for the disease. Granulomatous thyroiditis (de Quervain's) is characteristically preceded by several days of upper respiratory illness and presents with a tender thyroid. Histopathologically, granulomas are seen on

biopsy. Silent thyroiditis, commonly seen in elderly patients, is not a granulomatous process nor is it associated with respiratory symptoms or thyroid tenderness. Often, elderly patients present with arrhythmia and normal size thyroid. Postpartum thyroiditis occurs within weeks or months of delivery. A mild goiter is often palpated in patients with subacute thyroiditis. The decreased %RAIU associated with subacute thyroiditis is the result of an intact pituitary feedback mechanism, not because of damage and dysfunction of the gland. Uptake is suppressed in the entire gland, but the disease is often patchy or regional. During the initial stage of subacute thyroiditis, stored intracellular thyroid hormone is released into the blood (James et al, 2006).

This is caused by increased cell permeability as a result of the inflammatory process. As the inflammation resolves, serum thyroid hormone levels decrease and often fall into the subnormal range with a resulting rise in TSH. It is not uncommon for patients to become hypothyroid, during the recovery phase, manifested by a high TSH (James et al 2006).

The level of the %RAIU depends on the damaged thyroid stability to respond to TSH stimulation. The hypothyroidism usually resolves over weeks and months and the TSH and %RAIU return to normal. The rapidity of this process depends on the degree of damage (James et al, 2006)

2.5.5 Clinical Indications for Thyroid Scintigraphy:

Thyroid scans have been used diagnostically for decades for the evaluation of various types of thyroid disease. They are requested less today than in the past because of the availability of other thyroid imaging modalities and the aggressive use of diagnostic percutaneous aspiration biopsy of thyroid nodules. Because of the thyroid scan's functional nature, scintigraphy still provides valuable clinical information for many patients (James et.al, 2006).

Normal Thyroid Scintigraphy: Thyroid scans should always be correlated with physical examination of the thyroid gland and interpreted with knowledge of the patient's thyroid function studies and other imaging studies (James et al, 2006).

The normal thyroid has a butterfly shape with lateral lobes extending along each side of the thyroid cartilage. The lateral lobes are connected by an isthmus that crosses the trachea anteriorly below the level of the cricoid cartilage. However, the appearance of the gland is quite variable from patient to patient. The right lobe is often larger than the left. The lateral lobes measure 4–5 cm from superior to inferior poles and are 1.5–2 cm wide. The pyramidal lobe ascends from the isthmus or adjacent part of either lobe (more often the left lobe) to the hyoid bone. The normal gland has homogeneous and uniform distribution of radiotracer throughout. Some increased intensity may be seen in the middle or medial aspects of the lateral lobes, owing to the thickness of the gland in this location. The amount of activity in the isthmus varies greatly, with little or no activity in some patients and prominent activity in others. In normal adults, the thin

pyramidal lobe is usually not seen. The salivary glands are routinely seen on Tc-99m Pertechnetate imaging at 20 minutes post injection. However, they are not usually seen on I-123 scans imaged at 4 hours because the radiopharmaceutical has cleared. Higher generalized background is seen on Tc-99m Pertechnetate compared to I-123 imaging. Esophageal activity can be problematic with either agent. It is frequently not in the midline, being displaced by the trachea and cervical spine when the neck is hyper extended in the imaging position. It is more often seen just to the left of midline and can usually be confirmed by having the patient swallow water to clear the esophagus, followed by repeat imaging (James et al, 2006).

Abnormal Thyroid Scintigraphy: A systematic interpretation of the thyroid scintigram requires assessment of thyroid size and configuration and the identification of focal abnormalities. These include hot and cold nodules and extrathyroidal activity in the neck or mediastinum. The thyroid scan allows for correlation of palpable abnormalities with scintigraphic findings. This is frequently critical in assigning significance to a palpable abnormality. Radionuclide markers can aid in confirming that the palpated nodule correlates with the scintigraphic finding. Gland size can be estimated using the thyroid scan but this has limitations due to the scan's two-dimensional nature and the magnification and distortion caused by pinhole collimation. However, image appearance and surface radiomarkers provide some indication of size. Enlargement seen on the scan is often accompanied by a change from a relatively concave to a convex appearance of the lobes. The

major clinical applications for thyroid scintigraphy are listed in Box 5-2. The specific scan findings seen in various disease processes are discussed in this section.

Thyroid nodule: Thyroid nodules are quite common. They occur more often in women than men. The incidence of both benign and malignant nodules increases with age. Determining whether a nodule is benign or malignant is a common clinical problem. A nodule presenting in a young person, a male, or with recent nodule growth increases concern for malignancy. The presence of multiple nodules decreases the likelihood of malignancy. A nodule in a patient with Graves' disease requires evaluation (James et al 2006).
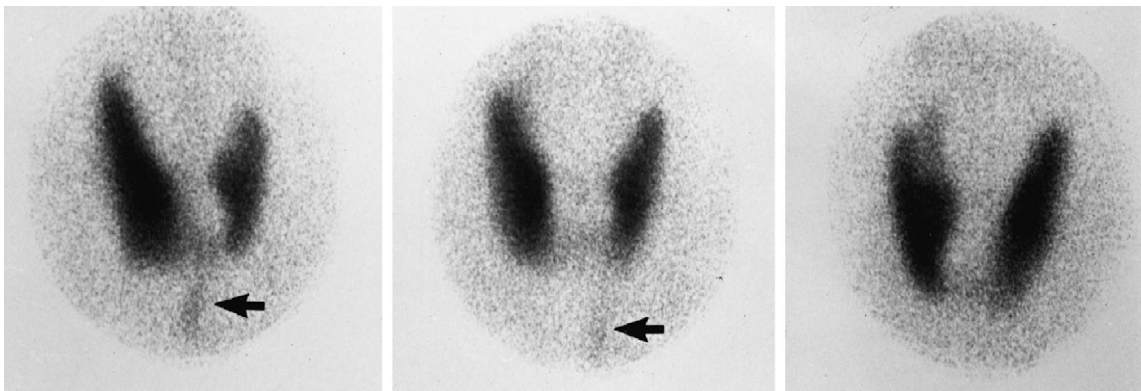

Figure (2-7): Anterior (ANT) and right and left anterior oblique (RAO, LAO) views obtained with Tc-99m Pertechnetate. Note the esophageal activity below the thyroid to the left of midline (arrows) *(James et al. 2006).*
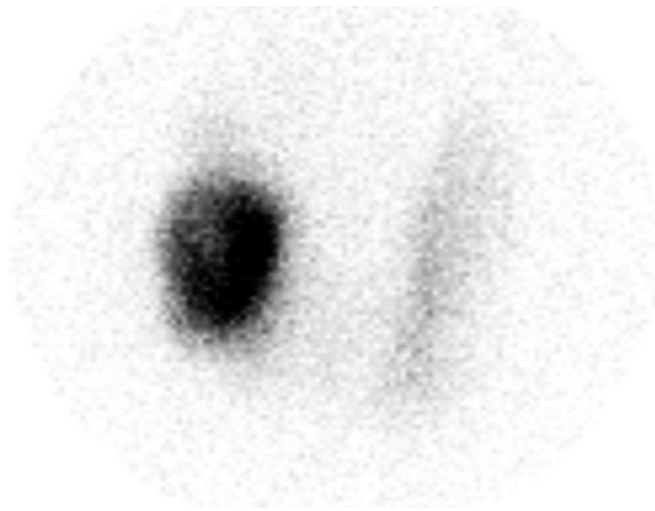
Figure (2-8): Toxic (hot) thyroid nodules (James et al 2006).

Radiation to the head and neck or mediastinum is associated with an increased incidence of thyroid cancer, particularly in children. Several decades ago, external radiation therapy was used to shrink asymptomatic enlarged thymus glands and to treat enlarged tonsils, adenoids, and acne. This radiation therapy, usually in the range of 10–50 rads, was associated with an increased incidence of thyroid cancer. The radiation released at Hiroshima, Nagasaki, and Chernobyl also resulted in an increased incidence of thyroid cancer. Radiation exposure up to 1500 rads increases the incidence of thyroid nodules and cancer. The mean latency period is approximately 5 years. For radiation greater than 1500 rads, the risk decreases, presumably due to tissue destruction. High doses of radiation used in the therapy of malignant tumors are more likely to cause hypothyroidism .Ultrasonography: Nodules can be confirmed on sonography when suspected on physical exam. Sonography can also detect additional

nodules to the palpated one and determine whether a nodule is solid or cystic. Purely cystic lesions are benign; however, cancer cannot be excluded if the cyst has a soft tissue component or cystic degeneration (James et al, 2006).

Thyroid Scintigraphy: The thyroid scan is more sensitive than physical examination for detecting nodules. Although ultrasonography is more sensitive than scintigraphy for detection of small nodules, the natural history and clinical significance of small nodules seen only on sonography is uncertain. The data used to assign risk to hot or cold nodules is based on scintigraphy correlation with pathology. The thyroid scan does not diagnose nodules per se. A hot or cold region on the scan may be due to various other pathologies discussed later (e.g., thyroiditis and scarring). A nodule is diagnosed by physical examination of the thyroid or detected by an anatomical imaging modality (e.g., ultrasonography, CT, or MRI)(James et al 2006).Thyroid scintigraphy can determine the functional status of a nodule detected by physical examination or anatomical imaging. Thyroid nodules are classified scintigraphically as cold (hypofunctioning compared to adjacent normal tissue), hot (hyperfunctioning with suppression of the extranodular gland), warm (increased uptake compared to adjacent tissue but without suppression of the extranodular tissue, or indeterminate (palpable but not visualized on scintigraphy). The scan can also show the presence of multiple nodules (multinodular goiter). This interpretation

system can provide a relative risk assessment for malignancy (James et al, 2006).

Cold Nodule: Greater than 85–90% of thyroid nodules are cold (hypofunctional) on thyroid scintigraphy, that is, they have decreased uptake compared to adjacent thyroid tissue. Many have benign etiologies, such as simple cysts, colloid nodules, thyroiditis, hemorrhage, necrosis, and infiltrative disorders such as amyloid or hemochromotosis. However, a significant subgroup of patients with cold nodules has malignancy as the etiology. The incidence of thyroid carcinoma in a single cold nodule is reported to be as high as 40% in surgical series but as low as 5% in general medical series. Overall, the incidence of cancer in a cold thyroid nodule is generally considered to be approximately 15–20%.With multinodular goiters, the incidence of malignancy in cold nodules is lower, less than 5%. Enlarging nodules or "dominant "nodules (i.e., those that are distinctly larger than the other nodules in a multinodular goiter) require further evaluation because of relatively increased risk (James et al, 2006).

Hot and Warm Nodules: Radioiodine uptake within a nodule denotes function. A functioning nodule is very unlikely to be malignant. Less than 1% of hot nodules harbor malignancy. The term hot nodule should be reserved for those that not only have high uptake in the nodule scintigraphically, but also have suppression of extranodular tissue .If extranodular tissue is not suppressed, it should be referred to as a warm nodule (James et al 2006).Hot nodules are caused by toxic adenomatous nodules. Warm nodules may be

caused by autonomous hyperfunctioning adenomas. However, they are not toxic, that is, they are not producing enough thyroid hormone to cause thyrotoxicosis and thus TSH is not suppressed. A warm nodule may also be due to nonautonomous hyperplastic tissue or even normal functioning tissue surrounded by poorly functioning thyroid. Differentiation can be made by administration of thyroid hormone (thyroid suppression test). Autonomous nodules cannot be suppressed. However, the suppression test is rarely needed in current practice. Large hot nodules greater than 2.5–3.0 cm usually produce overt hyperthyroidism. Some patients with smaller nodules have subclinical hyperthyroidism, which can be confirmed by a suppressed serum TSH but normal T4. In the past, a small autonomous nodule might be followed clinically because some stabilize, whereas others regress or undergo involution. Increasingly, nodules are treated at an early stage because of the low incidence of regression and increased awareness of adverse consequences associated with subclinical hyperthyroidism (e.g., bone mineral loss).Radioiodine I-131 is the usual therapeutic method of choice for toxic nodules. Radiation is delivered selectively to the hyperfunctioning tissue while sparing suppressed extranodular tissues. The suppression of normal tissue results in a low incidence of post therapy hypothyroidism. After successful treatment of the nodule, the suppressed tissue regains function. Surgery, usually lobectomy, may be indicated if there are local symptoms or cosmetic concerns. Indeterminate Nodule: When a palpable or sonographically detected nodule greater than a centimeter in

size cannot be differentiated by thyroid scan as hot or cold compared to surrounding normal thyroid, it is referred to as an indeterminate nodule. A cold nodule arising from the posterior aspect of the gland may have normal glandular activity superimposed over the nodule, making it appear to have normal uptake. For management purposes, an indeterminate nodule has the same significance as a cold nodule. The possibility of an indeterminate nodule highlights the need for close correlation between physical and scintigraphic findings Discordant Nodule Discordance in appearance between radioiodine and Tc-99m Pertechnetate scans is seen in a small minority of patients. A nodule may appear hot on Pertechnetate imaging but cold on radioiodine imaging because Tc-99m Pertechnetate is trapped but not organified (James et al, 2006).

Goiter: The term *goiter* refers to thyroid gland enlargement, but it is often qualified to indicate the cause of the enlargement (e.g., toxic nodular goiter, colloid goiter, or diffuse toxic goiter [Graves' disease]).

Graves' disease vs. Multinodular Toxic Goiter: In a patient with newly diagnosed thyrotoxicosis, the physical exam can usually differentiate the diffuse goiter of Graves' disease from a multinodular toxic gland. The thyroid scintigram can help make the distinction. Toxic nodular goiter has the characteristic scintigraphic pattern of increased uptake that corresponds to palpable nodules and suppression of extranodular thyroid tissue. This contrasts with the diffuse homogenous increased uptake of Graves' disease (12).

The pyramidal lobe, a paramedic structure arising superiorly from the isthmus (right or left lobe), is also usually well visualized with Graves' disease (James et al 2006).
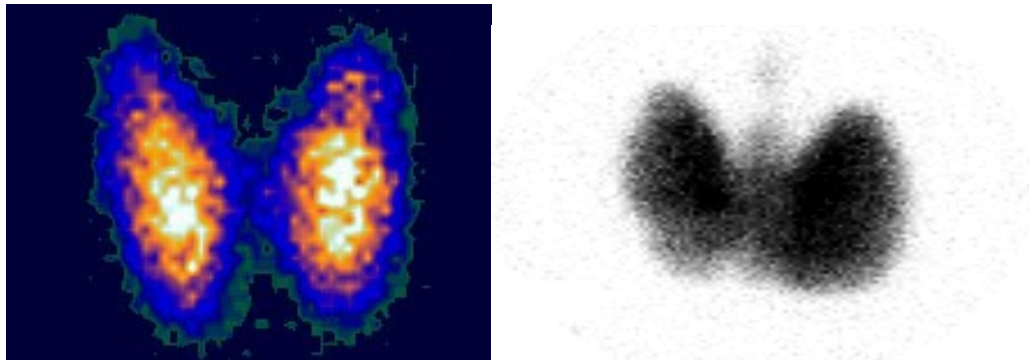
Figure (2-9): Graves' disease. Large goiter Note the pyramidal lobe.

Ectopic Thyroid Tissue: The thyroglossal duct runs from the foramen caecum at the base of the tongue to the thyroid. If it fails to migrate from its anlage, lingual or upper cervical thyroid tissue can present in the neonate or child as a midline mass with or without obstructive symptoms and often accompanied by hypothyroidism. Ectopic thyroid tissue may also be mediastinal (substernal goiter) or even pelvic/ovarian (struma ovarii). Scintigraphy: The typical appearance of a lingual thyroid is a focal or nodular accumulation at the base of the tongue and absence of tracer uptake in the expected cervical location. However, lingual thyroids usually function poorly. Lateral thyroid rests are also often hypofunctional.

However, rests can function, hyperfunction, or be involved with adenocarcinoma of the thyroid. Functioning ectopic thyroid tissue should be considered metastatic until proven otherwise (James et al, 2006).

Subacute thyroiditis: This entity is discussed in the section Thyrotoxicosis. With hyperthyroidism, the scan shows only suppression .During recovery phases, the appearance of the thyroid is variable and depends upon the severity and distribution of the disease. The scintigram may show inhomogeneity of uptake, regional areas of hypofunction, or even focal hypofunction (James et al 2006).

Chronic Thyroiditis (Hashimoto's Thyroiditis): Scintigraphic findings are highly variable. Diffuse enlargement is usual, although the scan may be normal early in the process. Uptake may be inhomogeneous throughout the gland or there may be focal cold areas without a palpable nodule. The pyramidal lobe is often seen in Hashimoto's disease (James et al *2006).*

Acute Thyroiditis: Suppurative bacterial infection is the usual cause for this rare condition. The thyroid is typically enlarged and tender. Focal abscesses will appear as cold regions scintigraphically. *Reidel'sstruma*is an uncommon form of thyroiditis where all or part of the gland is replaced by fibrous tissue. No uptake is seen in the region of fibrous tissue.

Thyroid Cancer: Whole body thyroid cancer scintigraphy has long been used for well-differentiated papillary and follicular thyroid cancer. It is often performed post-thyroidectomy prior to radioiodine I-131 therapy and for

evaluating response therapy. The most common sites of metastasis are locally in the lymph nodes of the neck, lung, mediastinum, and bones. Medullary carcinomas and anaplastic carcinomas do not concentrate radioiodine and are not detected with conventional thyroid scintigraphy.

Whole body thyroid cancer scanning requires patient preparation. The traditional approach is to withdraw hormone replacement therapy for 4–6 weeks so that patients may achieve a maximal endogenous thyroid stimulating hormone (TSH) response (>30 U/ml). To minimize symptoms of hypothyroidism, patients are sometimes switched to short-acting triiodothyronine (T3), which is discontinued 2 weeks prior to the scan. Imaging with I-131 is typically performed 48 hours after I-131 diagnostic dose administration (James et al, 2006).

More lesions are demonstrated in this time than at 24 hours due to background clearance and the higher target- to-background ratio. Serum thyroglobulin levels are also measured during maximum TSH stimulation (a sensitive tumor marker). For I-123, whole body imaging is acquired at 24 hours. Post thyroidectomy, it is not uncommon to have high intensity uptake in the thyroid bed (star artifact), which may preclude good visualization of the neck or mediastinum. The artifact is caused by septal penetration of high-energy photons through the collimator. A pinhole collimator that has no septa can better resolve the high intensity uptake in the neck. In the postoperative state, uptake in the neck may be due to residual normal

thyroid or to thyroid cancer. The scan cannot make the distinction. Activity outside the thyroid bed is very likely metastatic (James et al, 2006).

2.6 Radioactive Iodine:

2.6.1 Principles of Therapy:

Radionuclide therapy with unsealed sources has several underlying principles, which apply most too all forms of treatment. Where a treatment using a radionuclide is envisioned, it ideally represents a radioisotope–drug combination that is specifically suited for a disease in an individual patient. To begin with, the physical characteristics of the radioisotopes must be considered. Critical characteristics include type and range of emissions, half-life, and chemical characteristics. Most therapy agents utilize b-particle emissions for their ability to penetrate tissues. This deposition of energy in tissue by b emitters results in cellular damage. Among the b emitters there are several choices with respect to energy of the b emission. Lower energy b particles can travel a few cell diameters, or at most in the sub-millimeter range. These may be useful for microscopic targets and reducing normal tissue damage. Higher energy b particles such as those emitted by P-32, Y-90, and Ho-166 have excellent tissue penetration with a range beyond the source of several millimeters (Janet et al 2007). This may be desirable when a high homogeneous dose to a large target such as a lymphoma nodule or the bone from a bone surface or marrow source is being treated. Intermediate-range b particles such as those from iodine-131 (I-131) have a shorter path length and may result in less dose homogeneity to the tissue,

but still retain excellent therapeutic effect. Proponents of Auger emitters for radionuclide therapy posit that these low-energy b particles can cause therapeutic effect without excess tissue toxicity because of their short energy deposition range. A somewhat similar argument has garnered favor for support of the use of a-particle emitters for therapy. At-111, Bi-213, and some of the transuranic elements have been studied with varying degrees of success. A particles are highly energetic with these emitters. Investigators hypothesize that the heavy a particle has such momentum that it results in high levels of cell killing close to the origin of the radionuclide deposition. This is thought to result in low surrounding tissue toxicity and high levels of cell killing in tumors where the radiation is deposited. Gamma emissions from therapeutic radionuclide such as the 364 KeV in I- 131 are energetic enough to cause a generalized dose effect in an organ, or in the whole body and should be considered in treatment planning for the enhanced treatment effect they might provide as well as the toxicity they may cause .

The physical half-life of the therapeutic radionuclide is an important consideration and underlying principle for therapy planning. Rarely, except in thyroid treatment, is the simple salt form of the radionuclide used. It is most likely attached to a drug or particle that controls its biodistribution. The ideal therapeutic radiopharmaceutical is one that remains attached to the parent drug or its metabolites, and is excreted rapidly through a known simple route. Radiopharmaceuticals that undergo complex metabolism that results in free radio nuclides as well as labeled metabolites that are excreted by

several routes are more difficult to use(Janet et al 2007).They also create greater difficulty for realistic radiation absorbed dose estimation based on their observed biodistribution. In most cases, the most optimal combination is a radionuclide with a physical half-life that is similar to the drug or biologic agent half-life, so that the resulting effective half-life represents a length of time appropriate for maximum therapeutic effect and minimal non target toxicity (Janet et al, 2007).

Many therapeutic radio nuclides are radiometals and therefore pose challenges for radiopharmaceutical design. These radiometals often have large atomic radii and can be difficult to chelate or chemically attach to drugs and biologic agents. Weak chelation associations can result in transchelation to naturally occurring metalloproteins. This can result in undesired biodistribution of radiometal away from target sites. Certainly the chemical behavior of the therapeutic radionuclide contributes a great deal to ease of preparation, stability, and biological behavior in the patient. A special case is in the use of a emitters where radionuclide daughters, being different elements may have different chemical characteristics with respect to the radiolabeling strategy compared with the parent (Janet et al, 2007).

2.6.3 Biodistribution:

An important aspect of therapy with radionuclides is biodistribution of the radiopharmaceutical. While high target tissue binding is the most important goal, nonspecific binding or blood pool residence of the compound is an

important consideration. Also important is the biodistribution of metabolized components and their excretion routes. Ideally, a therapeutic radiopharmaceutical has high target binding and rapid excretion without redistribution to non-target tissues and compartments. A major responsibility of the nuclear medicine physician is to know and understand completely the biodistribution patterns of a radionuclide therapy combination. Not only is this important for safety, but for accurate dosimetry estimation. Often, observation of biodistribution requires imaging and quantification of radionuclide tissue concentration and time-activity data (3). Additionally, knowledge of the biodistribution of the pharmaceutical that will be radiolabeled will give an indication of the correct radioisotope to be chosen for the therapy indication (Janet et al, 2007).

Iodine-131: Iodine-131 has a convenient half-life and energy characteristics (T1/2 ¼ 8.1 days; Emax beta ¼ 600 keV). Normal physiological uptake of iodide (and hence its radioactive form) in functioning thyroid tissue is the primary reason for its role in treating several thyroid disorders and malignancies. This fact, coupled with the energetic beta emission, has made it a treatment standard. Sodium iodide has the convenience of easy oral administration, which further improves patient compliance. Its high-energy gamma radiation (364 keV), which requires additional radiation safety measures, can be considered advantageous for biodistribution studies and radiation-absorbed dose evaluation. Sodium iodide in liquid form is highly volatile and needs special handling in a fume hood with exhaust system to

avoid inhalation of the iodide vapor during labeling. It also means that personnel handling the radiopharmaceutical should be subjected to periodic assays to exclude uptake in their thyroid glands. However, I-131 remains the most commonly used therapy radionuclide in nuclear medicine. When used for treating nonthyroid malignancies, unwanted uptake of 131I in normal thyroid gland needs to be blocked by administering elemental iodide, in the form of Lugol's iodine or Strong Solution of Potassium Iodide (SSKI). It's easy labeling characteristics with the ability to covalently label proteins have made it the primary choice for labeling monoclonal antibodies while its longer half-life (eight days) is ideal in situations where there is slower penetration into a tumor(Janet et al, 2007).

2.6.4 Beta particles:

Radioisotopes with high proportion of beta emission have been used clinically and represent the largest group used in therapy. Beta particles have a finite and limited range in tissues and dissipate most of their energy (95%) within an organ. While beta particles are ideal for treating larger tumors because of longer path range in tissues, much of their energy (up to 99.9%) can fall outside the small diameter microscopic tumors(McEwan et al 2000). A plastic syringe shield is used for pure beta emitters to avoid bremstrahlung that would contribute radiation dose to the hands. Several beta emitters have found appropriate role in the palliation of patients with painful bone metastases (Silberstein et al 2000, Howell et al 1994). In theory, the dose

rate of particle emission has some bearing on treatment effects. Generally, radionuclides with higher dose rates are effective in treating tumors with shorter cell cycle time, that is, rapidly proliferating cells and vice versa (Howell et al 1994, Fowler et al, 1990). Radioisotopes without any gamma ray emission provide the advantage of convenient outpatient treatment, because of the lack of gamma radiation.

2.6.5 Radioiodine Therapy:

Radiotherapy with radioactive iodine-131 (RAI) has been used to treat benign thyroid diseases for over 50 years (Becker et al 1996). Diseases of thyroid hyperfunction that can be treated with RAI include Graves' disease (GD), solitary hyperfunctioning nodule, and toxic multinodular goiter. RAI may also benefit patients with subclinical hyperthyroidism, particularly patients at risk for cardiac or systemic complications. RAI is used less frequently for the treatment of euthyroid goiters. The preferred method for treating hyperthyroidism varies in different countries. In a survey of American Thyroid Association (ATA), European Thyroid Association (ETA), and Japanese Thyroid Association (JTA) members, 169 69%, 22%, and 11% of respondents, respectively, chose RAI as the therapy of choice for an index patient with GD (Wartofsky et al, 1991). In the same survey, antithyroid drugs were regarded as initial therapy in 30.5%, 77%, and 88% of ATA, ETA, and JTA respondents, respectively. Such variation likely stem from differences in perceived risks of

prescribing radioactive treatments, differences in cost, local requirements for hospitalization during treatment, patient compliance, response to antithyroid medications, and natural history of autoimmune thyroid disease in different populations. Differences in dietary iodine content may also significantly affect treatment response in various populations (Solomon et al, 1987). Most jurisdictions have specific regulations for possession and use of iodine-131 and other radionuclides. Physicians who use radioisotopes must be knowledgeable and in compliance with all applicable laws. Therapeutic decisions should always be made with consideration for the population from which the patient originates and to local standards of practice.

2.6.6 Biological basis of iodine accumulation in thyroid tissue:

The sodium iodide symporter (NIS) is responsible for the specificity of RAI for thyroid tissue. This transmembrane protein transports iodide against an electrochemical gradient via a sodium-dependent active transport mechanism by which two sodium ions are transported along with one iodide ion (Spitzweg et al, 2000). Synthesis of this protein is regulated by activation at the thyrotropin receptor (Saito et al, 1997). Following the characterization of the NIS gene in 1996, much research has been directed toward understanding the role of the NIS in autoimmune and malignant thyroid disease. The NIS protein is most abundantly expressed in thyroid tissue,

although it is also present in glandular and mucosal tissue, choroid plexus, ciliary body of the eye, and placenta. Normal NIS protein expression is limited to the basolateral membrane in a small percentage of thyroid follicular cells at any one time (Jhiang et al 1998). However, in autoimmune thyroid disease, thyrotropin receptor-mediated activation by stimulating auto-antibodies increases the NIS protein expression to the point that it is expressed on both basolateral and apical surfaces in the majority of thyroid follicular cells. Synthetic mechanisms responsible for iodine organification and incorporation into colloid matrix are also increased, leading to enhanced thyroid hormone turnover, resulting in the manifestations of hyperthyroidism. Radiotherapy of thyroid disease using iodine-131 relies on the emission of high-energy beta particles to cause damage to thyroid gland tissue. Iodine-131 has a physical half-life of 8.1 days, principal gamma-ray energy of 364 keV, and beta-particle emission with an average energy of 0.192 MeV. With a tissue range of 0.8 mm, beta-particle emission is responsible for the majority of local therapeutic effect. The ensuing inflammation caused by radiation is followed by fibrosis, resulting in the reduction of the synthetic capacity of the thyroid gland. For this type of therapy to be effective, thyroid tissues must accumulate and retain iodine-131 long enough for adequate amounts of radiation to be delivered. With increased iodine turnover in hyperthyroid disease states, such as GD, the effective biological half-life is shortened to an estimated four to six days. It is important to keep in mind that although hyperthyroidism related to GD may be eliminated by RAI, the underlying

autoimmune disease may persist indefinitely, and that continued follow-up is necessary to monitor associated autoimmune syndromes, such as ophthalmopathy.

2.6.7 Contraindications to Radioactive Iodine Therapy:

A patient who is pregnant should not be treated with RAI (Stoffer et al, 1967). RAI crosses freely into the placenta, and the fetal thyroid tissue is capable of accumulating iodine after the 12th week of gestation. Administration of RAI during this period may result in severe neonatal hypothyroidism. Fetal and neonatal thyroid irradiation may also increase the risk of developing thyroid cancer later. Retained activity in the maternal bladder may also increase the risk of malignancy by direct radiation exposure to the fetus. Women who are actively lactating or nursing also should not receive RAI. Iodine is excreted in breast milk. NIS protein expression is also increased significantly in mammary tissue during lactation, thus increasing the radiation exposure to the breast. Nursing should not be resumed until the birth of the next child. RAI has no role for the treatment of hyperthyroid conditions that are self-limited or when thyroid tissue is not hyperfunctioning. These conditions include silent, sub-acute and postpartum thyroiditis in addition to factitious thyroid disease.

2.6.8 Pretreatment studies:

Thyroid function tests should confirm results that are consistent with the disease to be treated. Women of childbearing age should have documentation that they are not pregnant at the time of treatment. Routine pregnancy testing should be offered prior to RAI therapy (Stoffer et al, 1967).

Traditionally, RAI uptake measurements have been used to determine the amount of radioactivity to administer for treatment. However, this amount may also be empirically determined. Regardless of the method for dose selection, routine thyroid uptake measurements are useful for confirming increased thyroid gland function prior to treatment. This helps avoid inappropriate treatment of hyperthyroid conditions not associated with increased thyroid function, such as silent thyroiditis or factitious hyperthyroidism. RAI uptake measurements can also help exclude a hyperfunctioning gland with "blocked" uptake. This condition, which will significantly reduce the effectiveness of RAI treatment, may follow exogenous iodine exposure, such as from intravenous contrast agents. Other substances which may contain large amounts of iodine include expectorants, kelp, agar, carageenan, Lugol's solution, potassium iodide solutions, and drugs, such as amiodarone. RAI uptake measurements should be performed following the withdrawal of such interfering materials in the same manner as done for treatment. Typically, thyroid gland uptake measurements are acquired at four to six hours and 24 hours following the ingestion of a test capsule of 0.15–0.37 MBq (4–10 mCi) of iodine-131. Alternatively, 3.7–7.4 MBq (100–200 mCi) of iodine-123 may be used. An estimate of the 24-hour

iodine-131 uptake measurement may be also be derived from the early measurement, allowing for testing and treatment to be completed in one day (Hayes et al 1990). Scanning is useful for the confirmation of hyperfunctioning nodules and the exclusion of cold nodules which need to be further evaluated. Although it is debatable whether a thyroid scan adds information that would alter the management of GD, scanning does provide confirmation of the diagnosis of GD while excluding the rare possibility of incidental thyroid cancer, which may manifest as a hypofunctioning nodule. Such nodules should be evaluated for possible malignancy prior to treatment with RAI.

2.6.9 Dose for Graves' disease:

The amount of RAI to be administered for treating hyperthyroidism related to GD may be selected empirically or determined by a dose calculation based on the assessments of thyroid mass and function. Standard treatment usually involves a single administration of RAI. The administration of small amounts of activity (e.g., 2 mCi) at frequent intervals is not recommended, because it allows patients to remain hyperthyroid for longer periods of time, and has not been proven superior at preventing iatrogenic hypothyroidism.

To deliver a specific dose to the thyroid, it is necessary to know the gland size, maximal uptake, and effective half-life of iodine in the targeted thyroid tissue. It may be assumed that the effective biological half-life of RAI is four to six days in the majority of patients with GD. For dosimetry calculation,

most physicians use a formula prescribing an activity per estimated gram of thyroid, corrected for the 24-hour uptake. A simple, commonly used formula for treating GD prescribes 2.96–7.4 MBq (80–200 mCi) per estimated mass of thyroid tissue in grams (Cooper et al, 1996):

> **Administered activity =Thyroid tissue mass (g) * Activity per g tissue/RAI uptake at 24 hour**

With RAI uptake expressed as a fraction of 100% uptake. (e.g., 30% uptake is 0.30).Although it may be possible to estimate thyroid mass by palpation, it is difficult to estimate the degree of thyroid hyperfunction (i.e., thyroid uptake) on the basis of clinical findings alone. Thus, most methods for calculating administered activity will require thyroid RAI uptake measurements, typically at 24 hours. A more complicated, but potentially efficacious approach has been the use of late RAI uptake measurements to allow the estimation of physiologic half-life of RAI (Bajnok et al, 1999).

Most recommended administered activities range between 3.7 and 7.4 MBq (100–200 mCi) per gram, corrected for percentage thyroid uptake. Administration of 2.96–4.44 MBq (80–120 mCi) per gram will generally deliver doses of 50– 100 Gy to the thyroid (Dayan CM, 2001). Lower doses may reduce the incidence of hypothyroidism following treatment, but will increase the likelihood that a second treatment will be needed. Administration of 5.5 MBq (150 mCi) per gram will yield a dose of approximately 120 Gy to the thyroid. Larger doses can increase the likelihood

of developing hypothyroidism in the post-treatment period, but should reduce morbidity related to prolonged hyperthyroidism. If a high success rate is the primary goal, doses between 200 and 300 Gy may be used. Occasionally, patients with GD may demonstrate RAI uptake more at four to six hours than at 24 hours. This condition of "rapid turnover" may necessitate the administration of larger amounts of radioactivity (5.5–7.4 MBq/g), owing to the shorter physiologic half-life of iodine in this situation. Larger amounts of radioactivity may also be reasonable in patients with relatively low iodine uptake (Cooper et.al, 1996).

Patients with persistent hyperthyroidism following a first treatment with RAI may benefit from additional treatments. Higher doses are often used for retreatment, which are typically given three to six months after the initial treatment. Previous RAI treatment failure does not lessen the chance of a successful retreatment (Leslie et al, 1998).

Although treatments based on dose calculations appear efficacious, they have not proven superior to the use of empirically selected administered activities. The advantages of using a fixed administered activity for treating hyperthyroidism are its simplicity and successful outcome in an acceptable number of patients. The effectiveness of such an approach appears comparable to a dose calculation method. In one prospective trial, patients with GD, hyperfunctioning solitary nodules and multinodular goiters, were randomized to receive a fixed radioiodine dose (5, 10, or 15 mCi, based on palpable gland size), versus Iodine-131 calculated dose based on thyroid

gland size and 24-hour radioiodine uptake (Jarlovet al, 1995). Comparable rates of euthyroidism, hypothyroidism, and persistent hyperthyroidism were seen in both groups. There were also comparable reductions in gland size. A number of other studies have also supported the equivalence of using several fixed administered activities versus a calculated activity for the treatment of GD or toxic multinodular goiter (Leslie et al 2003, Kok et al, 2000).

If a fixed amount of activity is chosen, it is still important to keep in mind that the effectiveness of therapy remains dependent on the total radiation dose to the target tissue. In a randomized trial comparing the administration of a standard activity (15 mCi) to an administered activity, calculated to give a target dose of 100 Gy, it was shown that the success rate of the treatment in either arm was dependent on both the thyroid volume and target dose(Peters et al 1997). If the estimated dose to the thyroid exceeded 200 Gy in patients receiving a standardized treatment with 15 mCi, a success rate of 80% was obtained.

2.6.10 Dose for toxic nodular goiter:

In addition to GD, thyrotoxicosis can also result from a single hyperfunctioning nodule, or multiple hyperfunctioning nodules (i.e., toxic multinodular goiter). Although antithyroid drugs can ameliorate hyperthyroidism, definitive treatment is more commonly accomplished with RAI or surgery. Less commonly, percutaneous ethanol injection has also been

used for large solitary nodules (Del et al 2001, Erickson et al, 1998). Compared with treatment with RAI, hypothyroidism is a more common sequel of surgery (Erickson et al, 1998). The choice of surgery versus radiation for nodular goiters is beyond the scope of this chapter, although surgery should be considered strongly in patients with goiters causing significant airway obstruction or an increased risk of harboring thyroid cancer. Treatment decisions for these patients should be made in consultation with a surgeon with expertise in thyroid surgery.

Most patients with toxic nodular goiters will remain hyperthyroid until definitively treated. Occasionally, central necrosis may occur in a single hyperfunctioning nodule with spontaneous resolution of hyperthyroidism, although this should not be anticipated in lieu of more definitive treatment. An initial course of antithyroid drugs may be considered in order to render the patient euthyroid before surgical or radioiodine treatment. Nodular goiters are believed to be more radio resistant than the diffuse goiter of GD. Large doses, between 150 and 300 Gy, have frequently been used for toxic adenomas (Gorman et al 1987). A calculated administered activity of 7.4 MBq (200 mCi) per gram to the nodule, corrected for 24-hour uptake, has been used successfully. Standardized administered activities at appropriate doses (e.g., 740–1110 MBq) may also prove effective. With administered activities of less than 370 MBq (10 milliCuries), treatment failures are common (Estouret al, 1997).

Radiation exposure to normal thyroid tissue in the setting of solitary toxic nodules has never been shown to increase the incidence of thyroid cancer. This is likely because uptake in the normal thyroid tissue is suppressed. Suppressed thyroid tissue may still receive a dose as high as 23 Gy (Gorman et al 1987). However, hypothyroidism following RAI treatment does seem to occur less frequently for solitary hyperfunctioning nodules compared with GD or multinodular goiter. In order to minimize the risk of hypothyroidism following treatment, a suppressed thyroid-stimulating hormone (TSH) level should be present, and a thyroid scan should be performed to exclude significant extra nodular uptake (Huysmans et al 1991). A reduction in the nodule size can be expected following RAI treatment (Nygaard et al, 1999).

For toxic multinodular goiters, doses of 150 Gy may be adequate to resolve hyperthyroidism. Administered activities between 3.7 and 7.4 MBq (100–200 mCi) per gram have been shown to be effective (Erickson et al, 1998). Fixed administered activities (e.g., 1110 MBq) have also been used. Not uncommonly, patients with toxic multinodular goiters may have large glands and 24-hour RAI uptake measurements that are not significantly elevated. This may necessitate the administration of relatively large amounts of radioactivity. In the United States, higher administered activities may be used for nonhospitalized patients, if it can be documented that radiation exposure to the public is not likely to exceed 5 mSv (0.5rem) (US Nuclear Regulatory Commission, 1997).

2.6.11Capsule versus Liquid iodine:

Radioiodine is available in a liquid solution or capsule. Capsules are more convenient, but have generally been more expensive. Liquid formulations may require extra measures to minimize radiation contamination at the time of administration. RAI in capsules and liquid are generally believed to be equivalent in efficacy, although there has been some concern regarding a reduction in RAI bioavailability from capsules, because of incomplete dissolution related to the amount of magnesium stearate in the capsule (Huysmans et al, 1994).

2.6.12Goals and expected outcomes of treatment:

With adequate doses of radioactivity, an 80% response rate should be expected. A primary goal of treatment is to resolve hyperthyroidism in as short a time as possible. However, with RAI doses calculated to achieve this goal in the majority of patients, a significant number of patients will ultimately become hypothyroid. The incidence of hypothyroidism was first estimated at 20% to 40% of patients one year after RAI therapy (Yu et al, 2002). With more conservative doses of RAI, the incidence of hypothyroidism may be lower, although, often at the expense of higher rates of persistent hyperthyroidism. Patient preferences, the availability of close follow-up, and potential risks from persistent hyperthyroidism should be considered when deciding between more definitive treatment with higher doses and the use of more conservative doses. Some authorities have maintained that

hypothyroidism, which is easily and inexpensively treated with thyroid hormone supplementation, is preferable to persistent hyperthyroidism, which, if not optimally treated, may produce significant morbidity. It is also commonly believed that hypothyroidism may be a frequent long-term consequence of autoimmune thyroid disease. This has led to the recommendation for higher treatment doses to reduce the need for additional treatments in patients who do not respond to initial treatments. If hypothyroidism is regarded as a potential therapeutic endpoint, patients should be given the understanding that they will likely require life-long thyroid hormone supplementation to maintain normal function in the future.

Hypothyroidism tends to occur more frequently in patients with small thyroid glands and lower 24-hour uptake measurements (Hagen et al, 1967). Other independent predictors of hypothyroidism following RAI treatment include a diagnosis of GD, the level of thyroid auto antibodies, and no antithyroid treatment given prior to RAI, nonpalpable goiter, and high RAI dose. In one series, the absence of risk factors was associated with a 12% probability of developing hypothyroidism, whereas with all factors, the probability increases to 96% (de Bruin et al 1994). Hypothyroidism may occur several years following RAI treatment, and may be more likely in patients who have had multiple RAI treatments (Ahmad et al, 2002). Regardless of whether the goal is to achieve euthyroidism or acceptable rates of hypothyroidism, all patients who have been treated with RAI should receive longitudinal clinical follow-up along with thyroid function studies. Patients with autoimmune

thyroid disease should also be monitored for complications, such as Graves' ophthalmopathy. In addition to abolishing hyperthyroidism, treatment with radioiodine should significantly reduce thyroid gland size in patients with GD. A 50% to 80% reduction in gland volume may be seen in proportion to the radiation dose given (Holm et al, 1982).

2.6.13 Patient preparation and adjuncts to treatment:

Clinical exacerbations of hyperthyroidism caused by RAI treatment are relatively uncommon. Pretreatment with antithyroid drugs have been shown to attenuate transient increases in thyroid hormone levels following treatment (Peters et al, 1996). They may also lower the baseline hormone levels, reducing the clinical significance of any transient increase in these levels (Koornstra et al, 1999). Beta blockers may reduce symptoms related to hyperthyroidism, although it should not be solely relied upon to prevent impending thyroid storm. To reduce symptoms which may occur during treatment, beta-blocker medications, such as propranolol, 80–160 mg/day, or atenolol, 50–150 mg/day, can be considered in patients without significant contraindications to this class of medication. Beta blockers may be continued during RAI treatment. To reduce morbidity from hyperthyroidism and prevent worsening of symptoms before the effects of radioiodine are realized, patients may also be given antithyroid medications several days before or after RAI treatment. If given, such medications should be discontinued three to five days prior to RAI administration. These drugs generally can be

resumed 3 to 10 days following treatment, or earlier, if clinically necessary. Pretreatment with propylthiouracil (PTU), with discontinuation up to one week prior to treatment, may increase the failure rate of radioiodine treatment (Burchet al, 2001). PTU interferes not only with iodine organification, but also may cause an iodide diuresis (Hancock et al, 1997). For this reason, some have advocated higher doses (e.g., increase by 25%) for patients receiving antithyroid medications shortly before or after RAI treatment (Mattyet al, 1968). Compared with PTU, pretreatment with methimazole may have a lesser effect on the failure rate of RAI treatment (Crooks et al 1960). Several prospective studies, where patients were randomized to no pretreatment with antithyroid drugs versus pretreatment with methimazole up to four to six days prior to RAI administration, found no significant differences in the success rate or the time to therapeutic response (Andrade et al 2001). The adverse effect of antithyroid medications on RAI treatment efficacy may be more significant for toxic nodular goiters than for GD (Brag et al, 2002).

Patients should not eat solid foods or drink dairy products for at least two hours before and after treatment. Water is advised, however, to reduce radiation exposure to the genitourinary tract. Multivitamins should be discontinued seven days prior to treatment. Low iodine diets for about one week prior to RAI treatment have also been advocated, although this has not been convincingly shown to improve response when RAI is used for the treatment of hyperthyroidism. Written informed consent should be obtained

at the time of treatment. Informed consent should include a review of the disease, the rationale for treatment, treatment alternatives, potential side effects and outcomes, and the need for follow-up, in addition to radiation precautions, which should be provided both verbally and in written form. Patients with GD should be counseled regarding the risks of ophthalmopathy. The prescribed activity should be verified in a dose calibrator and the patient's identity should be confirmed immediately prior to treatment.

2.6.14 Side effects:

Side effects of RAI given at doses to treat benign thyroid disease are generally mild, infrequent, and self-limiting. These include thyroid tenderness, salivary gland swelling, and nausea. In addition to permanent hypothyroidism, transient, hypothyroidism may also occur (Sawers et al. 2001). Transient hypoparathyroidism has also been reported (Connell et al, 1983). Thyroid tenderness and swelling may respond to nonsteroidal anti-inflammatory agents. Exacerbation of hyperthyroidism may also occur, but thyroid storm, although potentially fatal, is considered uncommon (Burch et al 1983). Severe side effects appear more likely in patients with large goiters, who may also be at risk of tracheal compression on very rare occasions (McDermott et al, 1983). Vocal cord paresis has also been reported as an extremely rare complication of RAI therapy (Becker et al, 1989).

Ophthalmopathy: Ophthalmopathy may be particularly severe in 3% to 5% of patients with GD. The ocular manifestations of GD appear more frequently

in women than men. Although it usually presents concomitantly with hyperthyroidism, it may precede or follow clinical hyperthyroidism (Marcocci et al, 1989). An area of controversy is whether treatment with radioiodine is associated with the onset or worsening of Graves' ophthalmopathy. Exacerbation of ophthalmopathy has been attributed to radioiodine-induced release of antigens shared by the thyroid and orbit. Conflicting results from studies of ophthalmopathy and RAI may be attributed to the retrospective and nonrandomized nature of most studies, inadequate control groups, and the nonstandardized assessment of ocular changes. Progression of ophthalmopathy may occur in approximately 15% of patients, especially those who smoke, have pre-existing eye disease, high levels of TSH-receptor antibody, or severe manifestations of thyroid disease (Wiersinga et al, 2002). Cigarette smoking has been associated with an increased risk for progression of ophthalmopathy following radioiodine therapy, and a decreased efficacy of orbital radiation and glucocorticoid therapy (Bartalena et al 1998). Concomitant treatment with glucocorticoids can protect against the progression of ophthalmopathy in patients with non-severe ophthalmopathy (Bartalena et al, 1998). As worsening of pre-existing eye disease is more frequent than new ophthalmopathy following RAI treatment, patients most likely to benefit from corticosteroids are those with clinically evident eye disease, especially if they continue smoking. Prednisone, 0.4–0.5 mg/kg per day, beginning immediately after radioiodine treatment, continued for one month, and then tapered over three months, has been shown to be effective

in a randomized controlled trial (Bartalena et al 1989). As both hyperthyroidism and corticosteroids may increase bone turnover, patients receiving long-term corticosteroids should be considered for evaluation of bone density and therapies to prevent osteoporosis. Pretreatment with methimazole does not appear to prevent the development or exacerbation of ophthalmopathy after RAI treatment (Kung et al 1994). Patients with more severe ophthalmopathy should receive prompt evaluation and treatment independent of RAI. Treatment for significant ocular disease includes high-dose glucocorticoids, orbital radiotherapy, orbital decompression, or a combination thereof. Patients with Graves' ophthalmopathy should be strongly encouraged not to smoke.

Cancer Risk from Radioactive Iodine Therapy: The possibility of an increased risk of cancer following radioiodine therapy for hyperthyroidism remains controversial despite numerous studies supporting the safety of RAI for this indication. A multicenter retrospective cohort study examined cancer mortality in over 35,000 patients after three treatment modalities for hyperthyroidism (Bartalena et al 1997). The total number of cancer deaths was not increased for this group as a whole. Interestingly, an increased risk of cancer mortality was seen in patients treated exclusively with antithyroid drugs. Radioiodine treatment was not associated with excess total cancer deaths, or to any particular cancer, with the exception of thyroid cancer, where there was a slight increase in thyroid cancer mortality following radioiodine therapy, although the underlying thyroid disease was suggested

to have played a role. Another study found that the incidence of thyroid cancer in radioiodine-treated patients over a 27-year period was not significantly different from its incidence in the general population (Ron et al, 1998).

One population-based study actually found a small decrease in the risk of several types of cancer following radioiodine therapy (Angusti et al, 2000). It is important to note that the number of children treated with RAI is small in the majority of these studies.

Genetic Effects to Offspring: There is no evidence that exposure to radioiodine affects the long-term outcomes of subsequent pregnancies and offspring (Franklyn et al 1999). A 370-MBq (10 mCi) dose of iodine-131 is estimated to deliver a dose of approximately 0.01–0.03 Gy to the ovaries, mostly from excreted RAI in the bladder. Radiation dose can be minimized with hydration and frequent voiding following treatment. Women of childbearing age should be counseled to refrain from becoming pregnant for at least six months following therapy. This is primarily to confirm treatment response, given that there are significant perinatal risks related to thyrotoxicosis (Schlumberger et al, 1996).

2.6.15 Patient instructions, precautions, and follow-up:

Following the administration of therapeutic doses of RAI, contamination from excretion of RAI in urine, perspiration, breast milk, and saliva, can be associated with internal accumulation of RAI by others who come in contact

with the patient. Potential avenues of radiation exposure to others include ingestion of iodine-131 excreted by the patient, and from emitted gamma rays from iodine- 131 Although there is little evidence to suggest that small amounts of radiation from iodine-131 treated patients can cause significant problems to others, guidelines have provided simple recommendations to reduce unnecessary radiation exposure, especially to pregnant women, infants, and children. It is a requirement of the United States Nuclear Regulatory Commission to give patients verbal and written instructions prior to treatment with RAI (Dotsch et al, 2003).

The Society of Nuclear Medicine has recommended that patients sleep alone for the first few days after treatment. For the first 72 hours, patients should not spend prolonged periods of time closer than three feet to any adult, or within the same room as any child. An easy to follow guideline is to maintain a distance of one arm's length between treated persons and others. Short periods of contact are acceptable. If caring for an infant, patients should minimize the amount of time spent in close proximity with the infant during this time (Shulman et al 1997). Specifically, infants should not be held for prolonged periods because of proximity to the thyroid or bladder. It is also recommended that time spent with pregnant women and young children be minimized for four to seven days after treatment. Work restrictions should be given to patients who may potentially expose pregnant women or children when performing their occupation (Ron et al, 1995).

Fluid intake and frequent voiding should be encouraged for at least the first 24 hours following treatment. Patients should be instructed to wake up at least once the night following treatment to empty their bladder. The toilet should be flushed two or three times. Hand washing should be performed routinely and frequently (Robbins et al, 2000). If patients perspire heavily, clothing should be washed separately. Because of contamination concerns, it is not recommended to treat women during their menses. Sharing food and eating utensils should be prohibited (Dobyns et al, 2008). Patients should wash their utensils separately or use disposable utensils. Lactating women who wish to be treated should be instructed to discontinue breastfeeding. Treatment should be withheld until lactation ceases. It may be possible to detect radioactivity in breast milk for several months following treatment. Patients should be instructed not to resume breastfeeding until the birth of another child.

Women capable of childbearing should be asked to avoid pregnancy for at least six months following treatment, in order to confirm resolution of hyperthyroidism in addition to minimizing risks from radiation. Patients should be told that symptoms would resolve over several weeks, and that they would require close follow-up, as hyperthyroidism may worsen during the intervening time (Rivkees et al, 1998). Symptoms of uncontrolled hyperthyroidism should be described, and patients should be informed to seek medical attention if such symptoms occur. They should also be made aware of the probable need for thyroid hormone supplementation in the

future (Rivkees et al, .2003). The risk of persistent hyperthyroidism and myxedema following treatment necessitates close follow-up that includes clinical examination and thyroid function tests. Patients with GD should be made aware that ophthalmopathy may occur or worsen. Patients should follow-up with their physician in four to six weeks. One study suggests that the assessment of treatment response may be most reliable at 12 to 14 weeks after therapy, although it may be possible to identify non optimal responders as early as six to eight weeks (Daae et al, 1980). Instructions for patients are summarized in Table 3. In the United States, the most current regulations for RAI therapy may be obtained from the U.S. Nuclear Regulatory Commission.

2.7. **Previous Study:**

Safa et.al 1975 aimed to evaluate the long-term results of ^{131}I therapy for children, he studied the course of 87 patients (three to 18 years old, 24 boys and 63 girls) treated from 1949 through 1968, for hyperthyroidism due to Graves's disease. Dose of ^{131}I per patient ranged from 2.9 to 31 mCi (mean ± S.D., 9.75 ± 6.5). Patients were followed for five to 24 years (mean, 12.3±3.5). Hyperthyroidism was controlled in 85 within one to 14 months (mean, 3.3±2.6). Recurrence of thyrotoxicosis due to toxic diffuse goiter, observed in only one case after 11 years, was successfully re-treated with [131]I. Reproductive history and health status of the progeny of [13l]I-treated patients were not different from those of the general population. No deaths

and no cancer or leukemia were observed in patients or their offspring. The major cause of goiter re growth was Hashimoto's thyroiditis. Hypothyroidism developed in 35 of 76 patients (46 per cent).[131]I deserves further use in treatment of hyperthyroid children with Graves's disease.

Gutiérrez et.al 1999 aimed to detect the incidence and persistence of potential chromosome damage induced by iodine-131 therapy, he applied the cytokinesis-block micronucleus assay to peripheral blood lymphocytes from hyperthyroidism and thyroid cancer patients treated with 131I. Two groups of patients were evaluated in a longitudinal study; one group was composed of 47 hyperthyroid patients and the other of 39 thyroid cancer patients. In the hyperthyroidism group, the micronuclei frequency was determined before 131I therapy and 1 week, 1 month and 3 months after it. Furthermore, an additional sample was taken from a subgroup of 17 hyperthyroidism patients 6 months after treatment. In the thyroid cancer group, the analysis was also conducted over time, and four samples were studied: before treatment and 1 week, 6 months and 1 year later. Simultaneously, a cross-sectional study was performed with 70 control subjects and 54 thyroid cancer patients who had received the last therapeutic dose 1–6 years before the present study. In the hyperthyroidism group a significant increase in the micronuclei average was found over time. In the sample obtained 6 months after therapy, the micronuclei mean frequency was practically the same as in the sample taken 3 months before. In the thyroid cancer group a twofold increase in the frequency of

micronuclei was seen 1 week after therapy. Although this value decreased across time, the micronuclei frequency obtained 1 year after 131I therapy remained higher than the value found before it. Concerning the data from the cross-sectional study, a significant increase in the frequency of micronuclei was detected in the subgroup of thyroid cancer patients treated between 1 and 3 years before the current study. These results indicate that exposure to 131I therapy induces chromosome damage in peripheral lymphocytes and that the cytokinesis-block micronucleus assay is sensitive enough to detect the genetic damage by exposure to sufficiently high levels of radiation from internal radioactive sources.

Dottorini et.al (1995) he was aimed to study was to evaluate female fertility, carcinogenic, and genetic effects after treatment with 131I of differentiated thyroid carcinoma. METHODS: A total of 814 females of child-bearing age were studied. The fertility of 627 females who received 131I therapy was compared to 187 untreated females. Birth histories of the children born from these women were registered. The carcinogenic effect was evaluated by comparing the incidence of tumors in 730 patients treated with 131I with an internal control group, as well as with local population incidence. The main result of his study was no significant difference in the fertility rate, birth weight and prematurity between the two groups. Only one case of a ventricular septal defect was observed in a child born to a women treated with 131I. The overall standardized incidence ratio (SIR) of second tumors was 1.19 (95% CI: 0.76-1.77) in patients treated with 131I. An elevated SIR

was registered for salivary gland tumors and melanoma. No case of leukemia was registered. Finally he conclude that the risk of long-term effects of 131I treatment of differentiated thyroid carcinoma is quite low. Iodine-131 may be safely used in treating cases with a high risk of recurrence.

P. Laurberg et.al (2001) stated that the relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U-shaped with an increase in risk from both low and high iodine intakes. Developmental brain disorders and endemic goiter caused by severe iodine deficiency may seriously deteriorate overall health status and economic performance of a population. Severe iodine deficiency with a median 24-hour urinary iodine excretion of the population below 25 µg needs immediate attention and correction. Less severe iodine deficiency with median urinary iodine excretion below 120 µg per 24 hours is associated with multinodular autonomous growth and function of the thyroid gland leading to goiter and hyperthyroidism in middle aged and elderly subjects. The lower the iodine intake, the earlier and more prominent are the abnormalities. At the other end of the spectrum, severely excessive iodine intake starting at median urinary iodine excretion levels around 800 µg per 24 hours is associated with a higher prevalence of thyroid hypofunction and goiter in children. A number of studies indicate that moderate and mild iodine excess (median urinary iodine >220 µ g per 24 hours) are associated with a more frequent occurrence of hypothyroidism, especially in elderly subjects. The exact mechanism leading to this has not been clarified, and more studies are

needed to define the limits of excessive iodine intake precisely. Due to the frequent occurrence of thyroid disorders, proper monitoring and control of the population iodine intake level is a cost-effective alternative to diagnosing, therapy and control of the many individual cases of thyroid diseases that might have been prevented.

Michael et.al (1998) he stated that radioactive iodine (RAI) therapy for hyperthyroidism was first used in 1941 by physicians at Massachusetts General Hospital in Boston.7 and 58 the first nuclide used was 130I, which has a half-life of 12.4 hours. In 1946, 131I became readily available from the Oak Ridge National Laboratory in Tennessee as a spin-off of atomic energy research conducted during World War II. The relatively low cost convenient half-life of 8 days and the effectiveness of treatment of hyperthyroidism with 131I rapidly led to its widespread adoption. It has become one of the standard therapies for hyperthyroidism and is now used throughout the world. Attempts have been made to use another isotope, 125I, for the treatment of hyperthyroidism in the hope of avoiding subsequent long-term hypothyroidism; however, it has no advantage over 131I. The properties of 123I that make it excellent for thyroid imaging—a short half-life, an appropriate gamma radiation emission energy, and a low radiation dose delivered to the thyroid gland—also make it ineffective for the ablation of thyroid tissue. Thus, only 131I is currently used for ablative thyroid therapy, both for hyperthyroidism and thyroid cancer.

Chapter Three

Chapter Three

Methodology

3.1. Materials:

Thyroid function test: 5 ml Blood sample, test tube, centrifuge, I^{125}, antibodies and gamma counter (PC-RIA.MAS STRATEC,Germany).Thyroid uptake: Radioisotope Tc99m (Tc99m/Mo99 generator-Monrol company, Turkey), Dose calibrator (PTW CURIEMENTOR –Germany) and Gamma camera (Dual Head –FOV: 53*39cm^2, Nucline^{TM} SPIRIT DH-V, Mediso company, Hungary).

3.2. Method:

A cross-sectional (descriptive) hospital based prospective study carried out to evaluate and to assess the role of I^{131} treatment of hyperthyroidism, patient referred to the thyroid clinic in nuclear department, radiation and isotopes center of Khartoum, C/O enlarged thyroid gland with thyroid hormone disturbance; physician advice the patient to perform laboratory investigation, and thoracic inlet x-ray used to evaluate the hormone level and the airway passage, thyroid function test performed using 5ml of blood, test tube, centrifuge to separate the plasma from the blood component, I125, antibodies, and Gamma counter (PC-RIA.MAS STRATEC, Germany), An elevated RAIU confirms that endogenous thyroidal secretion is the source of the hyperthyroidism and aids in excluding other etiologies of hyperthyroidism, such as silent thyroiditis, sub-acute thyroiditis, postpartum thyroiditis, iodine-induced hyperthyroidism, and factitious hyperthyroidism, all of which are associated with a low RAIU. Tc99m/ Mo99m generator, Dual head gamma Camera (FOV= 53X49cm2, Nucline™ SPIRT DH-V, MEDISO-Company, Hungary) SPECT imaging was used to scan the patient to assess cause of hyperthyroidism and the thyroid uptake was recorded, the level of thyroid hormone was recorded before starting radioiodine treatment and 3, 6, 9, 12 months after treatment in order to assess the level of thyroid hormone in these periods and therefore assessing the treatment response and the outcome.

3.2.1. Study Design:

This was analytical nuclear medicine study aimed to assess the efficiency of I-131 in treatment of hyperthyroidism

3.2.2. Area of Study:

This study was conducted at Khartoum state, Nuclear medicine department-radiation and isotopes center of Khartoum (RICK).

3.2.3. Duration of the Study;

This study conducted in period from August 2012 to December 2015

3.2.4. Sample of the Study:

This study consist of 120 patients drown from hyperthyroidism patients treated by radioactive iodine131 referred to thyroid clinic in RICK.

Inclusion Criteria: The study was carried out in patient having ages between 17 To 75 Years from both sex.

Exclusion Criteria: Patient undergoing anti thyroid medication for more than one year, ages below 17 and over 75years, Patients receiving radioactive iodine as a second dose and patient taking propylthiouracil (PTU) was clearly excluded from this study.

3.2.5. Method of Data Collection:

The data were collected using standard master data sheet contain the necessary study variables.

3.2.6. Data Collection Variables:

Patient age, gender, thyroid hormone level (T3, T4 and TSH), RIA dose, and thyroid uptake.

3.2.7. Example of master data sheet used for data analysis:

Age	Sex	Uptake	Dose	TFT before TX	TFT 3 months after Tx	TFT 6 months after Tx	TFT 9 months after Tx	TFT 12 months after Tx

3.2.8. Methods of Data Analysis

All data were presented as mean± SD values. Data were analyzed by pair sample two-tailed t-test and by correlation analysis with the use of the SPSS (Inc., Chicago, Illinois version 21.0). A value of $P < 0.05$ was considered significant.

Chapter Four

Chapter Four

Result

Table (4.1): shows the mean ± STD of thyroid function test values before and at constant interval after the treatment.

Period	T3	T4	TSH
Before treatment	6.94±6.28	222.124±110.47	0.3699±0.663
After 3 month	4.18±7.949	134.01±88.36	6.337±15.50
After 6 month	2.78±3.5	119.24±66.73	5.309±13.142
After 9 month	2.768±2.9	119.15±59.47	2.765±4.058
After 12 month	2.46±1.79	113.36±47.16	2.265±2.66

Table (4.2): The mean and STD values for patient age and the percentage of thyroid uptake.

Variables	N	Mean	STD
Age	120	42.98	12.099
Uptake	120	18.2852	12.17988

Table (4.3): illustrates the frequency distribution of the age groups for 120 patient with I-131 treatment

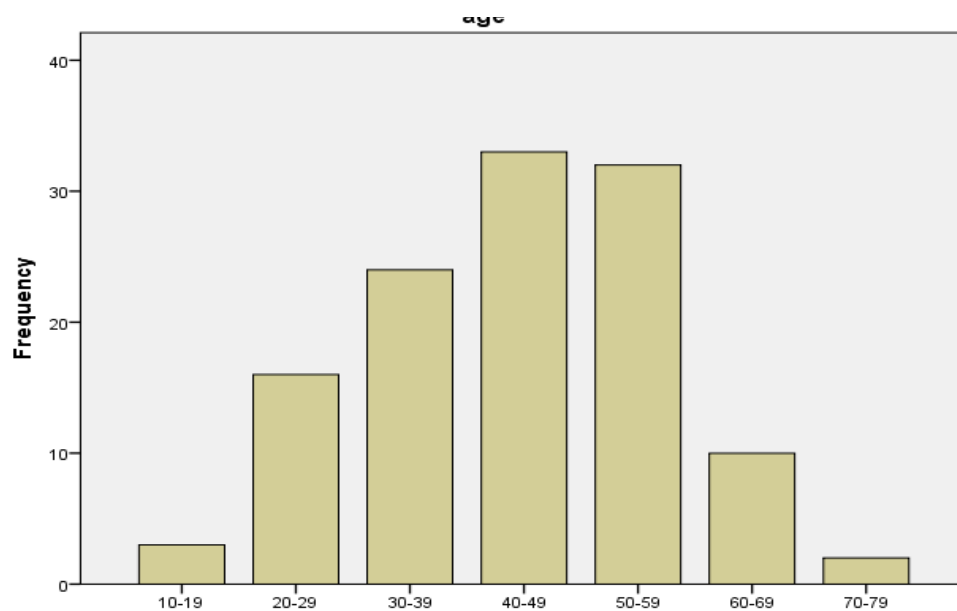| Age group	Frequency	Percent
10-19	3	2.5
20-29	16	13.3
30-39	24	20.0
40-49	33	27.5
50-59	32	26.7
60-69	10	8.3
70-79	2	1.7
Total	120	100.0

Figure (4.1) par graph demonstrate the frequency of age group distribution of collected data

Table (4.4): illustrates frequency distribution of male and female for 120 patient

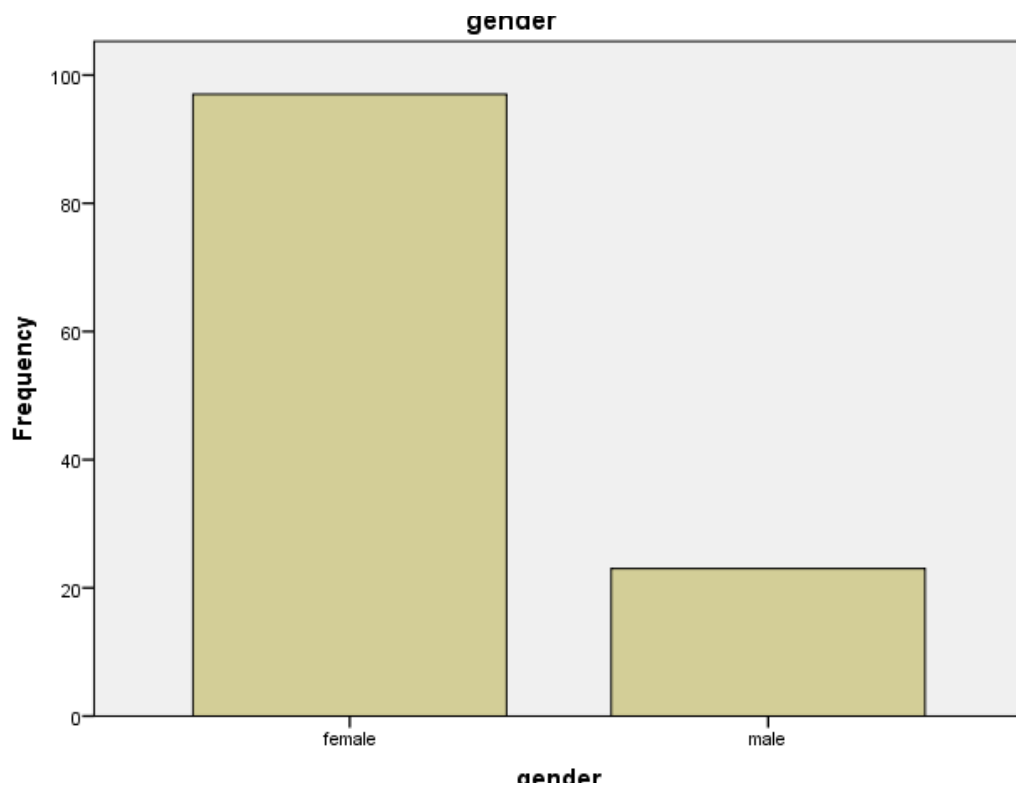| Variables	Frequency	Percent
Female	97	80.8
Male	23	19.2
Total	120	100.0

Figure (4.2): illustrates frequency distribution of male and female for 120 patient

Table (4.5): illustrates the frequency distribution of the most causes of the hyperthyroidism

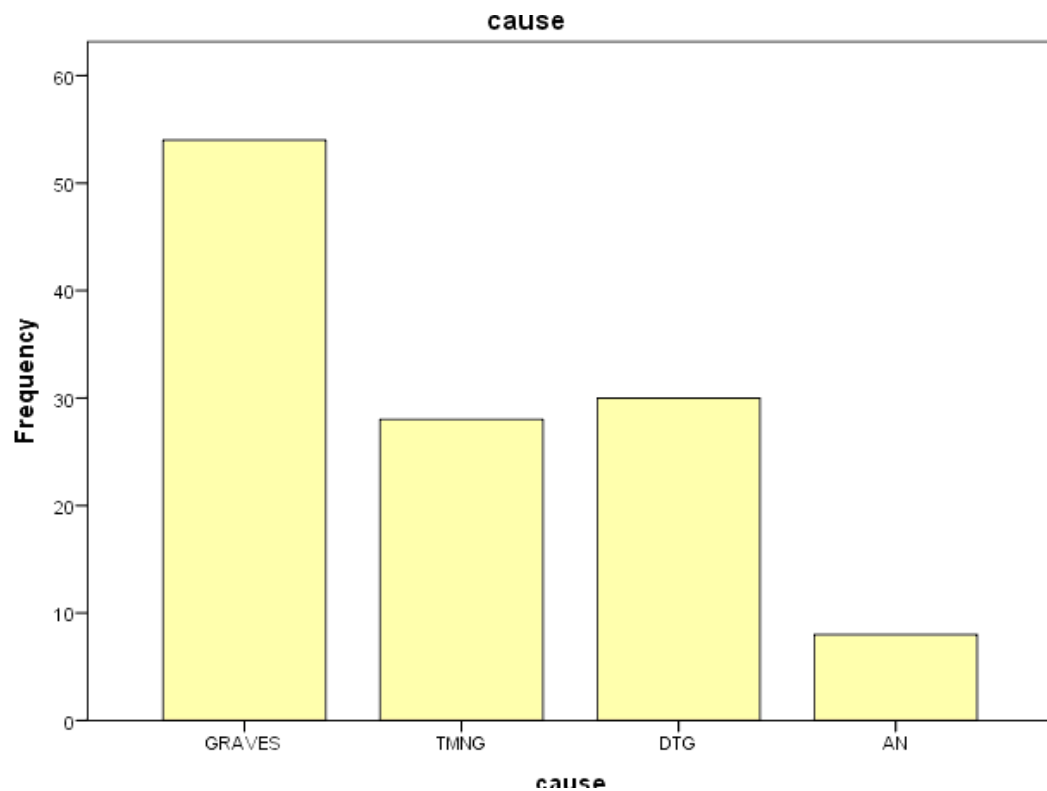| Variables	Frequency	Percent
GRAVES	54	45.0
TMNG	28	23.3
DTG	30	25.0
Nodules	8	6.7
Total	120	100.0

Figure (4.3): a par graph shows the frequency distribution of the most causes of the hyperthyroidism

Table (4.6) Demonstrates the performed significant two tailed t-test for to test the difference in mean values of thyroid hormone values before and after 9 month after the I131 treatment (test were significant at p<0.050

Pairs	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
T3(0) – 12 m T3	4.47675	6.45189	.58897	3.31052	5.64298	7.601	119	0.000
T4(0)-12 m T4	108.7617	121.3954	11.08185	86.82001	130.70633	9.815	119	0.000
TSH(0)-12m TSH	-1.89485	2.623865	.2395242	-2.36919	-1.4205681	-7.911	119	0.000

Figure (4.4): a line plot demonstrates the relation between T3 value and time after the treatment linear correlation showed that (y = -0.3455x + 5.8996, $R^2 = 0.7736$) in strong indirect relationship.

Figure (4.5): a scatter plot demonstrates the relation between T4 value and time after the treatment

Figure (4.6): a line plot demonstrate the relation between T4 value and time after the treatment

Figure (4.7): a line plot demonstrates the relation between TSH value and time after the treatment in which the value were increased as a function of time after treatment followed by gradual hypothyroidism take place. Linear correlation showed   that   y   =   -0.4347x   +   7.3437 $R^2 = 0.9446$. In period after the treatment.

Chapter Five

Chapter five

Discussion conclusion and recommendation

5.1 Discussion:

In 1941 Radio-iodine treatment of thyroid gland had been proposed as a modality of choice and has since evolved to the treatment modality of choice for the majority of adult patients particularly in USA, UK and Europe, while the drugs (anti-thyroid drugs) can cause complete remission in 10-40% of patient only, William H. et.al 2005. Administered dose is usually calculated with the goal of administering approximately 70–120 Gy (7000–12000 rad) to the thyroid gland [4]. *The calculation is made as follows: administered microcuries = µCi/g desired × gland weight (g) × 100 ÷ percent uptake (24 hours).* This equation demonstrates the effect of thyroid uptake in calculation

of administered dose.

This study was contained of 120 sample having a mean age of 42.98±12.099 year, and the most frequent gender treated with radioactive iodine was female (97, 80.8%), and male (23, 19.2%) as in table (4.4), the mean value of thyroid uptake percentage during these scan was (18.28±12.17). table (4.2). and the most affected age group was (40-49) having frequency of 33 (27.5%) as in table (4.3).

A mean dose used to ablate thyroid tissue was (13.45mCi). This was be decided upon (1) the amount of radioiodine administered, (2) the fraction deposited in the gland (uptake), (3) the duration of retention by the thyroid (biologic half-life), and (4) the radio sensitivity of the irradiated tissue. The main purpose of this study is to assess the level of thyroid hormones in patients with hyperthyroidism in five periods which are (before treatment, 3months after treatment, 6months, 9 months and 12months after treatment) for T3, T4 and level of TSH. The result showed that the mean value of these hormone was 6.9, 4.2, 2.8, and 2.5 (nmol/L) for T3, 222.1, 134, 119, 119.2 and 113.4 (nmol/L) for T4, and 0.37, 6.34, 5.3, 2.8, and 2.3 (nmol/L) for TSH respectively, table (1). These were compared to the normal level of thyroid hormone which are T3 (0.8-3nmol/L), T4 (50-150nmol/L) and TSH (0.4-4 nmol/L) and we noted an elevated thyroid hormones before treatment and then gradually decreased over the mentioned period of time for assessment this result reveals that the hormone level were decreased in response to the treatment.

A significant paired sample T-test was performed in order to test the difference between these values for the same patients in mentioned period. The result showed that there is a significant difference between the thyroid hormone level before I^{131}adminstration and after 3, 6, 9, and 12 months later after the treatment, at Confidence level of (CL=95%) and (p value= 0.05), the test were significant at P= 0.000, which mean that the thyroid hormone are significantly changing in these period which indicate the effectiveness of the I-131 to treat the hyperthyroidism and its causative factor such as TMNG, or Graves' disease.

Factor or disease that may lead to cause hyperthyroidism was also investigated and our result showed that 45 patient (54%) of the collected samples were caused by Graves' disease, 28 (23.3%) by TMNG, 30 (25%) due to Diffuse toxic goiter and 6.7% related to the autonomous nodules. William H. et.al 2005 stated that 95% of hyperthyroidism caused by Graves' disease and diffuse toxic goiter, as in table (5).Figure (4): showed that linear relationship between the T3 level and the time before and after the treatment which demonstrated the decrement of T3 value with period of time in which decreased by 0.3455 (nmol/L) for every one month increment in time after treatment by I-131 *(y = -0.3455x + 5.8996, R² = 0.7736).* Assessment of T3, T4, and TSH values after 6 month is consider significant in term of treatment response as stated by William H et.al 2005.

A strong correlation between T4 value and the time in similar manner as T3, that result may explained by physiological aspect of T3 value which is

derivative from the T4 as normal physiological process, so when level of T3 decreased T4 is decreased due to lack of T3 synthesized by thyroid tissue related to normal iodine uptake. The correlation showed that T4 level decreased by 7.746 (nmol/L) every month increments in period after thyroid treatment. **$y = -7.746x + 188.05$, $R^2 = 0.6472$. As in Figure** (5).

the effect of treatment on the level of TSH after the treatment, in normal pathophysiological process of hyperthyroidism TSH level where decreased, due to over expression of T3 and T4 in the blood, as stated by A. zeiessman et.al 2006. our study note the same result in which TSH having value of 0.37 (nmol/L) then starting to increase until starting the treatment, reaching a value of 6.34 (nmol/L) in three month (peak value), then starting to decrease as a function of time (month) indicating of hypothyroidism, in which decreased by 0.434 (nmol/L) for every one month increment in period after I131 administration. **$y = -0.4347x + 7.3437$ $R^2 = 0.9446$ as in figure (7).**This result was explained by William H et.al 2005, who stated that following radioiodine therapy, the patient should be advised to have serum thyroid hormone and TSH levels checked within 2 to 3 months. Patients may be symptomatically improved within 4 to 6 weeks, but clinically significant hypothyroidism rarely occurs before 2 to 3 months. Hypothyroidism is only a problem if not adequately treated, and many practitioners will initiate thyroxine replacement therapy at the earliest indication of post-therapy hypothyroidism.

5-2 Conclusion:

A process of introduction of NM treatment options for hyperthyroidism and thyroid disease as general had been evaluated by many literature, Hyperthyroidism is considered as one of common pathological problem associated with thyroid gland, in which thyroid hormone level were increased. This a prospective study attended to assess the efficiency of thyroid treatment using I-131 in treatment of hyperthyroidism in Sudanese population, A 120 patient were treated by using I131 at radiation and isotopes center of Khartoum in period from 2012 to 2015. Imaging procedure was done using Tc99m radiopharmaceutical where the Tc99m/ Mo99m Generator was used to produce Tc99m, dose caliber and Dual head Gama camera was used to scan these patient. The level of thyroid hormone were recorded before, and after 3, 6, 9, and 12 month after treatment in order to assess the decrement level of these hormone and therefore performing a quantitative assessment of hyperthyroidism treatment, the result showed that the mean value of these hormones was 6.9, 4.2, 2.8, and 2.5 (nmol/L) for T3, 222.1, 134, 119, 119.2 and 113.4 (nmol/L) for T4, and 0.37, 6.34, 5.3, 2.8, and 2.3 (nmol/L) for TSH respectively. Pair sample two tailed test was performed; a significant difference between the thyroid hormone level was noted before the RAI treatment and after 3, 6, 9, and 12 month later after the treatment, at Confidence level of (CL=95%) and (p value= 0.05), the test were significant at P= 0.000. Causative disease of hyperthyroid function

found to be due to Graves' disease in 45 patient (54%) of the collected samples, 28 (23.3%) by TMNG, 30 (25%) due to Diffuse toxic goiter and 6.7% related to the autonomous toxic nodules. This study concludes that hyperthyroidism treatment using I131 considered effective and cause significant difference in thyroid hormone level after treatment.

5-3 Recommendations:

Iodine containing food should be avoided one week prior to iodine administration to maximize RAI trapping and Organification, hence increase the therapeutic effect and also empty stomach enhancing iodine uptake, so NPO for 6 hours prior to RAI administration is of great importance.

Thyroid uptake study is of importance for all hyperthyroidism patients to adjust administered dose.

Written patient instructions for follow up should be given clearly explained to the patients. Thyroid clinic should be separate from oncology, for patients comfort and psychological aspects.

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Appendices

Age	Sex	Cause of hyperthyroidism	TFT Pre RAI	THYROID UPTAKE	RAI (mCi)	TFT 3 months post RAI			TFT 6 months post RAI			TFT 9 months post RAI			1
						T3	T4	TSH	T3	T4	TSH	T3	T4	TSH	T3

Master Sheet

Iodine 131 oral capsule